Perspectives

Pulmonary hypertension and nitric oxide depletion in sickle cell disease

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During the past decade a large body of experimental and clinical studies has focused on the hypothesis that nitric oxide (NO) depletion by plasma hemoglobin in the microcirculation plays a central role in the pathogenesis of many manifestations of sickle cell disease (SCD), particularly pulmonary hypertension. We have carefully examined those studies and believe that the conclusions drawn from them are not adequately supported by the data. We agree that NO depletion may well play a role in the pathophysiology of other hemolytic states such as paroxysmal nocturnal hemoglobinuria, in which plasma hemoglobin concentrations are often at least an order of magnitude greater than in SCD. Accordingly, we conclude that clinical trials in SCD designed to increase the bioavailability of NO or association studies in which SCD clinical manifestations are related to plasma hemoglobin via its surrogates should be viewed with caution. (Blood. 2010;116(5):687-692)

Introduction

More than 50 years ago, discoveries by Pauling, Ingram, and Neel provided key insights into both the structure and the genetics of sickle hemoglobin, thereby launching a new era of molecular medicine. Since then, we have learned a great deal about the polymerization of deoxyhemoglobin S, its kinetics and equilib-rium, and its potent inhibition by fetal hemoglobin (Hb F).1,2 Although these advances explain the dramatic impact of deoxygenation on the shape and rheology of sickle erythrocytes, they provide only a partial understanding of the in vivo pathogenesis of vaso-occlusion, the cardinal feature of homozygous sickle cell disease (SCD). Subsequent studies have demonstrated the importance of adhesion of sickle erythrocytes to vascular endothelium,3 the possible contribution of marginating leukocytes4 and the development of ischemia-reperfusion injury.3,5 It has become increasingly apparent that inflammation plays a critical role in both the initiation and propagation of vaso-occlusion.5

Clinicians charged with the care of sickle cell patients are struck for safe and, in most cases, effective induction of hydroxyurea in sickle cell patients may be due in part to other drug effects, including lowering of the white cell and platelet counts and reduction of adhesion of homozygous sickle (SS) red cells to the endothelium.13

Role of nitric oxide

During the past decade, numerous experimental and clinical studies have focused on the hypothesis that nitric oxide (NO) depletion in the microcirculation plays a central role in the pathogenesis of sickle vaso-occlusion and other manifestations possibly by inducing vasoconstriction, platelet activation, leukocyte adhesion, endothelial damage, oxygen free radical generation, and pulmonary hypertension. Indeed, several possible mechanisms might underlie low levels of NO in the vascular endothelium of sickle cell patients. Two pertain to hemolysis. The high rate of red cell destruction in sickle cell patients releases erythrocyte arginase into the plasma possibly lowering levels of arginine,14 the substrate for NO synthase. An alternate mechanism by which hemolysis might deplete NO has been proposed and vigorously promoted in multiple review articles/opinion pieces15-22 and educational programs.23,24 These reports advance the hypothesis that depletion of NO by elevated levels of free hemoglobin in the plasma is an important determinant of the clinical manifestations of SCD, particularly pulmonary hypertension which has been deemed a critical risk factor, greatly limiting life expectancy. On the basis of this notion, widespread screening programs and several therapeutic trials have been instituted. In this brief Perspective, we raise concerns regarding the robustness of this hypothesis, the interpretation of selected data, and the conclusions that have been drawn from them.
Pulmonary hypertension in SCD

In 2004, a report by Gladwin and his colleagues25 attracted considerable attention among those involved in the treatment of SCD and investigation of its pathogenesis. Pulmonary artery pressure was assessed indirectly by measurement of tricuspid regurgitant jet velocity (TRV) with transthoracic Doppler echocardiography in 195 consecutive sickle cell patients. Direct measurement of pulmonary artery pressure by 25 right heart catheterization in 18 patients correlated with estimates obtained from echocardiography with a correlation coefficient of almost 60%. Pulmonary hypertension was defined in this study as a TRV of at least 2.5 meters per second (m/s), equivalent to a pulmonary systolic pressure of more than 30-mm Hg. By this criterion, 32% of patients were considered to have pulmonary hypertension. Over a 30-month period of observation, 17% of this patient group died whereas only 2% died in the group with a TRV less than 2.5 m/s. The authors of this study concluded that “pulmonary hypertension is common in adults with SCD and is associated with an ominous outcome.”25, p894 They recommended “urgent” initiation of therapeutic trials designed to reverse or prevent this complication. Subsequently, 2 other studies of TRV in adult sickle cell patients were interpreted as confirming an association of pulmonary hypertension with increased mortality.26,27

