

ORIGINAL ARTICLE

Pulmonary Hypertension as a Risk Factor for Death in Patients with Sickle Cell Disease

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ABSTRACT

BACKGROUND

The prevalence of pulmonary hypertension in adults with sickle cell disease, the mechanism of its development, and its prospective prognostic significance are unknown.

METHODS

We performed Doppler echocardiographic assessments of pulmonary-artery systolic pressure in 195 consecutive patients (82 men and 113 women; mean [±SD] age, 36±12 years). Pulmonary hypertension was prospectively defined as a tricuspid regurgitant jet velocity of at least 2.5 m per second. Patients were followed for a mean of 18 months, and data were censored at the time of death or loss to follow-up.

RESULTS

Doppler-defined pulmonary hypertension occurred in 32 percent of patients. Multiple logistic-regression analysis, with the use of the dichotomous variable of a tricuspid regurgitant jet velocity of less than 2.5 m per second or 2.5 m per second or more, identified a self-reported history of cardiovascular or renal complications, increased systolic blood pressure, high lactate dehydrogenase levels (a marker of hemolysis), high levels of alkaline phosphatase, and low transferrin levels as significant independent correlates of pulmonary hypertension. The fetal hemoglobin level, white-cell count, and platelet count and the use of hydroxyurea therapy were unrelated to pulmonary hypertension. A tricuspid regurgitant jet velocity of at least 2.5 m per second, as compared with a velocity of less than 2.5 m per second, was strongly associated with an increased risk of death (rate ratio, 10.1; 95 percent confidence interval, 2.2 to 47.0; $P<0.001$) and remained so after adjustment for other possible risk factors in a proportional-hazards regression model.

CONCLUSIONS

Pulmonary hypertension, diagnosed by Doppler echocardiography, is common in adults with sickle cell disease. It appears to be a complication of chronic hemolysis, is resistant to hydroxyurea therapy, and confers a high risk of death. Therapeutic trials targeting this population of patients are indicated.

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PULMONARY HYPERTENSION DEVELOPS in most forms of hereditary and chronic hemolytic anemia, including sickle cell disease,¹ thalassemia,² hereditary spherocytosis,³ and paroxysmal nocturnal hemoglobinuria,⁴ suggesting that there is a clinical syndrome of hemolysis-associated pulmonary hypertension. This complication has been reported with increasing frequency in patients with sickle cell disease.^{1,5-11} Retrospective studies from tertiary care referral centers suggest a prevalence of pulmonary hypertension ranging from 20 to 40 percent.^{9,11,12} Although these studies have demonstrated that patients with sickle cell disease have lower pulmonary pressures and higher cardiac output than patients with primary pulmonary hypertension, the two-year mortality rates approach 50 percent in both groups.^{6,10,11,13} The frequent reports of sudden death in adults with sickle cell disease in the absence of coronary artery disease and the high risk of sudden death in patients with sickle cell disease and pulmonary hypertension may be related.^{5,6,14,15} Such a relation would suggest that pulmonary hypertension may be a major cause of death in patients with sickle cell disease.

METHODS

PATIENTS

To avoid tertiary care referral bias, we recruited 195 patients from the community through multimedia advertisements, community outreach, and regional clinics. All evaluated patients were screened by means of history taking and physical examination, laboratory studies, and transthoracic echocardiography. All patients provided written informed consent. The advertisements and protocol were approved by the institutional review boards of the National Heart, Lung, and Blood Institute and Howard University.

Patients with sickle cell hemoglobinopathy documented by high-pressure liquid chromatography were eligible for the study. Only outpatients in stable condition were included; patients who had had a vaso-occlusive crisis within the previous two weeks or an episode of acute chest syndrome within the previous four weeks were evaluated at a later time. Patients receiving transfusions were not excluded. In addition, 41 black control subjects, with age and sex distributions similar to those of the patients, were evaluated for race-based comparisons of laboratory and echocardiographic data.

ECHOCARDIOGRAPHY

Transthoracic echocardiography was performed in all patients with the use of the Acuson Sequoia (Siemens) and Sonos 5500 (Philips) systems. Cardiac measurements were performed according to the guidelines of the American Society of Echocardiography.¹⁶ Transmitral flow, Doppler determinations of the severity of valvular regurgitation, and left ventricular stroke volume were assessed and graded as previously described.¹⁷⁻¹⁹ Peak velocities of the E wave and A wave, the ratio of the E wave to the A wave, and the deceleration time were measured in a standard manner.²⁰ Isovolumic relaxation time was measured as the time from aortic valve closure to the start of mitral inflow.

Tricuspid regurgitation was assessed in the parasternal right ventricular inflow, parasternal short-axis, and apical four-chamber views, and a minimum of five sequential complexes were recorded. Continuous-wave Doppler sampling of the peak regurgitant jet velocity was used to estimate the right-ventricular-to-right-atrial systolic pressure gradient with the use of the modified Bernoulli equation ($4 \times [\text{tricuspid regurgitant jet velocity}]^2$).²¹ For the purpose of analysis, we prospectively defined pulmonary hypertension as a peak tricuspid regurgitant jet velocity of at least 2.5 m per second. Since most patients with clinically significant pulmonary hypertension have measurable tricuspid regurgitation,²¹ we assumed that pulmonary-artery pressures were normal in patients with trace or no tricuspid regurgitation.

Pulmonary-artery systolic pressure was quantitated by adding the Bernoulli-derived pressure gradient to the estimated mean right atrial pressure. The mean right atrial pressure was calculated according to the degree of collapse of the inferior vena cava with inspiration: 5 mm Hg for a collapse of at least 50 percent and 15 mm Hg for a collapse of less than 50 percent.²²

RIGHT HEART CATHETERIZATION

Right heart catheterizations were performed in 18 consenting patients with a tricuspid regurgitant jet velocity of at least 2.5 m per second.

