Relationship of erythropoietin, fetal hemoglobin, and hydroxyurea treatment to tricuspid regurgitation velocity in children with sickle cell disease

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Hydroxyurea and higher hemoglobin F improve the clinical course and survival in sickle cell disease, but their roles in protecting from pulmonary hypertension are not clear. We studied 399 children and adolescents with sickle cell disease at steady state; 38% were being treated with hydroxyurea. Patients on hydroxyurea had higher hemoglobin concentration and lower values for a hemolytic component derived from 4 markers of hemolysis ($P \leq .002$) but no difference in tricuspid regurgitation velocity compared with those not receiving hydroxyurea; they also had higher hemoglobin F ($P < .001$) and erythropoietin ($P = .012$) levels. Hemoglobin F correlated positively with erythropoietin even after adjustment for hemoglobin concentration ($P < .001$). Greater hemoglobin F and erythropoietin each independently predicted higher regurgitation velocity in addition to the hemolytic component ($P \leq .023$). In conclusion, increase in hemoglobin F in sickle cell disease may be associated with relatively lower tissue oxygen delivery as reflected in higher erythropoietin concentration. Greater levels of erythropoietin or hemoglobin F were independently associated with higher tricuspid regurgitation velocity after adjustment for degree of hemolysis, suggesting an independent relationship of hypoxia with higher systolic pulmonary artery pressure. The hemolysis-lowering and hemoglobin F–augmenting effects of hydroxyurea may exert countervailing influences on pulmonary blood pressure in sickle cell disease. (Blood. 2009;114:4639-4644)

Introduction

Studies in both adults[1] and children[2,3] with sickle cell disease have found correlations between hemolysis and pulmonary hypertension, a complication associated with increased mortality.[1] Intravascular hemolysis may contribute to a hemolytic vasculopathy in part by scavenging nitric oxide, a key modulator of microvascular function[4] and by limiting availability of arginine, the substrate for nitric oxide synthase.[5] Hemolysis, however, does not fully explain the finding of pulmonary hypertension in this setting. Pulmonary hypertension develops in patients with hemoglobin SC disease or Sβ⁺-thalassemia, conditions with a substantially lower hemolytic rate than that of homozygous hemoglobin SS disease.[1] Furthermore, once hemoglobin SC disease patients develop pulmonary hypertension, their prognosis is as poor as in hemoglobin SS patients with this complication.[6] Hydroxyurea decreases hemolysis[7,8] and induces nitric oxide in endothelial cells,[9] but the largest prospective studies of patients with sickle cell disease have not found less pulmonary hypertension among those receiving hydroxyurea.[1,3,10] It is also not clear whether high hemoglobin F levels reduce pulmonary hypertension risk in sickle cell patients. Some studies have found an association of high hemoglobin F with lower pulmonary hypertension risk,[11-14] but several others have detected no such association.[1,2,15-18]

We recently reported a prospective, multicenter study of 310 children and adolescents with sickle cell disease at steady state in which tricuspid regurgitation velocity of 2.6 m/s or higher occurred in 11% of participants and had independent associations with hemolysis and hemoglobin oxygen desaturation.[3] In addition, we have found that an elevated screening tricuspid regurgitation velocity in children and adolescents with sickle cell disease predicts functional impairment over 2 years of follow-up (V.R.G., unpublished observations, April 2009). The present report involves an investigation in these and additional participants of potential relationships among pulmonary hypertension and serum erythropoietin concentration, hemoglobin F levels, and hydroxyurea use. We also attempt to explain why, despite the well-documented beneficial effects of high hemoglobin F levels and hydroxyurea treatment, neither spontaneous nor hydroxyurea-induced elevations of hemoglobin F have been convincingly demonstrated to lower pulmonary hypertension risk in sickle cell disease patients.

Methods

Study participants

This report includes 399 children and adolescents with sickle cell disease from 3 to 20 years who were evaluated at steady state as previously described.[3] Of the children in the present report, 307 were also included in our previous publication[3] and 92 were newly enrolled. The patients had hemoglobin SS, SC, Sβ-thalassemia, or other major sickling phenotypes as confirmed by hemoglobin electrophoresis or high-performance liquid

chromatography. One hundred fifty patients (38%) were receiving hydroxyurea therapy. Doppler echocardiography was used to estimate systolic pulmonary artery pressure through measurement of the tricuspid regurgitation velocity. Transthoracic echocardiography was performed using the Philips Sono 5500/7500 or iE33, Acuson Sequoia, or General Electric VIVID 7 or VIVID I instruments. Cardiac images were obtained, measurements performed, and studies interpreted centrally according to guidelines of the American Society of Echocardiography. A nonencouraged 6-minute walk test was performed. Participants were recruited at 3 centers: Howard University, Children's National Medical Center, and the University of Michigan. The institutional review boards of all participating institutions approved the study protocol, and all subjects provided written informed consent to participate in accordance with the Declaration of Helsinki.

