Hemodynamic Predictors of Mortality in Adults with Sickle Cell Disease

Alem Mehari^{1,2*}, Shoaib Alam^{1*}, Xin Tian³, Michael J. Cuttica⁴, Christopher F. Barnett⁵, George Miles⁶, Dihua Xu³, Catherine Seamon⁷, Patricia Adams-Graves⁸, Oswaldo L. Castro^{1,2}, Caterina P. Minniti⁷, Vandana Sachdev¹, James G. Taylor VI⁷, Gregory J. Kato^{7†}, and Roberto F. Machado^{9†}

¹Cardiovascular and Pulmonary Branch, National Heart, Lung, and Blood Institute, Bethesda, Maryland; ²Howard University College of Medicine, Washington, DC; ³Office of Biostatistics Research, National Heart, Lung, and Blood Institute, Bethesda, Maryland; ⁴Pulmonary and Critical Care Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois; ⁵Division of Cardiology, University of California San Francisco, San Francisco, California; ⁶Laboratory of Pathology, National Cancer Institute, Bethesda, Maryland; ⁷Hematology Branch, National Heart, Lung, and Blood Institute, Bethesda, Maryland; ⁸University of Tennessee Health Science Center, Memphis, Tennessee; and ⁹Section of Pulmonary, Critical Care Medicine, Sleep and Allergy, University of Illinois, Chicago, Illinois

Background: Pulmonary hypertension (PH) in adults with sickle cell disease (SCD) is associated with early mortality, but no prior studies have evaluated quantitative relationships of mortality to physiological measures of pre- and postcapillary PH.

Objectives: To identify risk factors associated with mortality and to estimate the expected survival in a cohort of patients with SCD with PH documented by right heart catheterization.

Methods: Nine-year follow-up data (median, 4.7 yr) from the National Institutes of Health SCD PH screening study are reported. A total of 529 adults with SCD were screened by echocardiography between 2001 and 2010 with no exclusion criteria. Hemodynamic data were collected from 84 patients. PH was defined as mean pulmonary artery pressure (PAP) $\geq$ 25 mm Hg. Survival rates were estimated by the Kaplan-Meier method, and mortality risk factors were analyzed by the Cox proportional hazards regression.

Measurements and Main Results: Specific hemodynamic variables were independently related to mortality: mean PAP (hazard ratio [HR], 1.61; 95% confidence interval [CI], 1.05–2.45 per 10 mm Hg increase; $P = 0.027$), diastolic PAP (HR, 1.83; 95% CI, 1.09–3.08 per 10 mm Hg increase; $P = 0.022$), diastolic PAP – pulmonary capillary wedge pressure (HR, 2.19; 95% CI, 1.23–3.89 per 10 mm Hg increase; $P = 0.008$), transpulmonary gradient (HR, 1.78; 95% CI, 1.14–2.79 per 10 mm Hg increase; $P = 0.011$), and pulmonary vascular resistance (HR, 1.44; 95% CI, 1.09–1.89 per Wood unit increase; $P = 0.009$) as risk factors for mortality.

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*These authors contributed equally to this work.

†These senior authors contributed equally to this work.

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Correspondence and requests for reprints should be addressed to Gregory J. Kato, M.D., Hematology Branch, NHLBI, National Institutes of Health, 9000 Rockville Pike, Bethesda, MD. E-mail: gkato@mail.nih.gov

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AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

It is a matter of scientific controversy whether precapillary pulmonary hypertension (PH) in adults with sickle cell disease (SCD) leads to mortality and whether its characteristics are different from PH in other patients.

What This Study Adds to the Field

Our results indicate that mortality in catheterized adults with SCD is proportional to several gold-standard hemodynamic measurements of precapillary PH severity. This epidemiological evidence implies that precapillary PH promotes early mortality in this patient population.

Conclusions: Mortality in adults with SCD and PH is proportional to the physiological severity of precapillary PH, demonstrating its prognostic and clinical relevance despite anemia-induced high cardiac output and less severely elevated pulmonary vascular resistance.

Keywords: sickle cell; pulmonary hypertension; mortality; autopsy

Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure (mPAP) $\geq$ 25 mm Hg (1). Prospective (2–4) and retrospective studies (5, 6), most using Doppler echocardiography to estimate systolic pulmonary artery pressure (sPAP), report that 20 to 30% of adults with sickle cell disease (SCD) have higher than normal sPAP. Our group and others recently reported a PH prevalence of 6 to 11% in adults with, which is associated with increased hazard of death (7, 8). The hemodynamic characteristics of PH in adults with SCD are heterogeneous. PH may be precapillary (pulmonary arterial hypertension) or postcapillary (pulmonary venous hypertension) and may be passive or reactive in nature (9–14), emphasizing the need for right heart catheterization (RHC) to confirm the diagnosis of PH and for accurate hemodynamic stratification to determine treatment and follow-up.

