Clinical phenotypes and outcomes of precapillary pulmonary hypertension of sickle cell disease

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ABSTRACT

Rationale: Precapillary pulmonary hypertension (PH) is a devastating complication of sickle cell disease (SCD). Little is known about the influence of the SCD genotype on PH characteristics.

Objectives: To describe clinical phenotypes and outcomes of precapillary PH due to SCD according to disease genotype.

Methods: A nationwide multicentre retrospective study including all patients with SCD-related precapillary PH from the French PH Registry was conducted. Clinical characteristics and outcomes according to SCD genotype were analysed.

Results: 58 consecutive SCD patients with precapillary PH were identified, of whom 41 had homozygous for haemoglobin S (SS) SCD, three had S-β_0 thalassaemia (S-β_0 thal) and 14 had haemoglobin SC disease (SC). Compared to SC patients, SS/S-β_0 thal patients were characterised by lower 6-min walk distance (p=0.01) and lower pulmonary vascular resistance (p=0.04). Mismatched segmental perfusion defects on lung scintigraphy were detected in 85% of SC patients and 9% of SS/S-β_0 thal patients, respectively, and 50% of SS/S-β_0 thal patients had heterogeneous lung perfusion without segmental defects. After PH diagnosis, 31 patients (53%) received medical therapies approved for pulmonary arterial hypertension, and chronic red blood cell exchange was initiated in 23 patients (40%). Four patients were managed for chronic thromboembolic PH by pulmonary endarterectomy (n=1) or balloon pulmonary angioplasty (n=3). Overall survival was 91%, 80% and 60% at 1, 3 and 5 years, respectively, without influence of genotype on prognosis.

Conclusions: Patients with precapillary PH related to SCD have a poor prognosis. Thrombotic lesions appear as a major component of PH related to SCD, more frequently in SC patients.

Introduction

Pulmonary hypertension (PH) has been identified as a devastating complication of sickle cell disease (SCD) leading to a higher risk of mortality [1]. Screening studies combining transthoracic echocardiography and right heart catheterisation (RHC) for definite diagnosis have reported a PH prevalence ranging from 6 to 10% in SCD [2–4]. Among these patients, less than half had precapillary PH defined by mean pulmonary arterial pressure (mPAP) $\geqslant$25 mmHg and pulmonary artery wedge pressure (PAWP) $\leqslant$15 mmHg. Histological studies from SCD patients demonstrate pulmonary vascular remodelling and thrombotic lesions which may result in a progressive elevation of pulmonary vascular resistance (PVR) and ultimately right heart failure [4, 5]. Additional factors like shear stress, hyperviscosity or comorbidities (such as portal hypertension, chronic thromboembolic disease, interstitial lung disease, left cardiac dysfunction) could also contribute to the pulmonary haemodynamic derangement [6]. The complex and multifactorial physiological mechanisms of precapillary PH in this specific setting leads to a wide range of phenotypes and haemodynamic profiles. The effect of chronic haemolysis on nitric oxide (NO) depletion and endothelial dysfunction, combined with thrombotic lesions, seem to be the two main mechanisms responsible for chronic pulmonary vascular disease in SCD. Regardless of underlying mechanisms, it has been clearly established that PH contributes to impaired functional status in patients with SCD. Severe exertional dyspnoea and reduced exercise capacity, as measured by the 6-min walk distance (6MWD), has been observed in all clinical studies of SCD patients with PH. Furthermore, the prognosis of SCD patients with precapillary PH is severely compromised [2, 4, 7].

Despite the functional and prognostic implications of PH in SCD, specific guidelines on the management of SCD-associated precapillary PH are scarce due to a paucity of evidence [8].

All main genotypes of SCD seem to be associated with PH, and we hypothesised that some differences in the clinical and haemodynamic characteristics may exist that could influence outcomes and management. While haemolysis seems to be closely linked to the severity of PH in some patients, others are developing genuine chronic thromboembolic PH (CTEPH), justifying specific management [9–13]. A more precise description of phenotypes observed in all subpopulations of SCD patients with PH could support better personalised management. The aim of this study was to describe and compare the clinical characteristics and outcomes of all consecutives cases of precapillary PH related to SCD of the French PH Registry according to SCD genotype (homozygous for haemoglobin S (SS) SCD or S-β_0 thalassaemia (S-β_0 thal) versus haemoglobin SC disease).

Methods
Study population

Data from all consecutive SCD-associated precapillary PH patients referred to the French National Reference Centre for PH (Université Paris-Sud, Le Kremlin-Bicêtre) or expert centres from the French PH Network between January 2000 and December 2017 were collected from the French PH Registry.