Laboratory analyses

Serum concentrations of erythropoietin were measured with a commercially available enzyme-linked immunosorbent assay kit (R&D Systems) following the manufacturer's recommendations. Other measurements were performed as previously described.[3] Hemoglobin F was determined by high-performance liquid chromatography or hemoglobin electrophoresis by the laboratories of each institution. In some cases the hemoglobin electrophoresis results did not report a value for hemoglobin F; these cases were considered to have missing hemoglobin F data in this paper rather than assigning them 0 or an arbitrarily low hemoglobin F value.

Statistical analysis

For continuous variables that did not follow a normal distribution, the best transformation to a normal distribution was made for statistical analyses. To overcome colinearity of related markers and to point to underlying mechanisms, principal component analysis of 4 markers of hemolysis (reticulocyte count, and serum concentrations of aspartate aminotransferase, lactate dehydrogenase, and total bilirubin) was performed.[3] Principal component analysis produces several components equal to the number of variables in the analysis; each component represents a normalized standard distribution with a mean value of 0. In this analysis, the first component had an Eigen value of 2.56 (explaining 64% of variability) and was termed a hemolytic component. Continuous variables were compared between patients according to hydroxyurea treatment at the time of the study with analysis of variance models that adjusted for severe (ie, Hbs SS, Sβ[0]-thalassemia, and SD[LA]) versus mild (Hbs SC and Sβ[+]-thalassemia) sickling phenotype and other important covariates. Categoric variables were compared with the χ^2 test. The associations of erythropoietin and tricuspid regurgitation velocity with other variables were assessed by Pearson correlation or multiple linear regression. In these analyses, up to 5 outlier values were excluded. P values less than .05 were considered statistically significant. Analyses were performed with STATA 10.0 (StataCorp).

Results

Clinical and laboratory characteristics

Table 1 summarizes the general clinical characteristics of this cohort. Seventy-six percent had the severe sickling phenotypes of hemoglobin SS, Sβ[0] thalassemia, or SD[LA], and 38% were receiving hydroxyurea treatment at the time of the study. Twenty-two percent had tricuspid regurgitation velocity of 2.5 m/s or higher, and 11% had velocity of 2.6 m/s or higher. There was only 1 participant who had a tricuspid regurgitation velocity higher than 2.9 m/s.

Characteristics according to hydroxyurea treatment status

Table 2 shows that sickle cell disease patients taking hydroxyurea were older and more likely to have severe sickling phenotypes (hemoglobin SS, Sβ[0] thalassemia, or SD[LA]) than

Table 1. Clinical and laboratory characteristics of sickle cell disease patients

	n	Result
Age, y	399	12 (7-16)
Female sex, no. (%)	399	191 (48)
Severe sickling phenotype, hemoglobin SS, Sβ[0] thalassemia, or SD[LA], no. (%)	395	299 (76)
Hydroxyurea therapy, no. (%)	397	150 (38)
Chronic transfusion program, no. (%)	382	32 (8)
Oxygen saturation, %	379	98 (97-99)
Change in oxygen saturation during 6-minute walk, %	315	0 (−1-0)
Tricuspid regurgitation velocity, m/s	372	2.3 (2.1-2.5)
Tricuspid regurgitation velocity, 2.5 m/s or higher, no. (%)	372	81 (22)
Tricuspid regurgitation velocity, 2.6 m/s or higher, no. (%)	372	41 (11)
Hemoglobin, g/L	383	92 (81-106)
Mean corpuscular volume, fL	377	84 (77-90)
White blood cells, ×10⁹/L	377	9.9 (7.5-13.2)
Absolute neutrophil count, 1000/μL	375	4.6 (3.4-7.1)
Platelets, ×10⁹/L	377	381 (285-478)
Reticulocytes, ×10⁹/L	374	217 (147-315)
Lactate dehydrogenase, U/L	356	377 (277-522)
Aspartate aminotransferase, U/L	382	40 (29-53)
Total bilirubin, mg/dL	382	2.2 (1.4-3.3)
Hemolytic component	343	0.09 (−1.17 to 1.06)
Hemoglobin F, %	199	9.0 (3.1-16.5)
Hemoglobin F 8% or higher, no. (%)	199	112 (56)
Erythropoietin, IU/L	371	55 (30-96)