Pulmonary vascular lesions characteristic of precapillary PH, including plexiform lesions, have been described in one third to two thirds of patients with SCD in autopsy studies (15–18). Precapillary PH is characterized by a progressive elevation in pulmonary artery pressure and pulmonary vascular resistance, leading to right ventricular failure and death (19). Despite only modest elevation of estimated sPAP, patients with SCD and

estimated sPAP 2 SD above the normal mean have 10-fold higher risk for early mortality compared with patients with SCD without this echocardiographic abnormality (2–4, 20). However, these noninvasive data have provoked controversy (21–23), with some researchers expressing skepticism that PH in SCD is clinically significant (24). Few SCD studies have presented confirmatory physiologic measurements with RHC, the standard for PH diagnosis (4, 8–10, 25), and no prospective studies have adequately examined hemodynamic predictors of mortality other than the single threshold value of mPAP to diagnose PH.

Data from idiopathic pulmonary arterial hypertension studies identify baseline hemodynamic variables as an important predictor of survival (26–28). Other studies of idiopathic pulmonary arterial hypertension and precapillary PH associated with other disorders have shown clinical variables, such as poor exercise capacity as measured by the 6-minute walk distance (6MWD) test and advanced World Health Organization functional class (WHO FC), and certain biomarkers are predictors of a poor prognosis (29, 30). However, Simonneau and Parent have critically questioned the clinical relevance of PH in SCD (24), in part because of the atypically high cardiac output that is an adaptive response to severe anemia and the very low oxygen-carrying capacity in these patients and the pulmonary vascular resistance that, due to adaptation to high flow, is not as highly elevated. We recently reported the prevalence and prognostic significance of PH in a large cohort of adults with SCD (7), but all published analyses have only evaluated a threshold effect of mean pulmonary artery pressure that satisfies consensus diagnostic criteria. We hypothesize that that severity of PH, especially precapillary PH, is proportional to mortality in SCD. Our new analysis in this study demonstrates the quantitative relationship of well accepted right heart catheterization–defined precapillary PH variables to death in adults with SCD. Some of the results of these studies have been previously reported in the form of an abstract (31).

METHODS

This registry study was approved by the Institutional Review Board at the National Institutes of Health. All subjects provided written informed consent to studies in which clinical, laboratory, echocardiographic, and/or RHC data were obtained (ClinicalTrials.gov identifiers NCT00011648, NCT00081523, NCT00023296, and NCT00352430). Subjects who underwent RHC between March 13, 2002 and June 8, 2010 were included. The diagnosis of SCD was confirmed by HPLC of hemoglobin. The selection process is summarized in Figure 1. The cohort was assembled from 529 subjects with SCD enrolled and screened at the National Institutes of Health or at Howard University Hospital, of whom approximately 2% were referred with suspected or proven pulmonary hypertension. Out of the 529 subjects with SCD, 84 underwent RHC based on elevated tricuspid regurgitant velocity (TRV) on echocardiography and clinical suspicion of PH defined as $TRV \geq 2.8$ m/s accompanied by $6MWD < 500$ m or unexplained dyspnea or oxygen desaturation. RHC was performed in 33% of subjects with $TRV \geq 2.5$ m/s, 52% of subjects with $TRV \geq 2.8$ m/s, and 66% of those with $TRV \geq 3$ m/s. The PH group was categorized hemodynamically to have postcapillary PH if $mPAP \geq 25$ mm Hg and pulmonary capillary wedge pressure (PCWP) was >15 mm Hg, and precapillary PH if $mPAP \geq 25$ mm Hg, $PCWP \leq 15$ mm Hg (32). These results were presented in part at the annual meeting of the American Society of Hematology (31). Additional details are provided in the online supplement.

RESULTS

Study Population

Baseline characteristics of subjects who underwent RHC ($n = 84$) and the noncatheterized subjects with SCD ($n = 445$) are shown in Table E1 in the online supplement. Most study

Figure 1. Schematic diagram of study population. mPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; precapillary PH = pulmonary arterial hypertension; postcapillary PH = pulmonary venous hypertension; RHC = right heart catheterization; SCD = sickle cell disease.

participants were of African descent (98%), and the predominant sickle cell phenotype was hemoglobin SS disease (73%). Subjects who underwent RHC were older, with mean age of 41 ± 13 years compared with 35 ± 12 years for those not catheterized ($P < 0.001$). Several laboratory markers were statistically significantly different in SCD and PH compared with the noncatheterized patients with SCD (Table 1). Subjects with SCD and PH demonstrated significantly abnormal cardiopulmonary markers of clinical severity compared with those not catheterized, including higher TRV (3.2 ± 0.5 vs. 2.3 ± 0.5 m/s; $P < 0.001$), higher serum N-terminal prohormone of brain natriuretic peptide (NT-proBNP) level (median, 153 vs. 58 pg/ml; $P < 0.001$), and poor exercise capacity ($6MWD 387 \pm 118$ m vs. 486 ± 88 m; $P < 0.001$).