SCD was confirmed by haemoglobin electrophoresis. All patients were screened for PH with transthoracic Doppler echocardiography and were subsequently referred to a PH expert centre if PH was suspected. Precapillary PH was defined by a mPAP $\geqslant$25 mmHg and a PAWP $\leqslant$15 mmHg measured by RHC [14, 15]. Cases of postcapillary PH defined by mPAP $\geqslant$25 mmHg and PAWP >15 mmHg were excluded. Haemodynamic assessment was systematically performed at least 1 month after an acute vaso-occlusive crisis. In line with current guidelines, all patients with a diagnosis of precapillary PH confirmed by RHC underwent extensive investigations in order to identify possible causes or risk factors for pulmonary

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arterial hypertension (PAH), such as congenital heart disease, portal hypertension, HIV infection or connective tissue disease [14, 15]. Moreover, the presence of chronic lung disease and CTEPH was assessed by performing pulmonary function tests, high-resolution computed tomography of the chest, ventilation/perfusion (V/Q) lung scintigraphy followed by computed tomography pulmonary angiography (CTPA) and/or digital subtraction pulmonary angiography (DSA) if needed. Chronic restrictive lung disease was defined as a total lung capacity of <70% associated with a chest radiographic pattern of interstitial lung disease. Baseline evaluation included physical examination, assessment of modified New York Heart Association functional class (NYHA-FC), routine blood tests, non-encouraged 6MWD, pulmonary function tests and arterial blood gases. Characteristics of patients at baseline were compared according to the disease genotype.

The study complied with the Declaration of Helsinki. Although French law does not require ethics committee approval or informed consent for retrospective data collection, the data collected were anonymised and complied with the requirements of the Commission Nationale de l'Informatique et des Libertés, the organisation dedicated to privacy, information technology and civil rights in France. The committee approved the methods used to collect and analyse data on 24 May 2003 (approval number 842063).

Multidisciplinary management

All patients received supportive therapies in accordance with PH guidelines, *i.e.* diuretics to control signs and symptoms of right ventricular failure (including peripheral oedema) and long-term oxygen therapy if hypoxaemia was present. Initiation of long-term anticoagulation therapy was left to the discretion of physicians according to the assessment of the possible contribution from *in situ* thrombosis and/or thromboembolic disease to PH.

Off-label use of medical therapies approved for PAH, *i.e.* endothelin-receptor antagonists (ERA), phosphodiesterase type-5 (PDE-5) inhibitors or prostanoids, was decided after a multidisciplinary discussion of the expected benefits and risks of this medical strategy and was systematically recorded. CTEPH patients necessitating specific management with medical therapies, balloon pulmonary angioplasty or pulmonary endarterectomy were discussed in a multidisciplinary meeting including experienced surgeons for pulmonary endarterectomy, interventional radiologists/cardiologists, radiologists experienced in pulmonary vascular imaging and pulmonologists with expertise in PH, as recommended in the guidelines [14, 15].

Decisions to use hydroxyurea and/or initiation of chronic red blood exchange transfusion after precapillary PH diagnosis were also systematically validated by a multidisciplinary meeting and recorded.

Statistical analysis

Continuous variables are expressed as median (range) values. Differences in continuous variables, such as patients' age, 6MWD and haemodynamic characteristics, were compared using the Mann–Whitney U-test. Categorical variables were expressed as number and percentage and were compared using the chi-square test for independence. Baseline and post-baseline values for haemodynamic variables were compared using a Wilcoxon matched-pairs signed rank test. A p-value of <0.05 was considered statistically significant.

The Kaplan–Meier method was used to estimate survival at each time point. For the overall survival analysis after diagnosis, we used the first haemodynamic evaluation as the starting point to determine the survival duration. The cut-off date was 30 June 2018. Patients who were lost to follow-up were censored at the date of the last available visit.

Univariate analysis based on the Cox proportional hazards model was used to examine the relationship between survival and selected baseline variables. Results are expressed as hazard ratios with 95% confidence intervals.

Results

Patient demographics and clinical characteristics at the time of precapillary PH diagnosis

58 consecutive SCD patients with precapillary PH were identified, including 41 with SS, 3 with S-β_0 thal and 14 with SC disease. A comparison of clinical characteristics at baseline between SC and SS/S-β_0 thal patients is reported in table 1. A predominance of female patients in the SS/S-β_0 thal group and a predominance of male patients in the SC group was observed. As expected, the haemoglobin level was significantly higher and biomarkers of haemolysis (lactate dehydrogenase and bilirubin) were significantly lower in the SC group compared with the SS/S-β_0 thal group. Pulmonary function tests showed a significantly lower forced vital capacity (FVC) in the SS/S-β_0 thal group whereas diffusing capacity for carbon monoxide adjusted for haemoglobin and arterial blood gases (P_{aO_2} and P_{aCO_2}) were similar in both

groups. Distribution of NYHA-FC at time of diagnosis was similar between both groups of patients. In contrast, 6MWD was significantly lower in SS/S-β_0 thal patients. Finally, RHC showed a lower cardiac index and higher PVR in SC patients. The distribution of PVR according to genotype is illustrated in figure 1. A majority of SS/S-β_0 thal patients (54%) had PVR lower than 3 WU and a small proportion of patients had high levels of PVR (three patients presented with PVR >10 WU). In SC patients PVR values were more homogeneously distributed with a median of 5.3 WU.

11 patients presented with significant chronic restrictive lung disease. Two patients had portal hypertension, one connective tissue disease (antisynthetase syndrome with interstitial lung disease) and one mediastinal sarcoidosis.