STATISTICAL ANALYSIS

When tricuspid regurgitant jet velocity was analyzed as a continuous variable, undetectable values were assigned a value lower than any actually measured (1.3 m per second).²¹ We used t-tests and Wilcoxon rank-sum tests to compare continuous varia-

bles between patients with sickle cell disease and control subjects and the normal-approximation test to compare dichotomous variables, with no correction for continuity. For patients with sickle cell disease, associations between tricuspid regurgitant jet velocity and continuous variables were assessed by separate linear regression of each variable on tricuspid regurgitant jet velocity, defined as a categorical variable: 0 for values of less than 2.5 m per second, 1 for values of 2.5 to 2.9 m per second, and 2 for values of at least 3.0 m per second. Associations with dichotomous variables were assessed by means of the Armitage chi-square statistic for trend.

We used logistic-regression analysis of low values for tricuspid regurgitant jet velocity (less than 2.5 m per second) and high values (2.5 m per second or more) to obtain a set of variables that were independently associated with increasing jet velocity. Using both forward and backward selection methods in a stepwise procedure, we derived a model in which all variables had a calculated P value of less than 0.05 when they were added to the other variables in the model. We used proportional-hazards regression to assess variables that could be associated with an increased risk of death in patients with sickle cell disease. All regression analyses were performed with the use of log-transformed values (on a base 10 scale) for laboratory measurements in order to reduce the influence of extremely high values. Calculations were made with the use of Number Cruncher Statistical Systems software.

RESULTS

CLINICAL CHARACTERISTICS

The base-line characteristics of all 195 patients who were evaluated and the 41 black control subjects are shown in Table 1. The information for the patients is further categorized according to the values for tricuspid regurgitant jet velocity (less than 2.5 m per second, 2.5 to 2.9 m per second, and 3.0 m per second or more) in Table 2. The genotype on the basis of hematologic and hemoglobin characteristics was hemoglobin SS in 132 patients (69 percent), hemoglobin SC in 35 (18 percent), and hemoglobin S-thalassemia (β^0 or β^+) in 23 (12 percent). Data on genotype were missing for five patients.

PREVALENCE AND SEVERITY OF PULMONARY HYPERTENSION

Values for pulmonary-artery systolic pressure as estimated by Doppler echocardiography accurately

predicted pulmonary-artery systolic pressures measured during right heart catheterization (25 catheterizations performed in 18 patients) ($r=0.77$, $P<0.001$) (Fig. 1C). The patients with sickle cell disease had significantly higher mean values for tricuspid regurgitant jet velocity than did the controls ($P=0.003$) (Fig. 1A and 1B and Table 1). Thirty-two percent of patients with sickle cell disease had elevated pulmonary-artery systolic pressures, as defined by a tricuspid regurgitant jet velocity of at least 2.5 m per second (an estimated pulmonary-artery systolic pressure of at least 30 mm Hg). Nine percent had pulmonary hypertension with the use of the more conservative cutoff value for tricuspid regurgitant jet velocity of at least 3.0 m per second (an estimated pulmonary-artery systolic pressure of at least 41 mm Hg) (Fig. 1A). Of the 18 patients with a tricuspid regurgitant jet velocity of at least 2.5 m per second who underwent right heart catheterization, 17 had a mean pulmonary-artery pressure of more than 25 mm Hg (the definition of pulmonary hypertension used in the National Institutes of Health registry²³).

EFFECT OF PULMONARY HYPERTENSION ON VENTRICULAR SIZE AND FUNCTION

Higher values for tricuspid regurgitant jet velocity were associated with increased cardiac-chamber sizes (Table 2). There was a slight decrease in the ejection fraction at the highest levels of jet velocity ($P=0.10$). There was no association between jet velocity and stroke volume, and cardiac output increased slightly but not significantly with increasing jet velocity ($P=0.24$). There was qualitative evidence of left ventricular systolic dysfunction (an ejection fraction of 0.5 or less) in only 5 of the 195 patients.

Measurements of the left ventricular diastolic function are shown in Table 2. Only the deceleration time was weakly associated with tricuspid regurgitant jet velocity ($r=0.17$, $P=0.01$), but the mean values remained in the normal range for all categories of tricuspid regurgitant jet velocity. Variables indicative of diastolic dysfunction did not contribute significantly to the logistic-regression model (Table 3) or affect the risk of death, suggesting that pulmonary hypertension is largely independent of diastolic dysfunction.

EVALUATION OF RISK FACTORS AND EFFECTS OF HYDROXYUREA THERAPY

Logistic-regression analysis of clinical and laboratory values identified a number of factors associat-

Table 1. Characteristics of the Patients with Sickle Cell Disease and Control Subjects.*

Characteristic	Patients		Controls		P Value†
	Total No.	Value	Total No.	Value	
Age (yr)	195	36±12	41	37±11	0.50
Female sex (%)	195	58	41	59	0.94
Tricuspid regurgitant jet velocity (m/sec)	195	2.2±0.6	41	2.0±0.3	0.003
Left atrial size (mm)	193	41±6	41	33±5	<0.001
Right atrial area (cm ²)	180	18±5	33	14±3	<0.001
Ejection fraction	94	0.61±0.07	29	0.65±0.05	0.02
Blood pressure (mm Hg)					
Systolic	172	122±18	36	133±19	0.002
Diastolic	172	68±12	31	77±12	<0.001
Oxygen saturation (%)	117	96±3	37	99±1	<0.001
Body-mass index	134	25±7	36	28±4	0.01
Current smoking (%)	189	22	40	5	0.01
White-cell count (10 ⁻³ /mm ³)	189	10.3±3.8	41	5.8±2.0	<0.001
Platelet count (10 ⁻³ /mm ³)	187	360±132	41	271±60	0.001
Blood urea nitrogen (mg/dl)	190	11±11	41	12±4	0.003
Creatinine (mg/dl)‡	190	0.93±1.43	41	0.88±0.23	0.04
Bilirubin (mg/dl)					
Total	188	2.56±1.70	41	0.63±0.29	<0.001
Direct	189	0.49±0.42	40	0.14±0.05	<0.001
Alanine aminotransferase (U/liter)	190	27±15	41	22±12	0.04
Aspartate aminotransferase (U/liter)	188	41±22	41	23±8	<0.001
Total creatine kinase (U/liter)	186	93±183	40	217±158	<0.001
Lactate dehydrogenase (U/liter)	171	345±143	40	166±42	<0.001
Ferritin (mg/liter)	182	881±1355	38	76±61	<0.001
Iron (mg/dl)	170	102±55	37	79±38	0.01
Transferrin (mg/dl)	187	208±54	37	270±51	<0.001
Hemoglobin (g/dl)	189	9.6±1.9	41	13.5±1.6	<0.001
Arginine (mmol/liter)	168	41±15	36	67±18	<0.001
Arginine:ornithine ratio	168	0.73±0.41	36	1.20±0.49	<0.001

