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Potential Contribution of Pulmonary Thromboembolic Disease in Pulmonary Hypertension in Sickle Cell Disease

To the Editor:

Sickle cell disease (SCD) is characterized by vaso-occlusion and chronic hemolysis that impact the pulmonary and systemic circulation and leads to substantial morbidity and early mortality (1). An elevated tricuspid regurgitation velocity (TRV) is used to estimate pulmonary systolic pressure and as a screening modality for pulmonary hypertension (PH). A TRV $\geq$ 2.5 m/s identifies patients at higher risk of having PH (25% based on a mean pulmonary artery pressure of 25 mm Hg) and predicts a 3- to 10-fold-greater risk for mortality in SCD (2). Patients with SCD with an elevated TRV have: *1*) elevated markers of intravascular hemolysis and endothelial dysfunction in the pulmonary and systemic microcirculation; and *2*) either postcapillary or precapillary PH (2, 3). TRV elevations may be related to high cardiac output and episodic vaso-occlusive events and require confirmation by measuring plasma brain natriuretic peptide levels, assessing symptoms, such as exercise capacity, and confirmation by right-heart catheterization. Causes of PH in SCD include primary pulmonary vascular disease, PH secondary to left-sided heart failure with preserved or reduced ejection fraction, or secondary to chronic thromboembolic PH. Based on the multiple etiologies for PH in SCD, it has been classified as group 5 (unclear/multifactorial) by the Fifth World Symposium on PH (4).

Patients with SCD have a fourfold greater risk of venous thromboembolic events (VTEs) compared with individuals without SCD (5). In the Cooperative Study of SCD, the incidence of VTEs and pulmonary embolism (PE) was reported to be 5.2 and 3.6 events per 1,000 person-years, respectively (6). The hypercoagulable state in SCD is due to the pleotropic effects of intravascular hemolysis (ADP-, heme-, and oxyhemoglobin-mediated activation), platelet activation, endothelium dysfunction, and inflammation (1). The contribution of VTEs to high TRV values and PH in SCD has not been studied in large cohorts screened for PH. In this study, we assessed the possible association of PE with PH in two independent SCD cohorts using measured TRV values.

Methods

Derivation cohort from the Walk–Pulmonary Hypertension and SCD with Sildenafil Therapy screening study. The Treatment of Pulmonary Hypertension and SCD with Sildenafil Therapy (Walk-PHaSST) study was designed to assemble a large cohort of patients with SCD to screen their eligibly for sildenafil in a randomized clinical trial. This study recruited 720 adolescents and adults at 10 clinical centers in the United States and United Kingdom between 2007 and 2009. The University of Illinois at Chicago (UIC) was a participating site and we excluded 52 patients from UIC. Each study participant was comprehensively evaluated by collecting clinical, laboratory, and echocardiography data, as well as self-reported history of PE (7).

Validation cohort at the UIC. The UIC registry is a longitudinal cohort of patients with SCD recruited during a clinic visit. Between 2010 and 2016, this cohort has recruited and phenotyped 395 patients with SCD. Of these, 157 have had steady-state transthoracic echocardiograms performed as part of routine care and were included in this analysis. A history of PE was determined by a query for *International Classification of Diseases 9th* and *10th Revisions* diagnostic codes and manually confirmed by reviewing the electronic medical charts.

Potential confounders, including age, sex, severe hemoglobin genotype, reticulocyte count, and serum creatinine, were defined among those variables considered plausible confounders, and included in the multivariate analyses.

Results

Walk-PHaSST. A total of 31 (4.6%) patients with SCD had a self-reported history of PE. Patients with a history of PE were older and had an average TRV 0.3 m/s higher compared with those without a PE history (Table 1). After adjusting for age, sex, severe genotype, reticulocyte count, creatinine, and LV lateral E/A (left ventricular early to late diastolic transmitral flow velocity); patients

Table 1. Clinical and laboratory findings by history of pulmonary embolism

	History of PE$^-$	History of PE$^+$
Walk-PHaSST	*n* = 637	*n* = 31
Age, yr	36 (13.5)	41 (12.5)
Female, *n* (%)	342 (54)	20 (65)
SS genotype, *n* (%)	434 (76)	18 (64)
Hemoglobin, mg/dl	9.4 (1.9)	9.8 (2.0)
Reticulocyte count, 10^9/L	23.5 (12.9)	19.8 (13.4)
White blood cell count, 10^9/L	9.7 (3.8)	9.7 (3.0)
Platelet count, 10^9/L	354 (138)	337 (95)
Creatinine, mg/dl	0.87 (0.90)	0.93 (0.54)
N-terminal-pro-BNP, pg/ml*	65 (121)	65 (145)
Left ventricular lateral E/A	7.0 (2.8)	6.5 (1.9)
TRV, m/s	2.5 (0.40)	2.8 (0.54)
UIC	*n* = 137	*n* = 20
Age, yr	35 (13)	34 (8.8)
Female, *n* (%)	86 (64)	14 (70)
SS genotype, *n* (%)	115 (84)	15 (75)
Hemoglobin, mg/dl	9.1 (1.7)	9.3 (2.0)
Reticulocyte count, 10^9/L	32.0 (16.0)	32.0 (14.0)
White blood cell count, 10^9/L	9.8 (3.5)	9.8 (2.6)
Platelet count, 10^9/L	410 (150)	410 (150)
Creatinine, mg/dl	0.91 (0.68)	0.90 (0.52)
N-terminal-pro-BNP, pg/ml*	50 (16–169)	87 (33–366)
Left ventricular lateral E/A	—	—
TRV, m/s	2.4 (0.35)	2.7 (0.62)