TABLE 1 Characteristics at time of PH diagnosis according to the disease genotype

	Available data n	Overall population	SS/S-β_0 thal SCD	SC SCD	p-value
Number of patients n (%)	58	58 (100)	44 (76)	14 (24)	
Female n (%)	58	32 (55)	27 (61)	5 (36)	0.09
Age years	58	44 (18–67)	43 (18–61)	48 (18–67)	0.05
Body mass index kg·m^{-2}	58	22 (16–34)	21 (16–34)	26 (20–32)	**0.0002**
History of acute chest syndrome n (%)	58	36 (62)	31 (70)	5 (36)	**0.02**
Current smokers n (%)	58	6 (10)	6 (14)	0 (0)	-
Former smokers n (%)	58	6 (10)	6 (14)	0 (0)	-
Reported history of renal complications n (%)	58	17 (29)	15 (34)	2 (14)	0.2
History of leg ulcers n (%)	58	13 (22)	13 (30)	0 (0)	-
History of pulmonary embolism n (%)	58	21 (36)	14 (32)	7 (50)	0.2
History of deep vein thrombosis n (%)	58	5 (9)	4 (9)	1 (7)	0.8
Treatment regimens at time of PH diagnosis	58				
Hydroxyurea therapy n (%)		21 (36)	19 (43)	2 (14)	0.05
Regular transfusion programme n (%)		11 (19)	10 (23)	1 (7)	0.2
PH-associated risk factor n (%)	58				
Interstitial lung disease n (%)		11 (19)	7 (16)	4 (29)	0.3
Portal hypertension n (%)		2 (3)	2 (5)	0 (0)	-
Biology					
Haemoglobin g·dL^{-1}	57	9 (6.5–14.2)	8.4 (6.5–11.5)	10.6 (9–14.2)	**<0.0001**
Creatinine µmol·L^{-1}	54	83 (36–167)	83 (36–167)	85 (59–114)	0.8
Lactate dehydrogenase IU·L^{-1}	35	944 (317–3034)	1052 (334–3034)	458 (317–1457)	**0.03**
Total bilirubin µmol·L^{-1}	46	52 (8–233)	63 (11–233)	19 (8–37)	**<0.0001**
Arterial blood gases					
P_{aO_2} mmHg	46	69 (43–100)	68 (43–100)	73 (52–90)	0.2
P_{aCO_2} mmHg	46	37 (25–56)	37 (25–46)	38 (29–56)	0.8
Pulmonary function tests					
FVC %	51	63 (25–97)	60 (25–94)	73 (44–97)	**0.03**
FEV$_1$ %	52	67 (23–107)	63 (23–107)	76 (44–107)	0.06
TLC %	53	71 (36–99)	69 (36–99)	74 (52–96)	0.3
D_{LCO} %	48	48 (16–81)	46 (25–78)	58 (43–81)	**0.02**
D_{LCO} adjusted for Hb %	48	57 (22–98)	58 (22–81)	56 (51–98)	0.24
NYHA-FC n (%)	58				
I or II		19 (33)	15 (34)	4 (29)	0.7
III or IV		39 (67)	29 (66)	10 (71)	
6-min walk distance m	51	335 (0–569)	308 (0–544)	423 (0–569)	**0.01**
Haemodynamics					
RAP mmHg	58	8 (0–34)	7 (0–34)	8 (3–11)	0.1
mPAP mmHg	58	36 (25–62)	35 (25–62)	38 (26–54)	0.2
PAWP mmHg	58	9 (1–5)	9 (1–14)	10 (1–15)	0.2
Cardiac index, L·min^{-1}·m^{-2}	58	4.1 (1.8–7.5)	4.4 (1.8–7.5)	3.2 (2.1–4.9)	**0.002**
PVR Wood units	58	4.7 (1.4–21)	4.6 (1.4–21)	5.3 (1.8–10.7)	**0.04**
Mixed venous saturation %	40	62 (32–86)	63 (32–86)	61 (44–73)	0.6
BNP >100 ng·L^{-1} or NT-proBNP >300 ng·L^{-1}	50	23 (46)	19 (51)	4 (31)	0.3

BNP: brain natriuretic peptide; D_{LCO}: diffusing capacity for carbon monoxide; FEV$_1$: forced expiratory volume in 1 s; FVC: forced vital capacity; mPAP: mean pulmonary arterial pressure; NT-proBNP: N-terminal pro-brain natriuretic peptide; P_{aO_2}: arterial oxygen tension; P_{aCO_2}: arterial carbon dioxide tension; NYHA-FC: New York Heart Association functional class; PAWP: pulmonary arterial wedge pressure; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; RAP: right atrial pressure; TLC: total lung capacity.
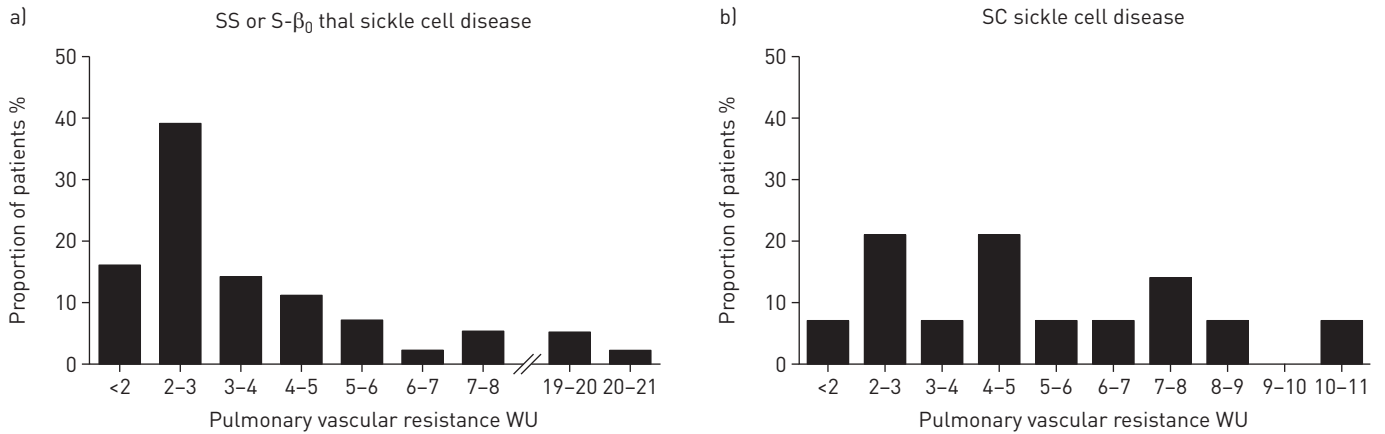
FIGURE 1 Pulmonary vascular resistance distribution according to sickle cell disease genotype.