* Plus-minus values are means ±SD. The body-mass index is the weight in kilograms divided by the square of the height in meters. To convert the values for blood urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for iron to micromoles per liter, multiply by 0.1791.

† Two-sided P values for continuous variables were calculated with the use of the t-test (log values were used for laboratory measurements), and P values for categorical variables were calculated with the use of the normal approximation test of proportions.

‡ The mean creatinine level was higher in the patients than in the controls, but the median level was higher in controls (0.9 vs. 0.7 mg per deciliter [80 vs. 62 μmol per liter], P<0.001 by the Wilcoxon rank-sum test); the mean log value, on which the tabulated P value is based, was also higher in the controls.

ed with high tricuspid regurgitant jet velocity; these factors, which accounted for approximately 35 percent of the variability in tricuspid regurgitant jet velocity (Table 3), include a self-reported history of renal or cardiovascular problems; elevated systolic blood pressure, plasma lactate dehydrogenase levels, and alkaline phosphatase levels; and decreased

plasma transferrin levels. In a model that included only men, priapism was an additional important variable (odds ratio for a jet velocity of at least 2.5 m per second, as compared with a value of less than 2.5 m per second, 5.0; 95 percent confidence interval, 1.5 to 17.0). Factors reflecting the presence of hemolysis, chronic anemia, and the need for fre-

Table 2. Characteristics of Patients with Sickle Cell Disease According to the Tricuspid Regurgitant Jet Velocity.*

Characteristic	Jet Velocity <2.5 m/sec		Jet Velocity 2.5–2.9 m/sec		Jet Velocity ≥3.0 m/sec		P Value†
	Total No.	Value	Total No.	Value	Total No.	Value	
Age (yr)	132	34±10	46	39±12	17	38±19	0.02
Female sex (%)	132	60	46	57	17	47	0.38
Left atrial size (mm)	130	40±5	46	44±7	17	45±11	<0.001
Right atrial area (cm ²)	122	17±4	43	19±4	15	22±5	<0.001
Ejection fraction	63	0.62±0.05	21	0.63±0.07	10	0.56±0.11	0.1
E wave:A wave ratio	127	1.6±0.5	42	1.7±0.7	15	1.5±1.1	0.98
Deceleration time (sec)	126	184±37	41	191±39	14	213±52	0.01
Isovolumic relaxation time (msec)	125	72±39	39	69±23	16	79±25	0.80
Blood pressure (mm Hg)							
Systolic	118	119±15	39	130±20	15	132±23	<0.001
Diastolic	118	67±11	39	67±13	15	73±11	0.15
Mean arterial‡	118	84±11	39	88±15	15	93±14	0.007
Stroke volume (ml)	50	75±20	22	80±15	7	72±23	0.78
Cardiac output (liters/min)	50	5.3±1.6	22	5.6±1.1	7	5.9±2.0	0.24
Oxygen saturation (%)	77	97±3	27	97±3	13	93±5	0.002
Body-mass index	87	25±6	34	26±7	13	26±7	0.33
Current smoking (%)	130	25	44	11	15	27	0.18
Hydroxyurea therapy (%)	129	36	43	40	16	38	0.76
History of acute chest syndrome (%)	129	83	46	85	16	81	0.92
History of stroke (%)	132	19	44	7	16	6	0.03
History of asthma (%)	131	20	46	24	16	19	0.72
Self-reported history of cardiovascular problems (%)	131	27	46	50	16	63	<0.001
Self-reported history of renal problems (%)	132	7	46	22	16	31	<0.001
History of leg ulcers (%)	129	22	45	27	16	31	0.39
>10 Blood transfusions during lifetime (%)	81	33	26	54	13	69	0.005
Priapism (% of men)	52	33	19	63	8	63	0.01
White-cell count (10 ³ /mm ³)	128	10±4	44	10±3	17	11±4	0.44
Platelet count (10 ³ /mm ³)	128	357±134	43	359±120	16	386±152	0.39
Blood urea nitrogen (mg/dl)	129	9±7	44	13±13	17	20±17	<0.001
Creatinine (mg/dl)	129	0.7±0.4	44	1.5±2.7	17	1.2±0.9	<0.001
Alkaline phosphatase (U/liter)	129	101±58	43	158±142	17	180±79	<0.001

quent blood transfusions, including low hemoglobin and hematocrit values, high lactate dehydrogenase and aspartate aminotransferase levels (but not high alanine aminotransferase levels, which are specific to liver dysfunction), high direct bilirubin levels, high iron and ferritin levels, low transferrin levels, and the receipt of a total of more than 10 transfusions, were all significant univariate predictors of a high tricuspid regurgitant jet velocity (Table 2).