Definition of abbreviations: BNP = brain natriuretic peptide; E/A = early to late diastolic transmitral flow velocity; PE = pulmonary embolism; PHaSST = Pulmonary Hypertension and Sickle Cell Disease with Sildenafil Therapy; SD = standard deviation; SS = hemoglobin SS; TRV = tricuspid regurgitation velocity; UIC = University of Illinois at Chicago.
Results are presented as mean (SD) unless otherwise specified.
*Median (interquartile range).

with PE history had an average 0.30 m/s (95% confidence interval [CI], 0.16–0.45; $P < 0.001$) higher TRV (Figure 1). Frequency of TRV $\geq$ 3.0 m/s was significantly higher in patients with versus without a history of PE (25% vs. 10%; $P = 0.01$). Frequency of NT-proBNP (N-terminal-pro hormone B-type natriuretic peptide) $>$ 160 pg/ml was 30% in patients with a history of PE versus 23% in patients without PE ($P = 0.49$). A total of 55% of patients with a history of PE versus 5% of patients without a history of PE were on anticoagulation treatment at the time of study, supporting the accuracy of self-reported history. After adjusting for confounders, patients with anticoagulation treatment had, on average, 0.33 m/s (95% CI, 0.21–0.44; $P < 0.001$) -higher TRV compared with patients without history of anticoagulation treatment. Frequency of NT-proBNP $>$ 160 pg/ml was 41% in patients with anticoagulation treatment versus 21% in patients without treatment ($P = 0.004$).

UIC. A history of PE was observed in 12.7% of patients. Patients with a history of PE had an average TRV that was 0.3 m/s higher than in those without a history of PE (Table 1). After similar adjustments as in the Walk-PHaSST cohort, patients with a PE history had an average TRV that was 0.34 m/s (95% CI, 0.31–0.59; $P < 0.001$) greater than in patients without a PE history (Figure 1). Frequency of TRV $\geq$ 3.0 m/s was significantly higher in patients with versus without a history of PE (25% vs. 6%; $P = 0.02$). Frequency of NT-proBNP $>$ 160 pg/ml was 45% in patients with a history of PE versus 26% in patients without PE ($P = 0.2$).

Discussion

Our results support an independent, strong relationship between elevated TRV and PE in SCD. Venous thromboembolism is a serious comorbidity in patients with SCD that leads to a threefold-higher risk for mortality (6). It is estimated that patients with SCD have a sixfold or greater risk for PE compared with the general population (6). We observed a combined prevalence of PE by medical history in 6.2% of patients with SCD.

In the general population, it is estimated that up to 9.1% of acute PE events lead to chronic thromboembolic PH (8). Pulmonary emboli may transform into fibrotic lesions under conditions of increased inflammation, by defective angiogenesis from abnormal calcium homeostasis, or abnormal circulating fibrinogen or phospholipids impairing thrombus resolution (8). The inability to resolve the thrombotic lesion leads to vascular wall remodeling with pathologic features that overlap with what is observed in primary PH. In two independent SCD cohorts, we demonstrate that the TRV is approximately 10% higher in patients with versus without a history of PE. To our knowledge, there is only one other single-center study indicating a relationship between elevated TRV and VTEs in patients with SCD (9). In that study, non–catheter-related VTEs were associated with a 1.7-fold-greater risk for TRV $\geq$ 2.5 m/s.

Transthoracic echocardiograms were ordered as part of routine clinical care in the UIC cohort, and there may have been selection bias. Future studies measuring pulmonary vascular resistance by right-heart catheterization may help elucidate the relationship between PE and increased TRV.

Altogether, these findings strongly suggest an important role of VTEs in SCD pulmonary hypertension. Screening of patients with SCD with a high TRV value for VTEs could help us identify patients at greater risk for chronic thromboembolic PH and eligible for available therapies, such as anticoagulation, surgical pulmonary artery endarterectomy, and the soluble guanylate cyclase stimulator, riociguat (10).

Author disclosures are available with the text of this letter at www.atsjournals.org.