Logistic regression analysis showed that TRV and 6MWD are significantly associated with PH diagnosis at RHC. $TRV \geq 2.8$ m/s was highly predictive of PH (compared with subjects with SCD and $TRV < 2.8$ m/s; relative risk, 13.05; 95% CI, 5.19–32.85; $P < 0.001$). Compared with the model with TRV alone, the C statistic (area under the ROC curve) was significantly improved from 0.84 to 0.88 with the addition of $6MWD < 500$ m in the multivariate model. The clinical relevance of this combined model to predict PH needs to be validated.

Hemodynamic Parameters

Fifty-five subjects (10.4%) out of the 529 screened SCD population, or 55 out of 84 (65.5%) of those who underwent RHC, were diagnosed with PH (Figure 1). The PH group was characterized by $mPAP 36 \pm 9$ mm Hg, $PVR 227 \pm 149$ dyn·s·cm⁻⁵, $PVRi 417 \pm 264$ dyn·s·cm⁻⁵·m⁻², central venous pressure 10 ± 5 mm Hg, and high cardiac output (8.4 ± 2.5 L/min) (Table 1). Similarly, the mean mixed venous oxygen saturation (SvO_2) ($69 \pm 8\%$) and PVC (4.5 ± 3.1 ml/mm Hg) were mildly depressed in subjects with SCD and PH. A higher percentage of subjects with SCD

TABLE 1. HEMODYNAMIC AND CLINICAL CHARACTERISTICS OF CATHETERIZED PATIENTS ACCORDING TO PULMONARY HYPERTENSION STATUS

Characteristic (N = 84)	PH (n = 55)	No PH (n = 29)	P Value
sPAP, mm Hg	58 ± 15	31 ± 6	<0.001
dPAP, mm Hg	26 ± 7	13 ± 4	<0.001
PP, mm Hg	32 ± 12	17 ± 5	<0.001
mPAP, mm Hg	36 ± 9	19 ± 4	<0.001
CVP, mm Hg (n = 83)	10 ± 5	6 ± 3	<0.001
PCWP, mm Hg	16 ± 5	11 ± 3	<0.001
TPG, mm Hg	21 ± 10	8 ± 3	<0.001
dPAP-PCWP, mm Hg	10 ± 8	2 ± 3	<0.001
Cardiac output, L/min	8.4 ± 2.5	9.3 ± 2.3	0.12
Cardiac index, L·min ⁻¹ ·m ⁻²	4.6 ± 1.5	5.3 ± 1.3	0.056
SV, ml	117 ± 35	133 ± 43	0.21
SVI, ml/m ²	64 ± 21	74 ± 24	0.063
PVC, ml/mm Hg	4.5 ± 3.1	8.4 ± 4.4	<0.001
PVR, dyn·s·cm ⁻⁵	227 ± 149	72 ± 37	<0.001
PVRI, dyn·s·cm ⁻⁵ ·m ⁻²	417 ± 264	131 ± 70	<0.001
SVR, dyn·s·cm ⁻⁵ (n = 82)	835 ± 333	740 ± 254	0.23
SvO ₂ , % (n = 78)	69 ± 8	73 ± 9	0.017
TRV, m/s	3.3 ± 0.5	2.9 ± 0.4	<0.001
6MWD, m (n = 80)	358 ± 115	437 ± 108	0.004
O ₂ saturation, per unit %	95 ± 4	97 ± 3	0.15
WHO FC III or IV, n (%)	18 (33)	4 (14)	0.07

Definition of abbreviations: CVP = central venous pressure; dPAP = diastolic pulmonary artery pressure; mPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PP = pulmonary artery pulse pressure; PVC = pulmonary artery capacitance; PVR = pulmonary vascular resistance index; sPAP = systolic pulmonary artery pressure; SV = stroke volume; SVI = stroke volume index; SvO₂ = mixed venous oxygen saturation; SVR = systemic vascular resistance; TPG = transpulmonary gradient; TRV = tricuspid regurgitant jet velocity; WHO FC = World Health Organization functional class; 6MWD = 6-min-walk distance.