Increasing age, oxyhemoglobin desaturation as measured by pulse oximetry, and increasing levels of blood urea nitrogen, creatinine, and direct bilirubin were significant univariate — but not multivariate — predictors of high tricuspid regurgitant jet velocity. The plasma arginine:ornithine ratio, probably reflecting arginase activity, was low in patients with sickle cell disease, and this ratio decreased significantly as tricuspid regurgitant jet velocity increased. The fetal hemoglobin level, the

Table 2. (Continued.)

Characteristic	Jet Velocity <2.5 m/sec		Jet Velocity 2.5–2.9 m/sec		Jet Velocity ≥3.0 m/sec		P Value†
	Total No.	Value	Total No.	Value	Total No.	Value	
Bilirubin (mg/dl)							
Total	128	2.5±1.7	43	2.6±1.4	17	3.1±2.2	0.25
Direct	129	0.41±0.23	43	0.57±0.51	17	0.89±0.88	<0.001
Alanine aminotransferase (U/liter)	129	27±16	44	29±15	17	27±13	0.52
Aspartate aminotransferase (U/liter)	128	39±21	43	45±23	17	48±25	0.03
Total creatine kinase (U/liter)	127	102±217	43	67±47	16	96±104	0.22
Lactate dehydrogenase (U/liter)	116	320±129	39	357±125	16	491±196	<0.001
Ferritin (mg/liter)	121	655±1112	44	1462±1866	17	985±894	<0.001
Iron (mg/dl)	116	94±52	39	109±56	15	140±53	0.001
Transferrin (mg/dl)	126	218±55	44	184±44	17	189±47	<0.001
Hemoglobin (g/dl)	128	9.9±1.7	44	9.2±2.0	17	8.5±2.0	<0.001
Fetal hemoglobin (%)	128	7.7±7.1	45	6.5±4.9	17	7.9±7.3	0.91
Hemoglobin A present (%)	127	39	45	53	17	53	0.08
Hemoglobin C present (%)	128	22	45	13	17	6	0.06
Hemoglobin S–thalassemia (%)	128	14	45	9	17	6	0.22
Arginine (mmol/liter)	111	42±15	41	39±15	16	40±15	0.38
Arginine:ornithine ratio	111	0.77±0.42	41	0.71±0.41	16	0.50±0.18	0.009

* Plus–minus values are means ±SD. The body-mass index is the weight in kilograms divided by the square of the height in meters. To convert the values for blood urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for iron to micromoles per liter, multiply by 0.1791.

† P values for continuous variables were calculated by linear regression of each variable according to the assigned category of jet velocity: 0 for values of less than 2.5 m per second, 1 for values of 2.5 to 2.9 m per second, and 2 for values of at least 3.0 m per second; log values (on a base 10 scale) were used for laboratory measurements. P values for categorical variables were calculated with the use of the chi-square test for trend.

‡ Mean arterial pressure was calculated with the use of the following equation: $(1/3 \times \text{systolic blood pressure}) + (2/3 \times \text{diastolic blood pressure})$.

hemoglobin S–thalassemia phenotype (β^0 or β^+), hydroxyurea therapy, the white-cell count, and the platelet count were not significantly associated with tricuspid regurgitant jet velocity, whereas the hemoglobin SC genotype was associated with a significantly reduced tricuspid regurgitant jet velocity ($P=0.02$ as calculated with the use of a t-test in which tricuspid regurgitant jet velocity was considered to be a continuous variable). Analysis of the patients who did not receive hydroxyurea or have hemoglobin C, as well as of all patients, showed no evidence of an association between the fetal hemoglobin level and tricuspid regurgitant jet velocity.

The number of episodes of the acute chest syndrome and the number of visits to the emergency room per year were not associated with tricuspid regurgitant jet velocity ($P=0.92$ and $P=0.68$, respectively). The fact that there were significantly more patients with a self-reported history of car-

diovascular problems who had pulmonary hypertension suggests that pulmonary hypertension and its complications, such as cor pulmonale, may be misdiagnosed as congestive heart failure.

RIGHT HEART CATHETERIZATION

Among the 18 patients who underwent right heart catheterization, the mean (\pm SE) values for pulmonary-artery systolic pressure (51.9 ± 4.1 mm Hg), diastolic pressure (26.1 ± 2.16 mm Hg), mean pulmonary-artery pressure (34.5 ± 2.7 mm Hg), pulmonary-artery wedge pressure (17.2 ± 1.2 mm Hg), cardiac output (10.2 ± 0.7 liters per minute as measured by thermodilution and 9.6 ± 0.4 liters per minute as calculated with the Fick equation), and pulmonary vascular resistance (148.5 ± 26.2 dyn·sec·cm⁻⁵) were similar to previously reported values in patients with sickle cell disease who had secondary pulmonary hypertension.^{6,8}