Results are in median and interquartile range unless otherwise indicated.

those not taking the medication. They had higher values for hemoglobin and mean corpuscular volume, and lower values for white blood cell and reticulocyte counts and the hemolytic component, indicating compliance with the medication and an effect of the drug on the body's hematologic status. In addition, hydroxyurea-treated patients had significantly higher values for hemoglobin oxygen saturation, hemoglobin F, and erythropoietin. The tricuspid regurgitation velocity did not differ according to treatment with hydroxyurea among all phenotypes as shown in Table 2 or when restricted to patients with hemoglobin SS (data not shown). For these analyses, we statistically adjusted for patients who were on a chronic transfusion program. Essentially the same results were found if these patients were excluded from the analyses.

Independent associations with erythropoietin concentration

With the exception of erythropoietin-expressing tumors and rare conditions of altered hypoxia sensing, erythropoietin expression sensitively reflects tissue oxygenation status.[19,20] In fact, hypoxia-inducible factor-α, the master regulator of the body's response to hypoxia, was discovered by studying the regulation of the erythropoietin gene.[19] In our data, bivariate analyses revealed significant relationships between lower hemoglobin concentration and log erythropoietin (n = 356, r = −0.66, $P < .001$), between lower hemoglobin oxygen saturation and log erythropoietin (n = 354, r = −0.28, $P < .001$), and between higher hemoglobin F percentage and log erythropoietin (n = 189, r = 0.21, $P = .003$). Multiple linear regression confirmed that lower hemoglobin concentration ($P < .001$) and higher log hemoglobin F percentage ($P < .001$) each correlated independently with higher log erythropoietin concentration among 179 patients with sickle cell disease (Table 3, "All patients"). In

Table 2. Clinical and laboratory characteristics of sickle cell disease patients according to hydroxyurea treatment

	Not on hydroxyurea		Hydroxyurea treatment		
	n	Result	n	Result	P*
Age, y	247	11 (10-12)	150	13 (12-14)	< .001
Female sex, no. (%)	247	123 (50)	150	67 (45)	.3
Severe sickling phenotype, hemoglobin SS, Sβ⁰ thalassemia, or SD^LA, no. (%)	244	171 (70)	149	127 (85)	.001
Oxygen saturation, %†	233	97 (97-98)	144	98 (98-99)	.001
Change in oxygen saturation during 6-minute walk, %†	183	0 (−1-0)	132	0 (−1-0)	.6
Tricuspid regurgitation velocity, m/s†	227	2.3 (2.2-2.3)	143	2.3 (2.2-2.3)	.5
Tricuspid regurgitation velocity, 2.5 m/s or higher, no. (%)	227	47 (21)	143	33 (23)	.6
Tricuspid regurgitation velocity, 2.6 m/s or higher, no. (%)	227	22 (10)	143	19 (13)	.3
Hemoglobin g/L†	235	91 (89-93)	147	97 (94-99)	.002
Mean corpuscular volume, fL†	230	81 (79-82)	146	92 (90-93)	< .001
White blood cells, ×10⁹/L†	230	10.7 (10.2-11.2)	143	8.8 (8.2-9.5)	.001
Absolute neutrophil count, ×10⁹/L	229	5.2 (4.8-5.5)	145	4.2 (3.7-4.6)	.00
Platelets, ×10⁹/L†	230	384 (364-408)	146	361 (331-388)	.2
Reticulocytes, ×10⁹/L†	227	240 (220-259)	146	198 (174-224)	.026
Lactate dehydrogenase, U/L†	219	403 (380-424)	136	365 (336-391)	.070
Aspartate aminotransferase, U/L†	232	42 (40-44)	149	36 (33-39)	.006
Total bilirubin, mg/dL†	232	2.4 (2.2-2.6)	149	2.0 (1.8-2.2)	.034
Hemolytic component‡	209	0.32 (0.12-0.52)	133	−0.36 (−0.63--0.08)	.001
Hemoglobin F, %†	121	9 (7-10)	76	13 (11-15)	< .001
Hemoglobin F 8% or higher, no. (%)	121	55 (45)	76	56 (74)	< .001
Erythropoietin, IU/L§	227	48 (44-52)	143	59 (52-66)	.012