*Data were summarized by the mean ± SD and by frequency (percentage).

with PH had advanced World Health Organization functional class (WHO FC III or IV 33 vs. 14%; $P = 0.07$) at the time of diagnosis compared with subjects with SCD without PH. The exercise capacity was significantly limited in the SCD-PH group (6MWD 358 ± 115 vs. 437 ± 108 m; $P = 0.004$) compared with those without PH.

Thirty-one (5.9% of the 529 screened subjects; 56.4% of the subjects with PH) had precapillary PH, and 24 (4.5% of the screened population; 43.6% of subjects with PH) were diagnosed with postcapillary PH, with mean values mPAP of 37 ± 9 mm Hg and PCWP 20 ± 4 mm Hg. Hemodynamic values in subjects with precapillary PH included mPAP of 36 ± 9 mm Hg, PCWP 12 ± 3 mm Hg, transpulmonary gradient (TPG) 24 ± 9 mm Hg, PVR 272 ± 156 dyn·s·cm⁻⁵, and CO 8.0 ± 2.7 L/min (Figure 1; Table E2). Sixteen of the 31 subjects with precapillary PH had a PVR of 240 dyn·s·cm⁻⁵ or higher.

Even though subjects with SCD and PH have a less severe hemodynamic profile compared with other forms of precapillary PH, functional capacity measures such as mean 6MWD and percentage of subjects in WHO functional class III and IV were severely abnormal, suggesting that even mild PH in adults with SCD is associated with significant functional impairment (Table E2). Both PH hemodynamic groups had worse functional capacity measured by 6MWD (postcapillary PH: 329 ± 119 m [$P < 0.001$]; precapillary PH: 379 ± 108 m; [$P < 0.001$]) when compared with uncatheterized patients with SCD (485 ± 88 m) (Tables E1 and E2). Both of the PH subgroups showed significantly higher LDH levels (postcapillary PH: 473 ± 247 IU/L [$P = 0.011$]; precapillary PH: 476 ± 229 IU/L [$P < 0.001$]) compared with uncatheterized control subjects with SCD (340 ± 151 IU/L) (Table E1). Subjects with postcapillary PH exhibited an elevated transpulmonary gradient (normal TPG < 12 mm Hg),

suggesting a subgroup of these subjects have reactive postcapillary PH.

Survival and Risk Factors for Mortality

Median follow-up time was 4.7 years, with a maximum follow-up of 11 years for all subjects alive, with 15% of enrolled subjects not yet due for biannual follow-up. A total of 77 deaths were observed. All-cause mortality was higher in patients with PH compared with patients without PH by RHC or the uncatheterized patients (log-rank test, $P < 0.001$). The 5-year mortality rates were 31.7, 15.9, and 14.4%, respectively. Death certificates were available for 15 out of 23 (65%) subjects with PH, and 80% of these subjects were reported to have had right heart failure or sudden cardiac death stated as a cause of death.

To identify hemodynamic risk factors associated with mortality, survival estimates since catheterization for 84 subjects undergoing RHC were used. Survival estimates for the subjects with SCD and PH versus those subjects without PH by RHC were 89 versus 100% at 1 years, 76 versus 93% at 3 years, and 63 versus 83% at 5 years from diagnosis by RHC, respectively. The estimated median survival time was 6.8 years after RHC for subjects with SCD and PH. The survival was not different among the precapillary and postcapillary PH subgroups (log-rank test, $P = 0.23$).

Several hemodynamic and laboratory variables were associated with mortality in the subjects undergoing RHC, particularly variables known to characterize severity of precapillary PH. In the univariate Cox regression analysis of all potential predictors, sPAP, dPAP, mPAP, dPAP – PCWP, TPG, PVR, PVRI, phenotype, WHO FC, 6MWD, direct bilirubin, alkaline phosphatase, and serum ferritin level were significantly associated with mortality (Table 2). Kaplan-Meier survival estimates dichotomized by mPAP ≥ 25 mm Hg, TPG ≥ 12 mm Hg, 6MWD, and WHO FC were statistically significant (Figure 2). The estimated unadjusted HRs for mortality were 3.02 (95% CI, 1.04–8.76; $P = 0.042$) for mPAP ≥ 25 mm Hg, 3.55 (95% CI, 1.43–8.80; $P = 0.003$) for TPG ≥ 12 mm Hg, 2.68 (95% CI, 1.06–6.77; $P = 0.031$) for 6MWD < 400 m, and 3.64 (95% CI, 1.65–8.05; $P < 0.001$) for WHO FC III–IV, compared with the corresponding counterpart of subjects undergoing RHC.