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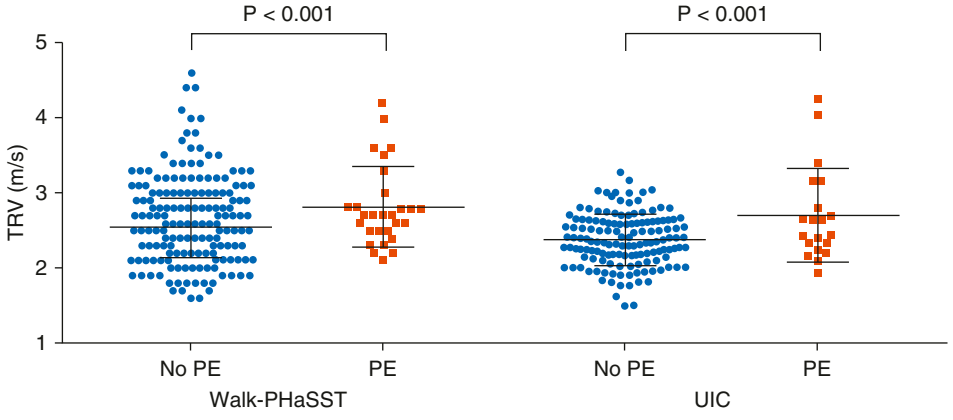

Figure 1. Mean (SD) tricuspid regurgitation velocity by history of pulmonary embolism (PE) in the Walk-PHaSST (Pulmonary Hypertension and Sickle Cell Disease with Sildenafil Therapy) and University of Illinois at Chicago cohorts. In each cohort, *P* values were calculated from a multivariate regression analysis adjusted for age, sex, severe genotype, reticulocyte count, creatinine, and LV lateral E/A (Walk-PHaSST). TRV = tricuspid regurgitation velocity; UIC = University of Illinois at Chicago.

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Recurrent Pulmonary Fibrosis in a Lung Allograft Secondary to *De Novo* Antisynthetase Syndrome

To the Editor:

Interstitial lung disease (ILD) is the second most common indication for lung transplantation, including connective tissue disease (CTD)-associated ILD (1). We report, for the first time, a convincing case of recurrence of nonspecific interstitial pneumonia of the fibrotic pattern (NSIP-F) in the lung allograft of a patient who received bilateral lung transplantation (BLT) for advanced idiopathic fibrotic NSIP (iNSIP-F) and manifested *de novo* clinical and serological features of antisynthetase syndrome (anti-SS) 36 months after transplant.

Case Report

A 51-year-old white female ex-smoker presented with a 2-year history of progressive dyspnea, cough, and fatigue without environmental exposures and no clinical or serological features to suggest CTD, including normal muscle enzymes and negative myositis antibodies. High-resolution computed tomography (HRCT) images revealed a pattern consistent with NSIP-F (Figure 1A). Forty-six months after diagnosis she underwent an uncomplicated BLT (cytomegalovirus antibody: donor negative/recipient positive) for progressive iNSIP-F requiring continuous supplemental oxygen despite corticosteroids and mycophenolate. The explanted lung confirmed histopathologic features of NSIP-F and superimposed organizing diffuse alveolar damage (Figures 1E and 1F). The donor, a 35-year-old female smoker, had a fatal subarachnoid hemorrhage but no personal or family history of pulmonary disease or CTD.

The post-transplant course was complicated by a single episode of acute cellular rejection (A3) at 1 month, which fully responded to a short course of augmented corticosteroids and a maintained antirejection regimen with tacrolimus and mycophenolic acid. She did well with no interruptions in immunosuppression, tacrolimus levels in the target range, and normal-appearing lungs on HRCT images. At 30 months after lung transplant she developed exertional dyspnea, new muscle weakness on examination, arthralgias, xerophthalmia, and xerostomia. Spirometry revealed a progressive restrictive lung defect, and HRCT images were consistent with NSIP (Figure 1C).

Anastomotic abnormalities, infection, and cellular- and humoral-mediated rejection were ruled out via bronchoscopy and the absence of any circulating donor-specific antibodies since the time of transplant. Twenty-four hour pH esophageal monitoring showed no evidence of gastroesophageal reflux. CTD serologies monitored proactively every year because of the prior diagnosis of iNSIP-F were negative until the fourth time, revealing positive antinuclear antibodies and an anti-Jo1 antibody. Creatine kinase levels were also regularly assessed and never elevated. Surgical lung biopsy of the right upper and lower lobes revealed histopathologic features of NSIP-F without cellular rejection or bronchiolitis (Figures 1E and 1F). The diagnosis of NSIP-F associated with anti-SS was ascertained by multidisciplinary discussion including an expert rheumatologist. Hydroxychloroquine and eventually rituximab were added to her regimen, with a marked decrease in the rate of lung function decline. The patient is now 10 years post transplant, continues to manifest clinical and serologic features of anti-SS with slowly progressive fibrotic changes, and has recently developed pulmonary hypertension with good response to sildenafil.

Discussion

Progressive pulmonary fibrosis (PF) accounts for 31.3% of all lung transplants reported to date (1). To our knowledge, this is the first report that convincingly documents recurrence of the NSIP-F in the