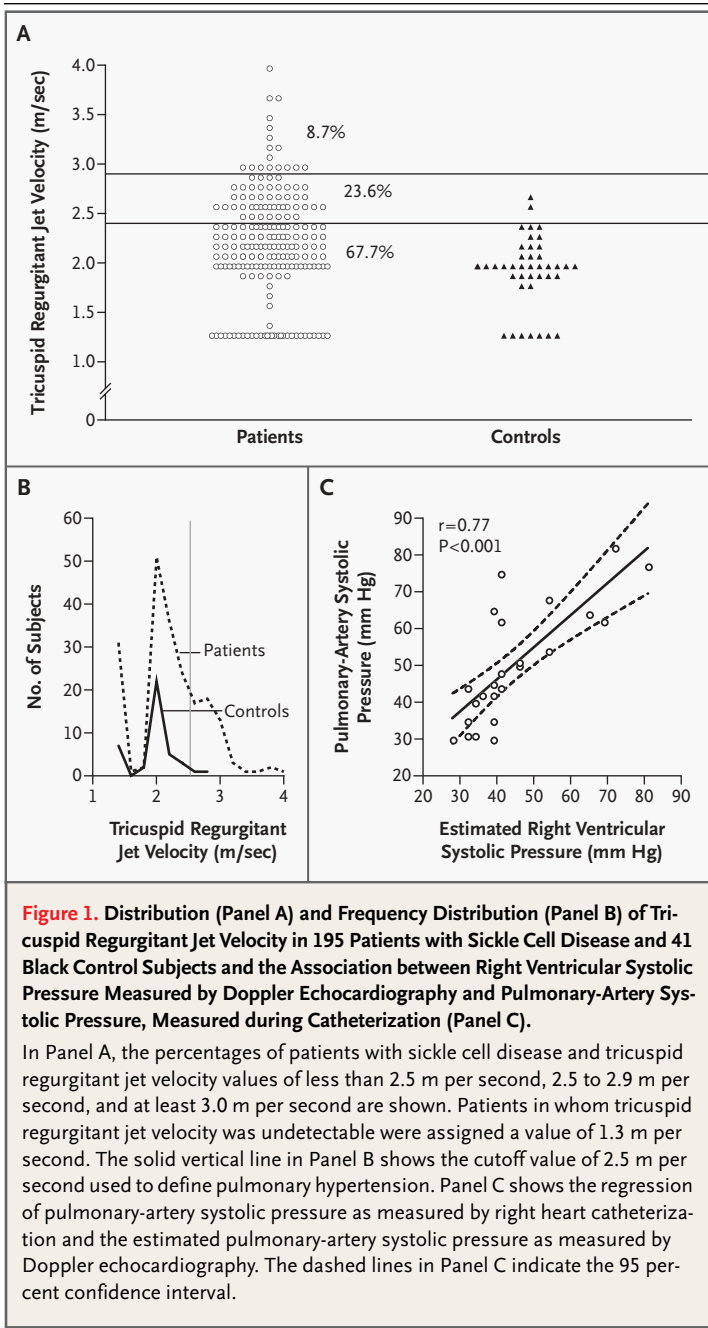
SURVIVAL

Among the 195 patients, 5 were lost to follow-up: all had a tricuspid regurgitant jet velocity of less than 2.5 m per second. Death certificates were used to confirm the death of any patient. No death certificates were found for these five patients who were lost to follow-up, suggesting that they are still living. The median follow-up was 18.3 months for the 128 patients with a tricuspid regurgitant jet velocity of

less than 2.5 m per second and 17.3 months for the 62 patients with a tricuspid regurgitant jet velocity of at least 2.5 m per second.

Proportional-hazards regression analysis showed that patients with a tricuspid regurgitant jet velocity of at least 2.5 m per second had a significantly higher mortality rate than those with a jet velocity of less than 2.5 m per second ($P < 0.001$) (Fig. 2); the rate ratio for death was 10.1 (95 percent confidence interval, 2.2 to 47.0). Analyses were also performed separately for age, cardiac output, stroke volume, the ratio for the E wave to the A wave, deceleration time, isovolumic relaxation time, hemoglobin level, fetal hemoglobin level, lactate dehydrogenase level, white-cell count, and creatinine level. Besides the tricuspid regurgitant jet velocity, the only significant univariate correlate of the risk of death was the creatinine level ($P = 0.007$). After adjustment for the tricuspid regurgitant jet velocity, the creatinine level was not significantly related to the risk of death ($P = 0.08$), whereas the jet velocity remained a significant independent correlate ($P = 0.004$).

Because we were concerned that pulmonary hypertension conferred a substantial risk of death, the study was not designed as a natural-history study. Patients and referring physicians were made aware of the results of echocardiography, and the patients who were identified as having severe pulmonary hypertension (on the basis of a tricuspid regurgitant jet velocity of at least 3.0 m per second) were offered treatments such as exchange transfusion, oxygen, and selective pulmonary vasodilator therapy according to a National Heart, Lung, and Blood Institute protocol. Eleven of the 17 patients with a tricuspid regurgitant jet velocity of at least 3.0 m per second began either an aggressive exchange-transfusion program or inhaled nitric oxide therapy after pulmonary hypertension was diagnosed, and 10 of these patients are still alive.



DISCUSSION

We found that the prevalence of pulmonary hypertension among patients with sickle cell disease was 32 percent, which is consistent with previously published retrospective studies. Despite having lower pulmonary-artery pressures and higher cardiac outputs than patients with primary pulmonary hypertension, patients with sickle cell disease and pulmonary hypertension had a significantly higher mortality rate than did patients with sickle cell dis-

ease who did not have pulmonary hypertension, a finding that is consistent with the results of previous retrospective studies.^{6,10,11,13} Our findings suggest that the noninvasive measurement of tricuspid regurgitant jet velocity by echocardiography can be used to identify patients at high risk for death and may thus be viewed as a prognostic tool analogous to transcranial carotid Doppler flow-velocity assessment, which is used to predict the risk of stroke in children with sickle cell disease.²⁴

The observation that markers of hemolysis are associated with pulmonary hypertension provides a link between sickle cell disease and other chronic hemolytic disorders and suggests that there is a distinct syndrome of hemolysis-associated pulmonary hypertension. Thalassemia, for example, is another chronic hemolytic disease that is associated with secondary pulmonary hypertension; the prevalence of pulmonary hypertension among patients with thalassemia ranges from 10 percent to 93 percent, depending on the patient population studied.^{2,25-28} Patients with sickle cell disease and patients with thalassemia both have chronic hemolysis, which results in the release of hemoglobin into plasma. Plasma hemoglobin can scavenge nitric oxide as well as catalyze the formation of reactive oxygen and nitrogen species, processes that can lead to acute and chronic pulmonary vasoconstriction.²⁹ Hemolysis could also release erythrocyte arginase, as suggested by recent reports that arginase activity may be increased (a possibility that is consistent with our finding that arginine:ornithine ratios were significantly lower in patients than in control subjects) and that the bioavailability of arginine and nitric oxide is reduced in patients with sickle cell disease.²⁹⁻³³ Hemoglobin-induced scavenging of nitric oxide results in transcriptional up-regulation of adhesion molecules such as vascular-cell adhesion molecule 1 and E-selectin and induces the expression of endothelin-1, a potent vasoconstrictor.³³⁻³⁵ Indeed, endothelin-1 levels are elevated in the plasma of patients with primary pulmonary hypertension and patients with sickle cell disease.^{36,37} The statistical linkage among pulmonary hypertension, systolic systemic hypertension, and the hemolytic rate (associated with nitric oxide scavenging²⁹) is consistent with previous clinical observations that systemic hypertension is a risk factor for stroke and early death in patients with sickle cell disease.³⁸⁻⁴⁰