To adjust for potential confounding factors, age, gender, phenotype (SS vs. SC or S-β thalassemia), hematocrit, hemoglobin F, hemoglobin S, creatinine, direct bilirubin, and NT-proBNP were included in the multivariate Cox regression analyses of mortality and each of the hemodynamic variables. The mPAP (adjusted HR, 1.61 per 10 mm Hg; 95% CI, 1.05–2.45; $P = 0.027$), dPAP (adjusted HR, 1.83 per 10 mm Hg; 95% CI, 1.09–3.08; $P = 0.022$), TPG (adjusted HR, 1.78 per 10 mm Hg; 95% CI, 1.14–2.79; $P = 0.011$), PVR (HR, 1.44 per Wood unit; 95% CI, 1.09–1.89; $P = 0.009$), and dPAP – PCWP (adjusted HR, 2.19 per 10 mm Hg; 95% CI, 1.23–3.89; $P = 0.008$) were predictive in a multivariate model, and sPAP was borderline significant (Table 3). The five multivariate models had comparable AIC values, suggesting that they had similar goodness of fit and the five hemodynamic variables had nearly equal HR for mortality controlling for multiple risk factors. Moreover, mPAP, TPG, and PVR were dichotomized around their median values (mPAP ≥ 28 mm Hg, TPG ≥ 12 mm Hg, and PVR ≥ 115 dyn·s·cm⁻⁵), respectively, and each of these dichotomized variables was statistically significant in the multivariate model (Table 3). Sickle cell variant phenotype was also a significant predictor of all-cause mortality in each of the multivariate models. Similar results were obtained when the analysis was limited to the 55 patients with PH (Table E3). Other factors were not statistically significant in the multivariate models, and the addition

TABLE 2. UNIVARIATE ANALYSIS FOR MORTALITY RISK FACTORS

Characteristic (N = 84)	Unadjusted HR (95% CI)	P Value
Age, per 10 yr	1.02 (0.76–1.38)	0.89
Phenotype (SS vs. SC or S- β thalassemia)	5.90 (1.01–43.6)	0.048
sPAP, per 10 mm Hg	1.30 (1.06–1.58)	0.009
dPAP, per 10 mm Hg	1.91 (1.25–2.92)	0.002
mPAP, per 10 mm Hg	1.62 (1.17–2.24)	0.003
TPG, per 10 mm Hg	1.82 (1.28–2.61)	<0.001
PVR, per 1 Wood Unit	1.35 (1.11–1.65)	0.002
PVRI, per 1 Wood Unit/m ²	1.20 (1.08–1.33)	<0.001
PP, per 10 mm Hg	1.29 (0.96–1.73)	0.091
dPAP-PCWP, per 10 mm Hg	2.26 (1.43–3.58)	<0.001
CVP, per 10 mm Hg (n = 83)	1.36 (0.65–2.83)	0.42
PCWP, per 10 mm Hg	0.97 (0.47–2.02)	0.93
Cardiac output, L/min	0.98 (0.85–1.13)	0.74
Cardiac index, L·min ⁻¹ ·m ⁻²	0.87 (0.66–1.13)	0.29
SvO ₂ , % (n = 78)	0.98 (0.94–1.03)	0.42
6MWD, per 100 m (n = 80)	0.56 (0.39–0.79)	<0.001
Oxygen saturation, per unit %	0.93 (0.85–1.02)	0.12
WHO FC (III–IV vs. I–II)	3.64 (1.64–8.05)	<0.001
Creatinine, mg/dl	1.09 (0.71–1.69)	0.69
Alkaline phosphatase, U/L per 100	1.71 (1.14–2.56)	0.008
Bilirubin, direct, mg/dl	1.63 (1.07–2.48)	0.018
Ferritin, μ g/L per 1,000 (n = 83)	1.26 (1.04–1.53)	0.016
Ferritin, >1,000 μ g/L (n = 83)	2.39 (1.11–5.14)	0.021

Definition of abbreviations: CVP = central venous pressure; dPAP = diastolic pulmonary artery pressure; dPAP – PCWP = diastolic pulmonary artery pressure minus pulmonary capillary wedge pressure; mPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PP = pulmonary artery pulse pressure; PVR = pulmonary vascular resistance; PVRI = pulmonary vascular resistance index; 6MWD = 6-min-walk distance; sPAP = systolic pulmonary artery pressure; TPG = transpulmonary gradient; WHO FC = World Health Organization functional class.

of other hemodynamic variables such as CI, CO, PCWP, SV, SVI, PVC, and SVR to the model produced virtually no change in the results.