The use of Doppler echocardiography for screening and diagnosing pulmonary hypertension in sickle cell patients raises several concerns. First, the test is not considered by many cardiologists to be a reliable index of pulmonary artery pressure. In particular, patients with normal or near normal systolic pulmonary artery pressure, as measured directly by right heart catheterization, often have a marked overestimation by Doppler TRV measurements.28 Moreover, the interpretation of modest elevations of TRV is particularly problematic in sickle patients in whom hypoxemia, in situ pulmonary artery thrombosis, and left ventricular dysfunction are commonly encountered independent causes of increased pulmonary artery pressure.29 Finally, it is likely that TRV is enhanced in severely anemic patients with increased cardiac output and high stroke volume. For these reasons, cardiologists at our institutions do not consider a TRV as low as 2.6 m/s to be a reliable indicator of pulmonary hypertension in sickle cell patients. Just as is the case for the general population, Doppler echocardiography is useful only as a screening tool; by itself it is insufficient for diagnosis of pulmonary hypertension.

Very recently, Bachir and her colleagues in France30 completed a prospective multicenter study in which 403 consecutive adult patients with SCD were assessed by echocardiography. A TRV of more than 2.5 m/s was encountered in 96 patients. In this group, right heart catheterization revealed normal pulmonary artery pressure in 72. Thus echocardiography was falsely positive in 75% of cases. In the remaining 24 patients with catheterization-documented pulmonary hypertension, 13 had elevated pulmonary capillary wedge pressure indicative of left ventricular dysfunction. In 5, the elevated pulmonary artery pressure was explained by hyperkinesis with high cardiac output coupled with normal pulmonary vascular resistance. These investigators concluded that pulmonary hypertension is an uncommon complication of SCD affecting 6% of these patients and that true pulmonary artery hypertension is even rarer, affecting 1.6%. These findings confirm the widely held notion that mild pulmonary hypertension in sickle cell patients is multifactorial, with contributors that include left ventricular failure and high cardiac output, along with in situ occlusion, microthrombi, and fat embolization. In the collective experience of the authors of this Perspective, fatal pulmonary hypertension (cor pulmonale) is an uncommon cause of death in SCD. This impression is supported by an earlier study of Powars et al31 as well as by Ataga et al26 who reported 10 deaths among a cohort of 96 patients followed over a nearly 3-year period. Although those with apparent pulmonary hypertension had a higher mortality rate than those with normal pulmonary arterial pressure, only 1 of these deaths was attributed to cor pulmonale. This 62-year-old patient had hemoglobin SC disease with a presumably low hemolytic rate. When all of these studies are weighed together, it seems likely that the high mortality rate in SCD patients with enhanced TRV is due to a complex combination of precipitating factors in a subset of patients with severe disease rather than due to pulmonary hypertension per se.

Rather than NO depletion, hypercoagulation and increased thrombosis seem more plausible explanations for the pulmonary hypertension seen in splenectomized patients with β-thalassemia major and intermedia as well as in those with unstable hemoglobin mutants and certain inherited and acquired red cell membrane disorders. Gross perturbations of membrane structure, which are especially evident after splenectomy, result in the exposure of procoagulant phospholipids on the surface of red cells and microparticles (“blood dust”), putting patients at high risk of developing thrombotic complications.32 Thus, pulmonary hypertension in SCD seems much more likely due to pulmonary embolization or in situ thrombosis than to NO scavenging by elevated plasma hemoglobin. It is likely that the marked distortions of red cell membrane structure due to repetitive cycles of sickling and unsickling pose a similar prothrombotic risk, particularly in patients without splenic filtering function. Indeed, evidence of organized thrombus and acute emboli are commonly seen in the lungs of SS patients who are autopsied.