Additional insults common to sickle cell disease and thalassemia that might lead to end-organ

Table 3. Logistic-Regression Analysis of a Tricuspid Regurgitant Jet Velocity Dichotomized as Less Than 2.5 m per Second or 2.5 m per Second or More.*

Independent Variable	P Value†	Odds Ratio (95% CI)‡
Systolic blood pressure	<0.001	2.9 (1.6–5.3)
Transferrin	<0.001	0.17 (0.07–0.38)
Alkaline phosphatase	0.04	1.7 (1.0–2.8)
Lactate dehydrogenase	0.008	2.7 (1.3–5.9)
Self-reported history of cardiovascular problems	0.02	2.9 (1.2–7.2)
Self-reported history of renal problems	0.02	5.5 (1.3–22.9)

* The analysis included 149 patients. Independent variables considered for the model were those thought to be possibly biologically related to tricuspid regurgitant jet velocity that were associated with a jet velocity of at least 2.5 m per second with a P value of 0.15 or less: age; deceleration time; systolic blood pressure; mean arterial pressure; oxygen saturation; receipt of a total of more than 10 blood transfusions; levels of creatinine, alkaline phosphatase, direct bilirubin, aspartate aminotransferase, lactate dehydrogenase, ferritin, iron, transferrin, and hemoglobin; presence of hemoglobin A; presence of hemoglobin C; and arginine:ornithine ratio. Log-transformed values were used for laboratory measurements to reduce the influence of extremely high values.

† P values were calculated with the use of the likelihood ratio test.

‡ For numerical values, the odds ratio is given for the 25th and 75th percentiles (with all other independent variables held constant), calculated as $e^{\text{coefficient} \times (75\text{th percentile} - 25\text{th percentile})}$. For all variables simultaneously, the odds ratio is the product of the odds ratios for the individual variables (reciprocal taken for transferrin), or 1272. CI denotes confidence interval.

dysfunction and pulmonary hypertension include iron deposition, cirrhosis, anemia with a high cardiac-output state, and asplenism. Although cirrhosis can result in secondary pulmonary hypertension, cirrhosis and hepatic synthetic dysfunction were not common in our patients with pulmonary hypertension. It is unclear whether the significant increases in alkaline phosphatase and direct bilirubin in patients with pulmonary hypertension were due to more subtle liver dysfunction or to a secondary effect of pulmonary hypertension and increased passive liver congestion. The absence of an association between cardiac output and tricuspid regurgitant jet velocity in our study argues against a role for chronic anemia and a high cardiac-output state, leading to vascular remodeling and arteriopathy. If anemia itself were responsible, one would expect to find reports of pulmonary hypertension associated with iron-deficiency anemia, the most common cause of anemia in the world.

We were surprised that hydroxyurea therapy was not associated with lower tricuspid regurgitant jet velocity and that there was no significant association between the fetal hemoglobin level or the white-cell count and tricuspid regurgitant jet velocity; both are independent markers of disease severity and predic-