Results are mean (95% confidence interval [CI] of mean) unless otherwise indicated.
*Comparison of patients on hydroxyurea with those not on hydroxyurea.
†Adjusted for sickling phenotype, age, sex, site, and chronic transfusion program.
‡Adjusted for sickling phenotype, sex, site, and chronic transfusion program.
§Adjusted for sickling phenotype, age, sex, site, hemoglobin concentration, and chronic transfusion program.

subanalyses of the patients being treated with hydroxyurea (Table 3, "Patients on hydroxyurea") and those not receiving hydroxyurea (Table 3, "Patients not on hydroxyurea"), the inverse relationship between hemoglobin concentration and erythropoietin persisted in both subgroups ($P \leq .005$). An independent positive association of hemoglobin F with erythropoietin was found in the patients receiving hydroxyurea ($P < .001$) but this relationship was not statistically significant in the analysis of patients not on hydroxyurea ($P = .09$).

Correlation of clinical features and laboratory values with tricuspid regurgitation velocity

Erythropoietin, hemoglobin F, and hemolytic component correlated positively with tricuspid regurgitation velocity, whereas hemoglobin concentration and hemoglobin oxygen saturation correlated negatively in analyses adjusted for age, sex, chronic

transfusion program, and research site (Table 4). When the same analyses were restricted to patients who were being treated with hydroxyurea, the hemolytic component ($P < .001$), erythropoietin level ($P < .001$), and hemoglobin F category ($P = .003$) correlated positively with tricuspid regurgitation velocity, whereas hemoglobin concentration ($P < .001$) and hemoglobin oxygen saturation ($P = .028$) correlated negatively. The positive correlation of hemoglobin F percentage ($P = .2$) with regurgitation velocity did not achieve statistical significance. When restricted to patients who were not taking hydroxyurea, the hemolytic component ($P < .001$) and erythropoietin concentration ($P < .001$) correlated positively with regurgitation velocity, whereas hemoglobin concentration ($P = .001$) correlated negatively. The positive correlations of hemoglobin F percentage ($P = .2$) and hemoglobin F category ($P = .1$) and the negative correlation of oxygen saturation ($P = .2$) with regurgitation velocity were not statistically significant (data not shown).

Table 3. Independent associations with erythropoietin (natural log) in multivariate analysis

	Beta (95% CI)	Standardized beta	P
All patients,* N = 179†			
Hemoglobin, g/L	−3.1 (−3.6--0.26)	−0.69	< .001
Hemoglobin F, %	0.02 (0.01-0.03)	0.27	< .001
Patients on hydroxyurea, n = 72‡			
Hemoglobin, g/L	−2.7 (−3.8--1.7)	−0.58	< .001
Hemoglobin F, %	0.03 (0.01-0.05)	0.32	.005
Patients not on hydroxyurea, n = 107§			
Hemoglobin, g/L	−3.3 (−3.9--2.8)	−0.80	< .001
Hemoglobin F, %	0.01 (0-0.02)	0.12	.09

*Includes patients for whom hemoglobin F and erythropoietin results were available. Variables entered into models were hemoglobin, hemolytic component, hemoglobin oxygen saturation, and hemoglobin F (%).
†R-square = 0.51. If hemoglobin F category of 8% or higher versus lower than 8% is used in the model, P value for hemoglobin F = .001.
‡R-square = 0.34. If hemoglobin F category of 8% or higher versus lower than 8% is used in the model, P value for hemoglobin F = .015.
§R-square = 0.61. If hemoglobin F category of 8% or higher versus lower than 8% is used in the model, P value for hemoglobin F = .3.

Table 4. Correlation of clinical features and laboratory values with tricuspid regurgitation velocity in patients with sickle cell disease

	n	Partial R*	P
Hydroxyurea therapy	356	0.07	.2
Hemoglobin	342	−0.32	< .001
Hemolytic component	308	0.38	< .001
Hemoglobin oxygen saturation	344	−0.11	.042
Hemoglobin F percentage	173	0.15	.048
Hemoglobin F category, 8% or higher versus lower than 8%†	173	0.26	.001
Erythropoietin, natural log	335	0.34	< .001

*Adjusted for age, sex, site, and chronic transfusion program.

†Ninety-four (54%) of the 173 patients had hemoglobin F of 8% or higher and 54% of these patients were on hydroxyurea.