A history of acute venous thromboembolism was reported in 7 out of 14 SC patients (50%) and 13 out of 44 SS/S-β_0 thal patients (32%) (p=0.20). V/Q lung scintigraphy was performed at baseline in 47 patients. Lung perfusion was normal in 15 patients (32%), heterogeneous in 17 (36%) and with mismatched segmental defects in 15 (32%). The proportion of patients with mismatched segmental perfusion defects was significantly higher in patients with SC SCD compared to patients with SS/S-β_0 thal (85% *versus* 9%, p<0.001) (figure 2a). CTPA was performed in all patients with abnormal V/Q lung scintigraphy and DSA was performed in 18 patients. Isolated poor subpleural perfusion in the capillary phase of DSA, defined as the absence of perfusion ⩽ 1.5 cm from the lateral pleura on the posterior–anterior views and by lateral views of the dorsal area [16], was observed in 14 patients (eight SS/S-β_0 thal and six SC). Lobar, segmental or subsegmental CTEPH was diagnosed in four patients (three SC and one SS) (figure 2b and c).
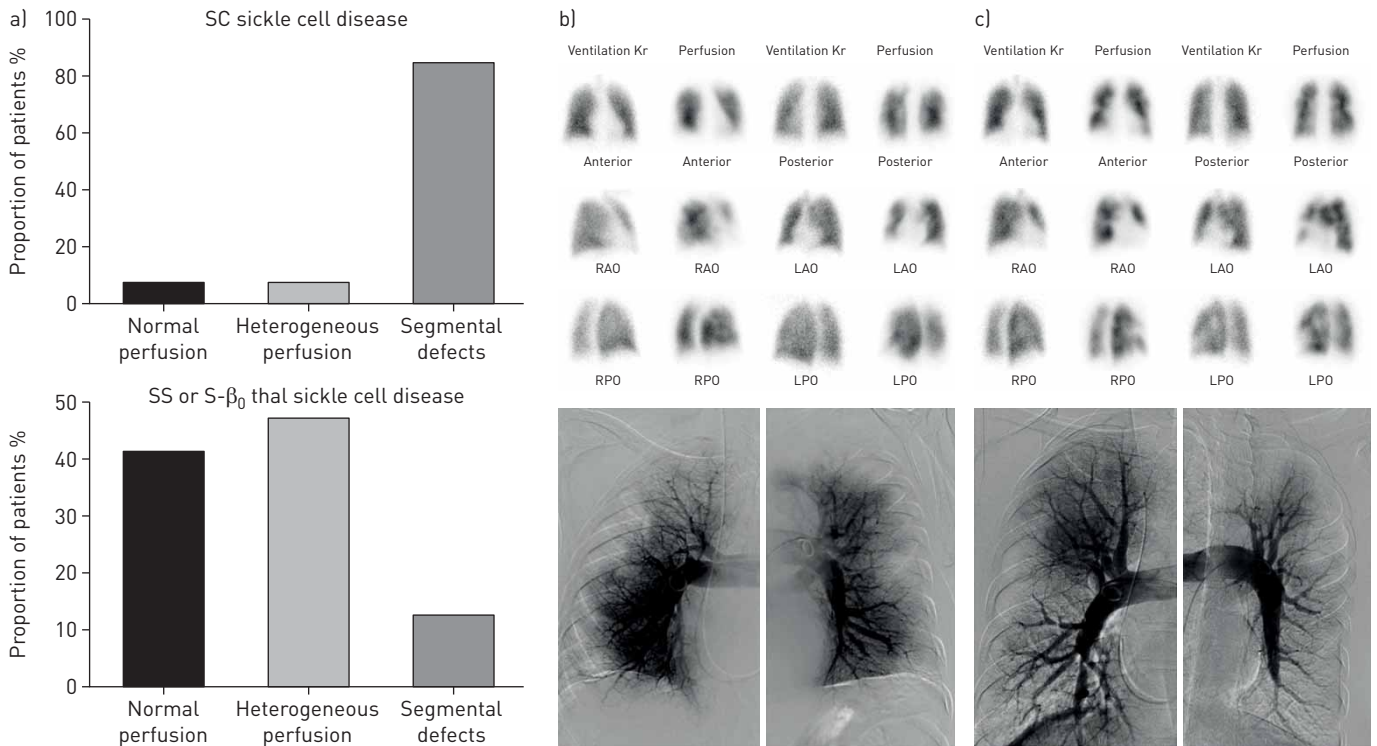

FIGURE 2 Ventilation/perfusion (V/Q) lung scintigraphy and digital subtraction pulmonary angiography (DSA) according to the disease genotype. a) The proportion of patients with normal perfusion, heterogeneous perfusion and segmental perfusion defects on V/Q lung scintigraphy according to the genotype of sickle cell disease. b) A case of homozygous for haemoglobin S (SS) sickle cell disease with heterogeneous perfusion on V/Q lung scintigraphy and diffuse subpleural hypoperfusion on DSA. c) An example of an SC sickle cell disease patient with segmental perfusion defects on V/Q lung scintigraphy and distal chronic thromboembolic pulmonary hypertension on DSA. RAO: right anterior oblique; RPO: right posterior oblique; LAO: left anterior oblique; LPO: left posterior oblique.