Histopathology

Six of the patients with PH who died underwent postmortem examination. The mean time from RHC to death in these subjects was 3.23 years (range, 0.07–7.91 yr). Mean mPAP was 41 mm Hg (range, 28–51 mm Hg), mean TPG was 26 mm Hg (range, 12–36), mean PVR was 273 dyn·s·cm⁻⁵ (range, 93–661), mean SvO₂ was 68% (range, 63–74), and mean 6MWD was 261 m (range, 126–399). Four out of the six subjects had precapillary PH, and two had postcapillary PH, one of which had a TPG of 24 mm Hg and PVR of 300 dyn·s·cm⁻⁵. Histopathologic examination showed dilated pulmonary arteries, widespread and extensive vascular changes with moderate to severe medial proliferation, and intimal thickening associated with grade III–IV plexiform lesions (31) in their pulmonary arteries (Figure 3).

DISCUSSION

There has been controversy regarding the prevalence of PH in SCD and its contribution to mortality (21, 22, 24). Our recent publication on this same cohort has documented the linkage of catheterization-proven pulmonary hypertension to mortality in adults with SCD. What this study adds to the literature is significant epidemiological evidence that mortality is proportional to several specific gold standard hemodynamic markers of severity of precapillary PH pathophysiology, such as PVR and TPG. Our new results also deemphasize the mortality significance of PCWP, a marker of postcapillary PH and left ventricular disease. Although a prospective registry study cannot prove the etiology of death in this cohort, this finding supports precapillary PH as a risk factor for early mortality in adults with SCD. Furthermore, by providing a detailed analysis of our previously published data from this cohort, we show that the mortality rate is proportional to the severity of PH as indicated by all measures of pulmonary artery disease, highlighted by the robust association of mortality to multiple physiologic

Figure 2. Kaplan-Meier survival curves after right heart catheterization for important clinical variables in adults with sickle cell disease. Curves indicate survival in years after catheterization for 84 adults with sickle cell disease. Significant differences in survival are observed subjects with mean pulmonary artery pressure (mPAP) $\geq$ 25 mm Hg (upper left) and transpulmonary gradient (TPG) $\geq$ 12 mm Hg (upper right), advanced World Health Organization Functional Class (WHO FC III or IV, lower left), or 6-minute walk distance (6MWD) < 400 m (lower right).

TABLE 3. MULTIVARIATE ANALYSIS FOR MORTALITY RISK FACTORS

Models*	Variable	Adjusted HR (95% CI)	P Value	AIC†
1	mPAP, per 10 mm Hg	1.61 (1.05–2.45)	0.027	192.4
2	dPAP, per 10 mm Hg	1.83 (1.09–3.08)	0.022	192.1
3	dPAP – PCWP, per 10 mm Hg	2.19 (1.23–3.89)	0.008	190.2
4	TPG, per 10 mm Hg	1.78 (1.14–2.79)	0.011	190.9
5	PVR, per Wood unit	1.44 (1.09–1.89)	0.009	190.5
6	sPAP, per 10 mm Hg	1.30 (0.99–1.71)	0.055	193.6
Dichotomized Variable by Median				
I	mPAP ≥ 28 mm Hg	4.76 (1.45–15.7)	0.010	189.5
II	TPG ≥ 12 mm Hg	3.19 (1.13–9.01)	0.029	192.1
III	PVR ≥ 115 dyn·s·cm ⁻⁵	3.41 (1.15–10.1)	0.027	192.0

Definition of abbreviations: CI = confidence interval; dPAP = diastolic pulmonary artery pressure; dPAP – PCWP = diastolic pulmonary artery pressure minus pulmonary capillary wedge pressure; HR = hazard ratio; mPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PP = pulmonary artery pulse pressure; PVR = pulmonary vascular resistance; 6MWD = 6-min-walk distance; sPAP = systolic pulmonary artery pressure; TPG = transpulmonary gradient.

*Age, gender, phenotype (SS vs. SC/β-thalassemia), hematocrit, hemoglobin F, hemoglobin S, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), creatinine, and direct bilirubin were included in each of the multivariate Cox regression models. Two patients with missing NT-proBNP were excluded.

†The Akaike information criterion (AIC) was used to compare different regression models. The models with smaller AIC have better fit to the data.

indicators of precapillary PH severity, including the PVR, TPG, and the gradient between pulmonary arterial diastolic and PCWP. In fact, we find that sPAP, PP, TPG, and PVR were nearly equally and independently associated with mortality when combined with the previously established SCD mortality serum biomarkers creatinine, alkaline phosphatase, and ferritin. These results emphasize that mortality rate in adults with SCD is proportional to the severity of precapillary PH. Consistent with this observation, patients with SCD with

PH can have histopathological changes more severe than might be expected from relatively modest hemodynamic abnormalities (Figure 3).