Multiple linear regression analysis of tricuspid regurgitation velocity

Both the degree of hemolysis as reflected in the hemolytic component and the erythropoietin concentration were significantly and independently associated with tricuspid regurgitation velocity among 294 patients (Table 5, "Analysis based on all participants with erythropoietin available"). Hemoglobin F percentage was available in a subset of 142 participants. Multivariate analysis in these patients showed that hemoglobin F was also an independent positive predictor of higher tricuspid regurgitation velocity in addition to the degree of hemolysis (Table 5, "Analysis based on participants with value for hemoglobin F available").

Discussion

This study indicates that serum erythropoietin and hemoglobin F levels, in addition to or in concert with hemolysis, are associated with higher tricuspid regurgitation velocities in children and adolescents with sickle cell disease. In our patient population and also in some published studies, hydroxyurea treatment failed to predict lower tricuspid regurgitation velocity, despite its association with lower hemolysis. Our findings suggest that this might be explained by the induction of higher erythropoietin and hemoglobin F levels.

Increased erythropoietin has been reported to protect from the development of pulmonary hypertension in some studies[21] and to be associated with the development of pulmonary hypertension in others.[22,23] In a study of 124 adults with sickle cell disease, no relationship between erythropoietin and pulmonary hypertension was detected.[24] We, however, observed that serum erythropoietin concentration is associated with higher tricuspid regurgitation velocity in sickle cell disease patients even after adjustment for the degree of hemolysis and other significant covariates, providing evidence for the concept that erythropoietin may be related to the development of pulmonary hypertension. Circulating erythropoietin concentrations reflect the degree of tissue hypoxia, and are known to increase with lower hemoglobin concentrations and hemoglobin oxygen saturations.[20] Therefore, the observed association of erythropoietin with higher tricuspid regurgitation velocity could be reflective of an association of hypoxia with elevated velocity rather than a primary relationship.

Hemoglobin F has high affinity for oxygen[25] due to its low affinity for 2,3-diphosphoglycerate.[26] Hemoglobin F also inhibits hemoglobin S polymerization,[27] which would be expected to reverse in part the low oxygen affinity of hemoglobin S that results from its polymerization.[28] Therefore, hemoglobin F could conceivably contribute to a relative tissue hypoxia, despite its well-documented effect in ameliorating the course of sickle cell disease and increasing patient survival.[29] In a sense, hemoglobin F's left shifting of the oxygen saturation curve is similar to what can be seen in sickle cell patients after red cell exchanges: both hemoglobin levels and blood oxygen affinity increase modestly after exchange and are associated with increased exercise capacity.[30] It is interesting also that thalassemia intermedia patients with high hemoglobin F levels have significantly higher erythropoietin concentrations than those with low hemoglobin F levels despite their similar degree of anemia.[31]

In the present study, lower hemoglobin concentration and higher hemoglobin F each correlated independently and strongly with higher erythropoietin concentration. Furthermore, in multiple linear regression analyses, both erythropoietin and hemoglobin F independently were associated with higher regurgitation velocities in an interchangeable manner. From this perspective, the associations of greater levels of erythropoietin and hemoglobin F with higher regurgitation velocities may serve to reflect the known association of hypoxia with the development of pulmonary hypertension in other conditions. On the other hand, erythropoietin has functions other than the stimulation of erythropoiesis, such as regulation of the development of endothelial progenitor cells,[32] and the inducement of such processes might contribute to vascular remodeling and the risk of pulmonary hypertension. Our finding of a positive association of hemoglobin F with tricuspid regurgitation velocity in children and adolescents is in contrast to studies in adults with sickle cell disease that reported no such association[17] or an association with lower regurgitation velocities.[12]

Hydroxyurea treatment lowers hemolysis[7,8] and decreases morbidity and mortality in patients with sickle cell disease.[33,34] Hydroxyurea may also have an impact on nitric oxide signaling by evoking nitric oxide synthase and decreasing arginine levels[9,35]; the agent promotes the synthesis of nitric oxide by endothelial cells.[9]

Table 5. Independent associations of tricuspid regurgitation velocity in multiple linear regression analysis models adjusted for age, sex, site, and chronic transfusion program.

	Beta (95% CI)	Standardized beta	P
Analysis based on all participants with erythropoietin available*			
Erythropoietin, IU/L, natural log	0.06 (0.02-0.11)	0.19	.003
Hemolytic component	0.05 (0.03-0.07)	0.27	< .001
Analysis based on participants with value for hemoglobin F available†			
Hemoglobin F (%)	0.006 (0.001-0.01)	0.19	.023
Hemolytic component	0.06 (0.03-0.08)	0.35	< .001

*n = 294; R-square = 0.19; variables entered into the analysis initially include erythropoietin, hemoglobin oxygen saturation, hemolytic component, and hydroxyurea therapy.