A comparison of characteristics according to the V/Q lung scintigraphy results is reported in table 2. Patients with mismatched segmental perfusion defects more frequently had a SC genotype and had significantly higher haemoglobin levels with significantly lower levels of bilirubin. In contrast, patients with normal V/Q lung scintigraphy had lower levels of haemoglobin with more severe haemolysis. In addition, these patients had more severely impaired 6MWD, as compared to patients with heterogeneous perfusion or mismatched segmental perfusion defects.

Management of precapillary PH

Medical therapies approved for PAH were prescribed off-label in 23 SS/S-β_0 thal patients (52%), at the time of PH diagnosis (n=14) or during follow-up (n=9). Most of them received a monotherapy (14 ERA, one PDE5i and two intravenous epoprostenol). Six patients received initial or sequential combination therapy: ERA and PDE5i (n=3), ERA and intravenous epoprostenol (n=2) and ERA, PDE5i and intravenous prostacyclin (n=1). During the follow-up period, ERA was withdrawn in one patient because of significant elevation of transaminase and in three other patients because of a high cardiac output combined with a postcapillary component induced by treatment. PDE5i was replaced by ERA in one case because of diffuse muscular pain. One SS patient underwent pulmonary endarterectomy surgery. A chronic red blood cell exchange programme was initiated in 22 SS/S-β_0 thal patients at the time of PH diagnosis (n=10) or during the follow-up period because of a progression of their pulmonary vascular

TABLE 2 Characteristics according to lung perfusion on ventilation/perfusion scintigraphy

	Normal perfusion	Heterogeneous perfusion	Segmental perfusion defects
Number of patients n	15	17	15
SC SCD n (%)	1 (7)	1 (6)	11 (73)***,###
Age years	43 (27–60)	40 (18–61)	46 (18–63)
History of pulmonary embolism n (%)	4 (28)	6 (35)	9 (60)*
History of deep vein thrombosis n (%)	1 (7)	1(6)	2 (13)
History of ACS n (%)	12 (80)	10 (59)	6 (40)
History of leg ulcers n (%)	5 (36)	2 (12)	0 (0)
Treatment regimens at time of PH diagnosis			
Hydroxyurea therapy n (%)	12 (80)	5 (29)	2 (13)
Regular transfusion programme n (%)	3 (20)	4 (24)	1 (7)
Biology			
Haemoglobin g·dL^{-1}	8.2 (6.6–9.6)	9.1 (6.5–11.5)	10 (7.3–14.2)**
Creatinine µmol·L^{-1}	81 (36–167)	86 (57–137)	86 (59–128)
Lactate dehydrogenase IU·L^{-1}	1083 (413–3034)	1034 (334–2691)	665 (317–1457)
Total bilirubin µmol·L^{-1}	57 (11–223)	69 (19–233)	21 (8–37)**,##
Arterial gas exchanges			
P_{aO_2} mmHg	68 (43–100)	64 (51–71)	74 (59–87)
P_{aO_2} mmHg	38 (27–46)	35 (25–45)	38 (29–56)
Respiratory test			
FVC %	60 (23–107)	72 (46–97)	72 (44–107)
FEV$_1$ %	54 (25–94)	68 (45–97)*	69 (44–97)*
TLC %	63 (36–99)	75 (49–97)	73 (55–91)
D_{LCO} %	37 (25–66)	52 (32–68)*	50 (28–81)**
D_{LCO} adjusted for Hb %	45 (34–86)	62 (37–81)*	56 (37–98)*
6-min walk distance m	246 (0–501)	366 (167–569)	369 (0–554)
Haemodynamics			
RAP mmHg	8 (3–18)	9 (0–34)	7 (0–11)
mPAP mmHg	37 (27–54)	37 (25–62)	38 (27–54)
PAWP mmHg	10 (3–14)	7 (1–12)*	9 (1–15)
Cardiac index L·min^{-1}·m^{-2}	4.8 (2.4–7.5)	3.8 (1.8–5.6)	3.3 (2.1–4.9)**
PVR Wood units	4.3 (1.7–21)	5.9 (1.9–20.7)	5.4 (1.7–10.7)*
Mixed oxygen venous saturation %	60 (32–72)	63 (47–80)	61 (44–86)

ACS: acute chest syndrome; BNP: brain natriuretic peptide; D_{LCO}: diffusing capacity for carbon monoxide; FEV$_1$: forced expiratory volume; FVC: forced vital capacity; mPAP: mean pulmonary arterial pressure; P_{aO_2}: arterial oxygen tension; P_{aCO_2}: arterial carbon dioxide tension; PAWP: pulmonary arterial wedge pressure; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; RAP: right atrial pressure; TLC: total lung capacity. *: p<0.05; **: p<0.01; ***: p<0.001 *versus* normal perfusion. ##: p<0.01; ###: p<0.001 *versus* heterogeneous perfusion.

disease (n=12). In comparison with patients not treated by exchange transfusions, those treated with exchange transfusions were more frequently in NYHA-FC III or IV (82% *versus* 50%, p=0.026) and had significantly higher median levels of right atrial pressure (8 *versus* 5 mmHg, p=0.005) and mPAP (36 *versus* 30 mmHg, p=0.017).

