unsaturated compounds in the cellular environment would be expected to generate toxic organic peroxides, providing a rationale for the reduced virulence phenotype of strains deficient in organic peroxidase reductase. It would be important for the host organism that its cells are also able to detoxify such organic peroxides. Thus, we suggest that protection against organic peroxides produced during phagocyte killing is a physiological role for GSHPx in red cells.

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This work was supported by National Institutes of Health grant HL56421 (Y-S.H.) and the Ginopolis Fund of Children's Hospital of Michigan.

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To the editor:

Long-term treatment with oral sildenafil in a thalassemic patient with pulmonary hypertension

Pulmonary hypertension (PHT), defined as Doppler peak systolic tricuspid gradient (TG) higher than 30 mmHg, develops in a high percentage of patients with β-thalassemia (10% in thalassemia major and greater than 50% in thalassemia intermedia [TI]). Recent studies correlate PHT with age and high cardiac output. In patients with TI, whether or not transfusion dependent, PHT is the main cause for congestive heart failure.[1] We report the case of a thalassemic patient with secondary PHT who has been successfully treated with sildenafil, a selective and potent inhibitor of cGMP-specific phosphodiesterase (PDE5) that promotes smooth muscle relaxation in lung vasculature.[2]

A 34-year-old male with β-thalassemia intermedia, splenectomized at the age of 18, started regular transfusion and iron chelation therapy in our center at the age of 32. Echocardiography showed a steady increase of pulmonary artery pressure (PAP) with right ventricular enlargement and moderate tricuspid valve regurgitation (TG systolic 56 mmHg, mean 42 mmHg). Left ventricular systolic function was preserved. Patient symptoms included reduced tolerance to exercise, dyspnea during light physical exertion, and thoracic constriction. There were no signs of iron overload. Pulmonary scintigraphy with 99 Tc demonstrated numerous defects in perfusion capacity of the right lung. Spirometry revealed medium-grade ventilation impairment with a restrictive pattern (Inspiratory Vital Capacity [IVC] = 2.66 L, 57% of the normal value, Forced Expiratory Volume L/s [FEV1] = 1.96 L, 52% of the normal value). Treatment was started with calcium antagonists but had to be quickly interrupted due to severe side effects. Based on the potential role suggested for sildenafil in the management of PHT,[3] sildenafil, 25 mg 2 times per day, was administered for 1 month and progressively increased to 50 mg 2 times per day. After 15 months of therapy, right ventricular dimension and mean TG were back to normal (TG systolic 40 ± 3 mmHg, mean 25 mmHg; $P < .03$). Respiratory function tests showed only a mildly restrictive ventilation pattern (IVC = 3.54 L, 76% of the normal value, FEVI = 3.03 L, 81% of the normal value). Systemic artery pressure was normal, and the patient's conditions had improved. The drug was well tolerated except for transient episodes of nasal mucosa congestion. Different to what has previously been described in a patient with sickle cell trait treated with sildenafil, no priapism or erectile dysfunction was observed in our patient.[4]

The etiology of PHT in thalassemic patients remains unclear.[5] Obstruction of pulmonary arteries by thrombotic events has been observed in autopsies of patients with β-thalassemia/HbE disease.[6] In fact, perfusion pulmonary scintigraphy with Tc99 of our patient shows multiple areas of perfusion impairment in pulmonary microcirculation (data not shown). Recent studies have demonstrated the importance of the procoagulant activity exerted by erythroblasts and damaged erythrocytes that have lost normal asymmetric distribution of membrane phospholipids.[5,7] A higher risk has been attributed to splenectomized TI patients, especially those who are not transfusion-dependent. The low hemoglobin levels in untransfused patients leads to compensatory erythroblast hyperplasia and elevated levels of erythroblasts in circulation.[7] This suggests that therapeutic strategies directed toward reduction of the raised pulmonary pressure should be combined with adequate transfusional support and iron chelation therapy[8] in order to reduce hypoxic stimulus on the pulmonary vessels.

In vitro study has shown that the activation of soluble guanylate cyclase-cGMP–dependent protein kinase pathway is associated with the induction of γ-globin gene expression.[9] This suggests that sildenafil is also capable of improving erythropoiesis in thalassemia patients. Since our patient is transfusion-dependent, it was not possible to correlate any improvement in erythropoiesis to treatment with sildenafil.

Previous experience has shown that calcium antagonists are effective in only 30% of patients with PHT[10] and that prostacyclin analogs are expensive and difficult to manage. The selective antihypertensive effect, the minimal risk of side effects, and the

option of oral administration make sildenafil an attractive alternative to conventional therapy for PHT. Further investigation is required to establish whether the decrease in PHT achieved by sildenafil has the potential to lower the risk of congestive heart failure in thalassemia patients.

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To the editor:

AML, angiogenesis, and prognostic variables

A previous letter to this journal discussed the importance of correlating increased bone marrow microvessel density with known prognostic variables in acute myeloid leukemia (AML)[1] since earlier reports have not addressed this issue.[2-5] One group correlated indirect evidence of angiogeneic potential (increasing levels of intracellular vascular endothelial growth factor [VEGF] protein) in newly diagnosed AML with shorter overall and disease-free survival and also found VEGF protein to be an independent prognostic variable. However, no relationship between VEGF protein with the traditional prognostic variables such as white blood cell or blast count, age, cytogenetic changes, performance status, or presence of an antecedent hematologic disorder was found.[6]

To address this issue, we collected 4 nonneoplastic control bone marrow specimens and 21 specimens that contained at least 80% AML from different treatment protocols. All samples were from the time of diagnosis unless otherwise noted in the data table. In a blinded fashion, we cultured 5×10^5 cells $\times$ 72 hours in 700 μL EGM (Clonetics) without human epidermal growth factor or bovine brain extract additives and 2% fetal bovine serum in 24-well plates in triplicate. The conditioned media from each well was collected, filtered, and placed over

Table 1.

Case	Age (y)/sex	Cytogenetics, dysplasia, relapse information	FAB	Prognostic category	% change in endothelial proliferation
1	55/F	De novo, Inv(16), + 22	M4	F/I	− 12
2	50/M	De novo, 46XY	M5a	F/I	− 27
3	55/F	De novo, 46XX	M1	F/I	− 20
4	40/M	De novo, t(15;17), add 7(q36)	M3	F/I	− 32
5	19/M	Inv 16	M4Eo	F/I	− 42
6	32/M	De novo, + 11	M1	F/I	− 13
7	76/M	De novo, + 8	M0	F/I	− 50
8	67/M	t(15;17)	M3	F/I	− 41
9	68/F	De novo, + 4, + 11	M4	F/I	− 21
10	18/F	Relapsed, t(6;9)	M1	U	− 15
11	66/M	De novo, 46XY, relapse within 2 months	M2	U	+ 53
12	64/M	+ 8, dyspoiesis	M1	U	+ 5.5
13	68/M	History of MDS, 46XY	M2	U	− 31
14*	31/F	t(11;19), relapsed within 6 months, dyspoiesis	M4	U	+ 35
15	54/M	11q23	M5a	U	− 19
16	83/F	Multiple relapses	M5a	U	+ 5
17	68/F	t(9;22) and − 7	Mixed lineage	U	+ 3
18*	42/M	Complex karyotype	M1	U	+ 0
19*	55/M	History of MDS	M5	U	− 27
20	61/F	History of CMML, complex karyotype	M4	U	− 12
21	53/F	History of MDS, complex karyotype	M2	U	− 26

*Sample analyzed was from time of relapse (after treatment).
FAB indicates French-American-British classification.