†n = 142; R-square = 0.21; variables entered into the analysis initially include hemoglobin F percentage, hemoglobin oxygen saturation, hemolytic component, and hydroxyurea therapy. With hemoglobin F category in the model, P value for hemoglobin F = .002.

These factors may serve to protect from pulmonary hypertension. However, although some investigators have reported that hydroxyurea therapy provides a protective effect from pulmonary hypertension,[12] most reports including the largest, prospective investigations of pulmonary hypertension in sickle cell disease have not found such a protective effect.[1,10,17] The present study provides some possible insights into this observation. Compared with children not receiving hydroxyurea at the time of study, those receiving hydroxyurea had higher hemoglobin levels, mean corpuscular volumes, and hemoglobin F concentrations, and lower leukocyte counts, indicating their compliance with the regimen for a sufficient time to experience its effects on hematopoiesis. At the same time, our patients on hydroxyurea had higher erythropoietin concentrations, as has been previously reported in sickle cell disease patients on this drug,[36,37] and higher hemoglobin F percentages, features that are associated with higher tricuspid regurgitation velocities. Interestingly, a nitric oxide signal for fetal hemoglobin induction has been described.[9] Tricuspid regurgitation velocities did not differ according to whether the children were receiving hydroxyurea, suggesting that factors associated with higher tricuspid regurgitation velocities may have been balanced by those associated with lower velocities. Alternatively, the fact that the patients included in this study had received hydroxyurea in a nonrandomized manner represents a potentially important confounder. We cannot rule out the possibility that patients receiving hydroxyurea were at higher risk for pulmonary hypertension before starting therapy than those not treated with hydroxyurea, and that they might have had higher tricuspid regurgitation velocities if they were not on hydroxyurea. Consistent with this possibility, a recent publication reported reduction in mean pulmonary artery pressures with hydroxyurea therapy in 5 patients.[38] On the other hand, prospective administration of hydroxyurea in the Multicenter Study of Hydroxyurea in Sickle Cell Anemia did not influence concentrations of N-terminal pro–brain natriuretic peptide, an index of pulmonary hypertension.[10]

There are several additional limitations to our study. First, we did not collect information on how long the children had been receiving hydroxyurea or what their doses were. Second, although, as shown in Table 1, there were significant differences in hemoglobin concentration, hemoglobin F percentage, and mean corpuscular volume according to hydroxyurea in the present study, these differences were not as great as those reported in the HUG-KIDS study.[39] Thus, the hydroxyurea group may not have been receiving optimal amounts of hydroxyurea and this may have contributed to a lack of association with lower tricuspid regurgitation velocity. Third, we have not controlled for low arginine bioavailability that may be independently associated with high tricuspid regurgitation velocity in adult studies.[1,5] Fourth, the reliability of a single echocardiographic measurement of tricuspid regurgitation velocity has not been established in children with sickle cell disease. Fifth,

hemoglobin F results were not available for approximately one-half of the group studied.

Our findings have implications for future studies examining the causes and treatment of pulmonary hypertension in patients with sickle cell disease. It is likely that the etiology of pulmonary hypertension in this setting is multifactorial. Furthermore, children may be different from adults,[40] and the clinical implications of an elevated tricuspid regurgitation velocity are largely unknown in the pediatric population. The independent association of erythropoietin with higher tricuspid regurgitation velocity suggests that the safety of high doses of human recombinant erythropoietin in patients with sickle cell disease should be studied further, specifically, whether erythropoietin therapy may increase tricuspid regurgitation velocity even as it increases hemoglobin concentration. Prospective studies of the effect of hydroxyurea therapy on pulmonary artery pressure in patients with sickle cell disease should also be carried out. These trials should indicate whether the degree of hemolysis reduction by hydroxyurea compensates for the drug's effect in increasing hemoglobin F and erythropoietin levels.

Authorship

Contribution: V.R.G. and O.L.C. participated in study design, data analysis, and writing the paper; A.C., S.R., C.P.M., C.S., D.D., N.D., O.O., G.J.K., and M.T.G. participated in study design, data collection, and writing the paper; M.N. participated in data analysis and writing the paper; and X.N., T.A., and S.N. participated in study design, collecting laboratory data, and writing the paper.

Conflict-of-interest disclosure: V.R.G. has received research grants from Biomarin and TRF Pharma and has received consulting fees from Ikaria. The remaining authors declare no competing financial interests.

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