11 SC patients had segmental perfusion defects. All of them were treated with long-term anticoagulation. Eight were treated with medical therapies including monotherapy with ERA (n=5), monotherapy with PDE5i (n=1) and combination therapy with guanylate cyclase stimulator riociguat and ERA (n=2). Three SC patients were treated with balloon pulmonary angioplasty in combination with PAH-targeted therapy in one. A red blood cell exchange programme was initiated in one SC patient.

RHC was repeated after a median time of 9.6 months in 16 patients who did not benefit from surgical, interventional or medical therapy for PH and had no change in SCD management as first line therapy. In this group of patients, we observed a non-significant change in median PVR after PH diagnosis from 2.7 WU to 3.5 WU (p=0.09). In contrast, patients who received medical therapies approved for PAH and/ or SCD management had a decrease in median PVR from 4.6 to 3.3 WU (p=0.0014) after a median follow-up of 6.6 months. Individual data of PVR at baseline and first evaluation are illustrated in supplementary figure S1.

Survival and baseline prognostic factors

Over a median (interquartile range) follow-up period of 38 (11–56) months, 21 patients (36%) died. Overall survival rates were 91%, 80% and 60% at 1, 3 and 5 years, respectively. Causes of death were recorded in 14 out of 21 cases (67%). Among them, 13 patients died from right heart failure and one from sudden death. The results of univariate analysis of baseline variables and survival are shown in table 3. Mortality was not associated with the sex of the patient or any haemodynamic variables. Only NYHA-FC III or IV was associated with worse survival. The prognosis of the SS/S-β_0 thal and SC groups was similar. Baseline 6MWD and PVR did not influence survival (figure 3).

Discussion

We report here the baseline clinical characteristics and long-term outcomes of a population of SCD patients with precapillary PH diagnosed by RHC (after screening with transthoracic Doppler echocardiography). Our results highlight the wide spectrum of phenotypes observed in this population, and the influence of the SCD genotype on clinical and functional characteristics. Thromboembolic mechanisms seem to play a major role in the occurrence of precapillary PH in SCD, especially in the setting of a SC genotype. Indeed, SC patients presented with a history of acute venous thromboembolism

TABLE 3 Prognostic factors (univariate analysis)

	Hazard ratio (95% CI)	p-value
Age years	1.03 (0.98–1.08)	0.2
Female	1.85 (0.74–4.59)	0.5
BMI kg·m^{-2}	1.1 (0.98–1.23)	0.09
SC genotype	0.89 (0.25–3.13)	0.9
NYHA-FC I or II	0.19 (0.05–0.7)	0.01
6MWD>360 m	0.63 (0.26–2.8)	0.3
Abnormal V/Q lung scintigraphy	0.4 (0.13–1.21)	0.1
Haemodynamics		
RAP mmHg	0.96 (0.88–1.04)	0.3
mPAP mmHg	1 (0.95–1.04)	0.9
PAWP mmHg	0.98 (0.87–1.12)	0.8
Cardiac index L·min^{-1}·m^{-2}	0.93 (0.68–1.27)	0.6
PVR Wood units	0.99 (0.92–1.08)	0.9
Biology		
Haemoglobin g·dL^{-1}	0.92 (0.67–1.25)	0.6
Lactate dehydrogenase IU·L^{-1}	1 (1–1.001)	0.4
Creatinine µmol·L^{-1}	1.01 (0.99–1.03)	0.2
High BNP or NT-proBNP	1.3 (0.46–3.65)	0.6