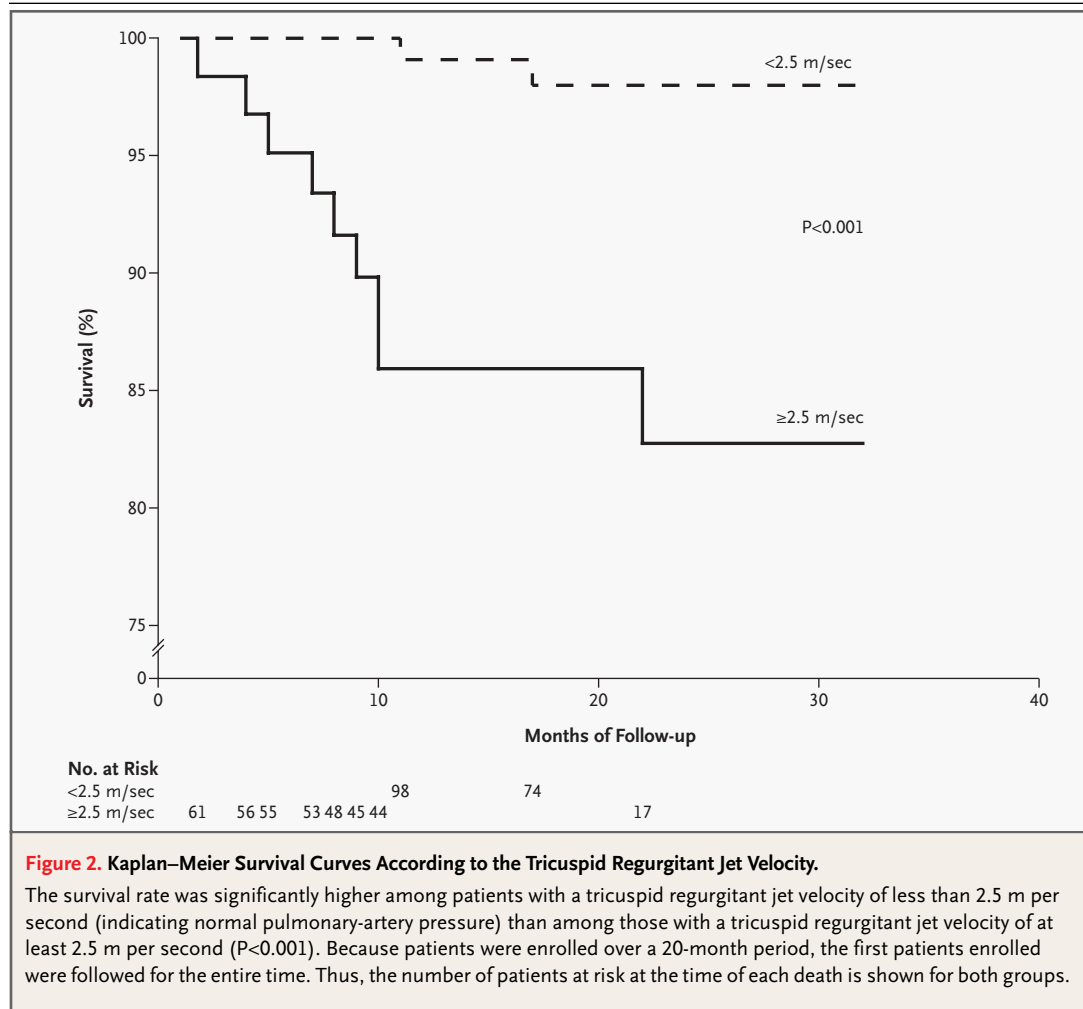


Figure 2. Kaplan–Meier Survival Curves According to the Tricuspid Regurgitant Jet Velocity.

The survival rate was significantly higher among patients with a tricuspid regurgitant jet velocity of less than 2.5 m per second (indicating normal pulmonary-artery pressure) than among those with a tricuspid regurgitant jet velocity of at least 2.5 m per second ($P<0.001$). Because patients were enrolled over a 20-month period, the first patients enrolled were followed for the entire time. Thus, the number of patients at risk at the time of each death is shown for both groups.

tors of the outcome in sickle cell disease.⁴¹ Although neither prospective nor randomized, our study suggests that hydroxyurea and other drugs that increase the expression of fetal hemoglobin may not prevent pulmonary hypertension. We speculate that this may be explained by the relatively limited induction of fetal hemoglobin associated with such therapy, the lack of full fetal-cell penetrance, and the presence of persistent hemolysis in most of our patients. Analysis of polymerization tendencies suggests that fetal hemoglobin levels of more than 25 percent in a pancellular distribution would be required to eliminate intracellular polymerization and hemolysis.^{42,43} This possibility is supported by the observation that hemoglobin C, which is present in all erythrocytes and reduces the rate of hemolysis, was associated with a reduced tricuspid regurgitant jet velocity.

In conclusion, pulmonary hypertension is com-

mon in adults with sickle cell disease and is associated with an ominous outcome. Our results support the use of Doppler echocardiographic screening in all adults with sickle cell disease to identify a high-risk group that may benefit from intervention. Therapeutic trials of oxygen, warfarin, transfusion, and pulmonary vasodilator and remodeling medications are urgently required to evaluate their potential to decrease the substantial morbidity and mortality associated with pulmonary hypertension in this population.