Left ventricular dysfunction, characterized by markers of diastolic heart failure, is frequently encountered in adults with SCD and has been associated with risk of mortality additive to echocardiographic markers of PH (33). In our cohort, these subjects are represented by the postcapillary subgroup. Although the postcapillary PH subgroup shares a high mortality rate, the PCWP is not significant as a predictor of mortality, suggesting that precapillary PH physiology dominates mortality risk in SCD. Consistent with this interpretation, the mean TPG is above 12 mm Hg in the postcapillary PH group, suggesting that even the postcapillary PH group shares some physiological characteristics of the precapillary remodeling. Likely our catheterized cohort lacks sufficient statistical power to characterize potential interaction between precapillary PH and postcapillary PH upon prognosis, as previously suggested (33). However, RHC physiologic markers of left ventricular dysfunction in adults with SCD and PH appear to have less prognostic significance than those of precapillary PH.

Our findings are in agreement with previous studies describing the hemodynamic etiology of PH in SCD as heterogeneous (8, 9). Our findings are similar to a French study that classified its adult subjects as 46% precapillary (11/24) and 54% postcapillary among subjects with SCD and PH (8). Unlike the French study, which reported PH in only 25% of subjects who underwent RHC (n = 96) and in 6% in the whole screened cohort (n = 385), we found prevalence of PH of all types of 65.5% (55/84) in those who underwent RHC or 10.4% (55/531) in our screened cohort. These differences may be related in part to the French protocol including all subjects with TRV ≥ 2.5 m/s regardless of 6MW but also their exclusion of subjects with liver dysfunction, chronic renal insufficiency, or low total lung capacity. Exclusion of these subjects likely underestimated the true prevalence of PH because markers of renal insufficiency,

Figure 3. Pulmonary vascular pathology in patients with sickle cell disease (SCD). Microscopic examination of lung tissue reveals widespread proliferative arteriopathy, vascular changes, and thrombosis consistent with pulmonary arterial hypertension. Representative photomicrographs from six patients with SCD who died and underwent autopsy in this study show dilated vasculature, medial hypertrophy, intimal proliferation of pulmonary arteries, and numerous complex plexiform lesions scattered throughout the lung parenchyma. (A) A 54-year-old man with mean pulmonary artery pressure (mPAP) of 31 mm Hg and pulmonary vascular resistance (PVR) of 105 dyn·s·cm⁻⁵ who died with pneumonia. (B) A 30-year-old man with mPAP of 28 mm Hg and PVR of 226 dyn·s·cm⁻⁵ who died with acute cor pulmonale during acute chest syndrome. (C) A 44-year-old woman with mPAP of 51 mm Hg and PVR of 830 dyn·s·cm⁻⁵; sudden death at home. (D) A 35-year-old man with mPAP of 44 mm Hg and PVR of 366 dyn·s·cm⁻⁵; sudden death at home. (E) A 54-year-old man with mPAP of 51 mm Hg and PVR of 285 dyn·s·cm⁻⁵ who died of hepatic cirrhosis complicating progressive right heart failure. (F) A 48-year-old woman with mPAP of 41 mm Hg PVR of 300 dyn·s·cm⁻⁵ who died of right heart failure decompensated by sepsis-related bone marrow embolism. The micrographs illustrate the severity of histopathologic findings of pulmonary arterial hypertension in SCD that is often much greater than might be expected for the degree of hemodynamic abnormality.

hepatic dysfunction, and iron overload are independent risk factors for high estimated pulmonary artery pressure in patients with SCD (3, 4). The French study appeared to apply RHC to a larger proportion of subjects with normal pulmonary pressure because in our cohort subjects with RHC-proven PH had mPAP of 37 ± 9 mm Hg, compared with their mPAP of 30 ± 0.46 mm Hg. Given that our study had no exclusion criteria, the prevalence rate of 10.4% is likely to be more accurate. Our prevalence rates are consistent with a recent screening study from Brazil (34).

The 10.4% prevalence of PH and the prevalence of precapillary PH of 6% in adults with SCD from the largest cohort of prospectively identified subjects with SCD and PH ranks highly among populations predisposed to PH. This prevalence would place SCD as second only to scleroderma (12%) among associated conditions under WHO group I precapillary PH (35, 36) and comparable to portopulmonary hypertension (1–6%) (37) and HIV infection (0.5%) (38).

PH associated with SCD is characterized by relatively modest elevations of mPAP and PVR and a high cardiac output, as seen in this study and others (9, 10). Despite these seemingly favorable hemodynamic findings, subjects with SCD and PH have a marked reduction in their functional capacity and high mortality, suggesting that any level of PH in these severely anemic patients portends a poor prognosis. Several echocardiographic studies have reported that subjects with SCD and a high estimated sPAP have a poor prognosis, with HRs for death ranging from 4.4 to 10 (2–4, 6, 20). We currently find greater median survival in SCD-PH of 6.8 years compared with Castro's report in symptomatic subjects of 2.1 years (10). This improved survival might arise from several possible reasons. Presymptomatic screening in our study may be leading to case ascertainment at an earlier age and stage of disease. A much larger number of therapies approved for PH in the general population have become available over the intervening years, potentially permitting better PH control. Last, supportive care of SCD with hydroxyurea or chronic transfusion has been more aggressively promoted in the last decade, and anecdotal evidence indicates that in some cases this may lead to better control of pulmonary arterial pressures (39, 40).