BNP: brain natriuretic peptide; PAWP: pulmonary arterial wedge pressure; mPAP: mean pulmonary arterial pressure; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA-FC: New York Heart Association functional class; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; RAP: right atrial pressure; V/Q: ventilation/perfusion.
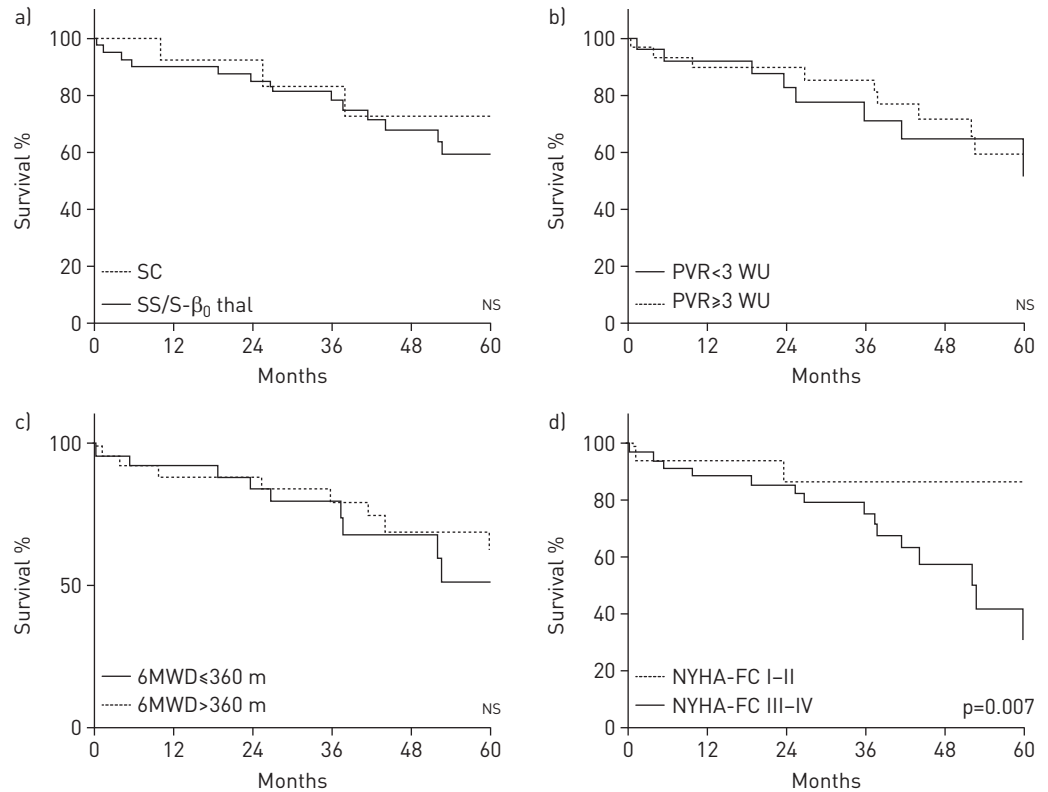
FIGURE 3 Overall survival according to a) sickle cell disease genotype, b) pulmonary vascular resistance (PVR), c) 6-min walk distance (6MWD) and d) New York Heart Association functional class (NYHA-FC). NS: not statistically significant.

in more than 50% of cases and V/Q lung scintigraphy showed mismatched segmental perfusion defects in more than 80%. In SS/S-β_0 thal patients, heterogeneous lung perfusion associated with poor subpleural perfusion on DSA was observed in half of the cases. The functional status of these patients is influenced by their underlying genotype and the presence of a thromboembolic component, with higher 6MWD reported in SC patients and in those with a diagnosis of CTEPH. By contrast, the SCD genotype and haemodynamics did not influence prognosis. Only NYHA-FC III or IV at diagnosis was associated with worse survival.

Precapillary PH appears as a late complication of SCD with a median age of 43 years at the time of diagnosis in our study, irrespective of the SCD genotype. This is in agreement with previous screening studies performed in SCD [2–4, 17]. Exercise capacity and haemodynamics were influenced by SCD genotype with a significantly higher 6MWD observed in SC patients, while cardiac index was lower and PVR levels were higher. We can stipulate that haemodynamic variables are not only influenced by the severity of pulmonary vascular disease but also by rheologic aspects of anaemia in addition to the viscosity differences between SS/S-β_0 thal and SC patients. While SS SCD and S-β_0 thal are associated with more severe haemolysis and anaemia, haemoglobin SC disease is characterised by higher haemoglobin levels leading to hyperviscosity. According to the Hagen–Poiseuille equation, PVR is dependent on fluid viscosity, which can be influenced by several variables such as haematocrit, genotype and severity of haemolysis in SCD [18, 19]. The exercise capacity of SS/S-β_0 thal patients is also influenced by factors other than PH itself, as these patients present with lower levels of haemoglobin and more restrictive lung disease. Previous studies have reported a high rate of dyspnoea in SS SCD, due to multiple causes including anaemia, musculoskeletal disorders, cardiopulmonary complications and others [20].

Our study supports the contributory role of thromboembolic mechanisms in precapillary PH and, more frequently, in those with the SC genotype. SCD is associated with a chronic hypercoagulable state due to multiple mechanisms including chronic haemolysis itself, inflammation, asplenism, oxidative stress or intrinsic coagulation activation [21]. This is associated with a higher risk of acute venous thromboembolic events [22]. We observed in our study a high prevalence of former acute venous thromboembolic events in SCD patients with precapillary PH, reaching 30% in the SS/S-β_0 thal genotype and 50% in the SC

genotype. The low prevalence of deep vein thrombosis compared to the high prevalence of pulmonary artery thrombosis could suggest a key role played by local thrombotic processes. Similarly, MEKONTSO DESSAP et al. [23] observed a prevalence of pulmonary artery thrombosis of 17% in acute chest syndrome, while all patients were free of proximal deep venous thrombosis. Previous autopsy studies reported in situ thrombosis in small pulmonary vessels in a high proportion of patients [5]. In our cohort, V/Q lung scintigraphy was frequently abnormal in this population as previously described [17], with a high frequency of mismatched segmental perfusion defects in SC patients. Similarly, a recent study observed that perfusion abnormalities on V/Q scintigraphy were associated with a higher proportion of PH [24]. In our present report, we have performed DSA in 18 patients, making it possible to identify two main patterns: patients with isolated poor subpleural perfusion and patients with lobar, segmental or subsegmental CTEPH lesions, as illustrated in figure 2. Interestingly, there was a predominance of male patients in the SC population. This is consistent with previous studies that showed a lower risk of viscosity-related morbidity in female patients due to a lower Hb level linked to menstrual blood losses [25].