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REFERENCES

1. Collins FS, Orringer EP. Pulmonary hypertension and cor pulmonale in the sickle hemoglobinopathies. *Am J Med* 1982;73:814-21.
2. Aessopos A, Farmakis D, Karagiorga M, et al. Cardiac involvement in thalassemia intermedia: a multicenter study. *Blood* 2001;97:3411-6.
3. Hayag-Barin JE, Smith RE, Tucker FC Jr. Hereditary spherocytosis, thrombocytosis, and chronic pulmonary emboli: a case report and review of the literature. *Am J Hematol* 1998;57:82-4.
4. Heller PG, Grinberg AR, Lencioni M, Molina MM, Roncoroni AJ. Pulmonary hypertension in paroxysmal nocturnal hemoglobinuria. *Chest* 1992;102:642-3.
5. Haque AK, Gokhale S, Rampy BA, Adegboyega P, Duarte A, Saldana MJ. Pulmonary hypertension in sickle cell hemoglobinopathy: a clinicopathologic study of 20 cases. *Hum Pathol* 2002;33:1037-43.
6. Castro OL, Hoque M, Brown BD. Pulmonary hypertension in sickle cell disease: cardiac catheterization results and survival. *Blood* 2002;101:1257-61.
7. Adedeji MO, Cespedes J, Allen K, Subramony C, Hughson MD. Pulmonary thrombotic arteriopathy in patients with sickle cell disease. *Arch Pathol Lab Med* 2001;125:1436-41.
8. Norris SL, Johnson C, Haywood LJ. Left ventricular filling pressure in sickle cell anemia. *J Assoc Acad Minor Phys* 1992;3:20-3.
9. Simmons BE, Santhanam V, Castaner A, Rao KR, Sachdev N, Cooper R. Sickle cell heart disease: two-dimensional echo and Doppler ultrasonographic findings in the hearts of adult patients with sickle cell anemia. *Arch Intern Med* 1988;148:1526-8.
10. Van Enk A, Visschers G, Jansen W, Statius van Eps LW. Maternal death due to sickle cell chronic lung disease. *Br J Obstet Gynaecol* 1992;99:162-3.
11. Sutton LL, Castro O, Cross DJ, Spencer JE, Lewis JF. Pulmonary hypertension in sickle cell disease. *Am J Cardiol* 1994;74:626-8.
12. Castro O. Systemic fat embolism and pulmonary hypertension in sickle cell disease. *Hematol Oncol Clin North Am* 1996;10:1289-303.
13. Powars D, Weidman JA, Odom-Maryon T, Niland JC, Johnson C. Sickle cell chronic lung disease: prior morbidity and the risk of pulmonary failure. *Medicine (Baltimore)* 1988;67:66-76.
14. Escoffery CT, Shirley SE. Causes of sudden natural death in Jamaica: a medicolegal (coroner's) autopsy study from the University Hospital of the West Indies. *Forensic Sci Int* 2002;129:116-21.
15. Liesner RJ, Vandenberghe EA. Sudden death in sickle cell disease. *J R Soc Med* 1993;86:484-5.
16. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. *J Am Soc Echocardiogr* 1989;2:358-67.
17. Appleton CP, Jensen JL, Hatle LK, Oh JK. Doppler evaluation of left and right ventricular diastolic function: a technical guide for obtaining optimal flow velocity recordings. *J Am Soc Echocardiogr* 1997;10:271-92.
18. Chopra HK, Nanda NC, Fan P, et al. Can two-dimensional echocardiography and Doppler color flow mapping identify the need for tricuspid valve repair? *J Am Coll Cardiol* 1989;14:1266-74.
19. Lewis JF, Kuo LC, Nelson JG, Limacher MC, Quinones MA. Pulsed Doppler echocardiographic determination of stroke volume and cardiac output: clinical validation of two new methods using the apical window. *Circulation* 1984;70:425-31.
20. Quinones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr* 2002;15:167-84.
21. Berger M, Haimowitz A, Van Tosh A, Berdoff RL, Goldberg E. Quantitative assessment of pulmonary hypertension in patients with tricuspid regurgitation using continuous wave Doppler ultrasound. *J Am Coll Cardiol* 1985;6:359-65.
22. Kircher BJ, Himelman RB, Schiller NB. Noninvasive estimation of right atrial pressure from the inspiratory collapse of the inferior vena cava. *Am J Cardiol* 1990;66:493-6.
23. Rubin LJ. Primary pulmonary hypertension. *N Engl J Med* 1997;336:111-7.
24. Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. *N Engl J Med* 1998;339:5-11.
25. Du ZD, Roguin N, Milgram E, Saab K, Koren A. Pulmonary hypertension in patients with thalassemia major. *Am Heart J* 1997;134:532-7.
26. Hahalis G, Manolis AS, Apostolopoulos D, Alexopoulos D, Vagenakis AG, Zombos NC. Right ventricular cardiomyopathy in beta-thalassaemia major. *Eur Heart J* 2002;23:147-56.
27. Derchi G, Fonti A, Forni GL, et al. Pulmonary hypertension in patients with thalassemia major. *Am Heart J* 1999;138:384.
28. Grisaru D, Rachmilewitz EA, Mosseri M, et al. Cardiopulmonary assessment in beta-thalassemia major. *Chest* 1990;98:1138-42.
29. Reiter CD, Wang X, Tanus-Santos JE, et al. Cell-free hemoglobin limits nitric oxide bioavailability in sickle-cell disease. *Nat Med* 2002;8:1383-9.
30. Morris CR, Kuypers FA, Larkin S, Vichinsky EP, Styles LA. Patterns of arginine and nitric oxide in patients with sickle cell disease with vaso-occlusive crisis and acute chest syndrome. *J Pediatr Hematol Oncol* 2000;22:515-20.
31. Morris CR, Morris SM Jr, Hagar W, et al. Arginine therapy: a new treatment for pulmonary hypertension in sickle cell disease? *Am J Respir Crit Care Med* 2003;168:63-9.
32. Aslan M, Ryan TM, Adler B, et al. Oxygen radical inhibition of nitric oxide-dependent vascular function in sickle cell disease. *Proc Natl Acad Sci U S A* 2001;98:15215-20.
33. Gladwin MT, Schechter AN, Ognibene FP, et al. Divergent nitric oxide bioavailability in men and women with sickle cell disease. *Circulation* 2003;107:271-8.
34. De Caterina R, Libby P, Peng HB, et al. Nitric oxide decreases cytokine-induced endothelial activation: nitric oxide selectively reduces endothelial expression of adhesion molecules and proinflammatory cytokines. *J Clin Invest* 1995;96:60-8.
35. Lin G, Macdonald RL, Marton LS, Kowalczyk A, Solenski NJ, Weir BK. Hemoglobin increases endothelin-1 in endothelial cells by decreasing nitric oxide. *Biochem Biophys Res Commun* 2001;280:824-30.
36. Hammerman SI, Kourembanas S, Conca TJ, Tucci M, Brauer M, Farber HW. Endothelin-1 production during the acute chest syndrome in sickle cell disease. *Am J Respir Crit Care Med* 1997;156:280-5.
37. Rybicki AC, Benjamin LJ. Increased levels of endothelin-1 in plasma of sickle cell anemia patients. *Blood* 1998;92:2594-6.
38. Rodgers GP, Walker EC, Podgor MJ. Is "relative" hypertension a risk factor for vaso-occlusive complications in sickle cell disease? *Am J Med Sci* 1993;305:1524-6.
39. Pegelow CH, Colangelo L, Steinberg M, et al. Natural history of blood pressure in sickle cell disease: risks for stroke and death associated with relative hypertension in sickle cell anemia. *Am J Med* 1997;102:171-7.
40. Ohene-Frempong K, Weiner SJ, Sleeper LA, et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. *Blood* 1998;91:288-94.
41. Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease: life expectancy and risk factors for early death. *N Engl J Med* 1994;330:1639-44.
42. Atweh GF, Schechter AN. Pharmacologic induction of fetal hemoglobin: raising the therapeutic bar in sickle cell disease. *Curr Opin Hematol* 2001;8:123-30.
43. Noguchi CT, Rodgers GP, Serjeant G, Schechter AN. Levels of fetal hemoglobin necessary for treatment of sickle cell disease. *N Engl J Med* 1988;318:96-9.

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