At their usual baseline, due to their high cardiac output, subjects with SCD with normal mPAP have PVR between 22 and $62 \text{ dyn} \cdot \text{s} \cdot \text{cm}^{-5}$ (11). Although PVR is useful, the current precapillary PH classification does not require it as a diagnostic criterion (1, 41). PVR values may not adequately characterize pulmonary vascular disease in the severely anemic population because the associated high cardiac output induces a compensatory decrease in PVR, and the low blood viscosity of anemia reduces developed pressure at any given rate of flow.

Our study reports hemodynamic markers of PH severity as risk factors for poor survival in SCD. Caution is required in comparisons with pulmonary arterial hypertension in other populations in which cardiac output or stroke volume is associated with risk of mortality. In subjects with idiopathic pulmonary arterial hypertension, the NIH registry suggested that three hemodynamic variables (increased PAP, increased CVP, and decreased cardiac index) predicted increased risk of death (26). Although we observed trends in our analyses, some of these traditional hemodynamic parameters were not independently associated with mortality in our cohort, suggesting that there may be a different mode of demise in SCD-PH. Another potential explanation for these findings would be the high variability observed in the data related to right ventricular function given the confounding effects of anemia on cardiac output and filling pressures. Additionally, the acute increase in pulmonary artery pressure in the sickle cell vasoocclusive pain crisis (42) and the acute chest syndrome associated with mortality (43) might be more

likely to be lethal in these patients with SCD and PH with diminished functional reserve. Finally, TPG and PVR are independent risk factors for death, suggesting that these measures may be more relevant indices of pulmonary vascular dysfunction in patients with SCD and PH. Not surprisingly, rising mPAP was proportional to survival. Subjects with mPAP ≥ 28 mm Hg (median value in our RHC cohort) had 4.8-fold higher hazard of dying compared with those with a mPAP < 28 mm Hg. The hazard increased by 1.6 for every 10 mm Hg increase in mPAP. Similarly, Castro and colleagues reported that each 10 mm Hg increase in mPAP was associated with a 1.7-fold increase in death rate (10). The prognostic value of PVR and TPG is shared with scleroderma-associated precapillary PH (44), PH after heart transplantation (45), and portopulmonary hypertension after liver transplantation (46).

Our results confirm several associations previously described in adults with SCD with echocardiographic-estimated high pulmonary artery pressure. Lower hemoglobin and hematocrit and higher serum levels of AST and LDH than the general sickle cell control group in this study are associated with PH proven by RHC, as seen previously with echocardiography (2–4, 47–50). These markers have also been linked to accelerated hemolysis and alterations in nitric oxide bioavailability (48, 51). Alkaline phosphatase and ferritin were elevated in subjects with SCD with PH and were risk factors for death in the univariate and multivariate analyses, confirming previous findings from echocardiography (4). Another previously identified risk factor, direct bilirubin, reflects an association observed in precapillary PH without SCD (52). Increasing age is reported with an increased risk of PH in previous studies (2, 4), but mortality was not explained by old age among patients with PH in our study. Our results indicate that subjects with SCD and PH had 3-fold increased risk for death than subjects with SCD of similar age who were documented by RHC not to have PH.

A number of limitations must be noted. First, our registry study was performed in a single center, with a retrospective analysis of prevalent and incident cases. As a consequence, survival rates might have been overestimated and the prevalence of PH could have been overestimated due to referral bias. Additional limitations are the observational nature of our findings and our inability to draw conclusions regarding cause and effect. Because RHC was not performed in every subject initially screened for PH, we cannot calculate the precise sensitivity and specificity of TRV as a predictor of PH by RHC.

Conclusions

PH documented by RHC is strongly associated with worse functional capacity and increased risk of death in adults with SCD. Several measures of precapillary disease severity are independently associated with survival in this cohort. Multifactorial pathophysiologic pathways likely play a combined role in SCD-PH, but our data provide definitive physiological evidence that, despite the atypical hemodynamic features imparted by the compensatory response to severe anemia in SCD, the dominant features of precapillary PH, including mPAP, PVR, and TPG, are proportional to the poor prognosis in catheterized patients with SCD and PH. Additional clinical research with intervention targeted at precapillary PH is warranted in this complex and high-risk population.

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