These observations have important implications for the management of SCD patients with precapillary PH. Screening for thromboembolic disease by V/Q scintigraphy is a mandatory initial step in the care of SCD patients with PH. Indeed, a diagnosis of CTEPH yields specific management options including pulmonary endarterectomy for operable patients with proximal lesions or medical therapies with or without balloon pulmonary angioplasty for inoperable patients. Several cases of successful pulmonary endarterectomy have been reported in SCD patients [9–12]. In our study, three SC patients with inoperable CTEPH were treated with balloon pulmonary angioplasty [26, 27], leading to 29% and 43% decreases in PVR in two patients, and normalisation of mPAP at rest in the third one (data not shown). Moreover, the high proportion of lung perfusion segmental defects in SC patients supports the use of anticoagulation to reduce the risk of thromboembolic disease and of phlebotomy to decrease viscosity-related morbidity in those patients.

V/Q lung scintigraphy was normal in one third of SCD patients with precapillary PH and included a vast majority of patients with SS/S-β_0 thal, who have a pronounced haemolytic phenotype (lower haemoglobin levels, higher haemolytic biomarkers and higher frequency of ulcers). Despite lower levels of PVR in this subpopulation, these patients had severe exercise limitation. Chronic blood cell exchange programmes or hydroxyurea could be interesting options in this subpopulation [28].

Our study confirms the poor prognosis of precapillary PH complicating SCD with a survival rate of 70% at 3 years. It also illustrates the difficulty in identifying robust prognostic factors in this population. Paradoxically, the SC genotype was not associated with a better prognosis in the present study. However, because this genotype is frequently associated with CTEPH, the impact of recent therapeutic advances, such as balloon pulmonary angioplasty, will have to be analysed in the future. Recently, a case series study reported a beneficial effect of riociguat in six patients with SCD and PH related to chronic thromboembolic disease [29]. One important piece of information is that haemodynamic parameters such as PVR did not influence outcomes. In a previous study, pulmonary pressures and PVR were identified as haemodynamic predictors of mortality in a cohort of adults with SCD. In contrast with our study, patients with and without PH were included, highlighting the prognostic impact of PH related to SCD [4]. Only NYHA-FC I and II at time of diagnosis was associated with a better prognosis, but it was present in only one third of patients. This observation illustrates the potential interest of PH screening in SCD.

Specific clinical trials are lacking or have failed to demonstrate a positive effect of medical therapies approved for PAH in precapillary PH due to SCD. In addition, the reinforcement of SCD management with hydroxyurea and/or chronic transfusion may be an interesting management approach but no prospective evaluation has been performed to test these therapeutic approaches on outcomes of patients with precapillary PH due to SCD [28]. Despite the lack of evidence, 50% of our patients were treated with medical therapies approved for PAH and a red blood cell exchange programme was initiated after the diagnosis of PH in one third of them. Our study did not find any impact of these approaches on long-term survival, but its retrospective nature and the small number of patients are not adequate to detect a significant effect. Because of the dramatic impact of PH on the functional status and vital prognosis of SCD patients, multicentre prospective studies are warranted. Interestingly, we observed that patients who did not receive medical therapies approved for PAH and/or reinforcement of SCD treatment with red blood cell exchanges or hydroxyurea as first line therapies displayed a progressive haemodynamic compromise (increased PVR at follow-up).

Our results have limitations inherent to retrospective studies and relatively limited numbers of patients. Due to the nature of our registry being mainly focused on PH, available data on acute complications of SCD during the follow-up period and their potential impact on survival are lacking. However, cause of death was due to PH in all cases, when identified. Moreover, SCD patients with precapillary PH were

evaluated over a long period of time (from 2000 to 2017), and the initial management of PH was influenced by the available tools and growing expertise. Also, it is difficult to interpret the respective effects of medical therapies approved for PAH and of hydroxyurea and red blood cell exchange programmes, which are often used together initially or sequentially in our management strategy as recommended by the 2014 American Thoracic Society clinical practice guideline for the management of PH of SCD. This gives 1) a weak recommendation for medical therapies approved for PAH for select patients with SCD with RHC-confirmed pre-capillary PH with elevated PVR, and 2) a strong recommendation for hydroxyurea as a first line therapy and a weak recommendation for chronic transfusions as an alternative therapy [8]. We believe that our observations will enrich the literature and may help guide the future development of novel treatment strategies, which are urgently needed.

In conclusion, our series shows that precapillary PH complicating SCD is a severe and complex condition with an important impact on survival, irrespective of SCD genotype. Thromboembolic mechanisms contribute to a large proportion of SCD patients with precapillary PH, especially in the SC genotype. This finding supports systematic CTEPH screening with V/Q lung scintigraphy in SCD patients with precapillary PH. The high prevalence of precapillary PH in SCD, its impact on outcomes and the association between NYHA-FC at diagnosis and prognosis support PH screening programmes by transthoracic Doppler echocardiography in SCD. Finally, management with medical therapies approved for PAH and reinforcement of SCD management may have a positive impact on haemodynamics, but further studies are needed to update the guidelines for treating precapillary PH complicating SCD [8]. The clinical heterogeneity of SCD patients with precapillary PH underscores the importance of a careful aetiological assessment for each patient, managed by a multidisciplinary team involving PH and SCD experts.

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