Association of hyperhemolysis and pulmonary hypertension

In their initial report, Gladwin et al33 noted that patients with pulmonary hypertension had associated elevations of presumed markers of hemolysis, specifically elevated serum lactate dehydrogenase (LDH), and speculated that scavenging of NO by increased levels of plasma hemoglobin contributes importantly to pathogenesis. Subsequently, Ataga et al30 also found an association between the development of pulmonary hypertension and the degree of hemolysis in 86 adults with SCD. A similar association using TRV has been reported in children in studies by Onyekwere et al (52 patients),33 Liem et al (51 patients),34 Ambrusko et al (44 patients),35 and Mimniti et al (310 patients).36 The lattermost study36 proposed a more complex “hemolytic index” to achieve statistical significance. In contrast, studies by DeCastro et al of 125 adults27 and by Pashanker et al of 62 children32 found no such association between TRV and hemolysis.

Hyperhemolysis and NO scavenging

Both in vitro and in vivo experimental studies have provided support for the contribution of plasma hemoglobin to depletion of NO. Reiter et al38 confirmed earlier reports that plasma hemoglobin...
levels are elevated in SS patients. A Western blot showed that in 6 SS patients, plasma hemoglobin was qualitatively higher than normal controls. Quantitation of plasma heme levels revealed skewed distribution with a third of the patients between 5 and 20μM heme (equivalent to ~ 8-30 mg of hemoglobin/dL) and the remainder just slightly above normal. These results are consistent with older reports of plasma hemoglobin levels in SS patients.39

With optimal handling and methodology a mean of 8 mg/dL was found in patients not in acute crisis, compared with a range in normals of 0.1 to 1.2 mg/dL. SCD patients have elevated plasma hemoglobin levels but they are modest compared with values obtained in many other hemolytic disorders, paroxysmal nocturnal hemoglobinuria (PNH) in particular. Reiter et al38 also showed that oxyhemoglobin is the predominant form in the plasma of SS patients and reacts rapidly with NO to form methemoglobin and nitrate. A subsequent study in dogs showed that the induction of acute intravascular hemolysis by water infusion had systemic hemodynamic effects that were prevented by simultaneous administration of inhaled NO.40

### Hyperhemolysis and SS clinical phenotype

These and other experimental studies have led to the speculation that the degree of hemolysis in sickle cell patients is a critical determinant of clinical subphenotypes. Given that all SCD patients have a marked shortening of red cell life span, those with especially severe hemolysis will have particularly high levels of plasma hemoglobin and thus more NO scavenging. On that basis, patients with “hyperhemolysis” would be predicted to have more pronounced vascular complications.

This hypothesis has been tested in several clinical studies. Kato et al41 examined a cohort of 213 patients and found the expected highly significant direct correlation of serum LDH with reticulocyte count, plasma hemoglobin, and nonconjugated bilirubin and inverse correlation with blood hemoglobin and serum haptoglobin. They found that the 15% of patients with total LDH greater than 1 SD above the overall mean had statistically significant higher incidence of pulmonary hypertension, leg ulcers, risk of death, and (among males) priapism. In 33 of these patients, fractionation of the serum LDH showed elevations only of the LDH1 isoenzyme, suggesting that increases in total LDH probably arose from red cell lysis. However, more than 40 years ago, Neely et al42 demonstrated no correlation between plasma hemoglobin and red cell derived LDH in SCD. A hepatic contribution seems likely in the larger patient cohort reported by Kato et al41 since total LDH also correlated strongly with alanine aminotransferase (ALT) and with conjugated bilirubin.

Shortly thereafter, Nolan et al43 reviewed data from the Cooperative Study for Sickle Cell Disease (CSSD). Compared with 979 male patients without priapism, 273 patients with this complication had significantly lower hemoglobin levels and higher reticulocyte counts, along with higher serum total LDH, total bilirubin, and aspartate aminotransferase (AST). Those with priapism also had significantly higher white blood cell and platelet counts.

In a separate retrospective study of CSSD patients, Nolan et al44 reported that compared with 516 patients without leg ulcers, 243 patients with this complication had minimal but statistically significant reduction in hemoglobin levels and elevations in serum total LDH, total bilirubin, and AST. However, the reticulocyte counts in the 2 groups were virtually identical (12% vs 11%) even though this very small difference was statistically significant. Moreover, those with leg ulcers were several years older.

Stroke is a major complication and cause of death, particularly in children with SCD.45 Bernaudin and colleagues46 studied a cohort of 373 children between the ages of 3 and 8 with SCD and found highly significant associations between abnormal cerebral blood flow and G6PD deficiency, absence of α-thalassemia, higher reticulocytes, higher serum LDH, and lower hemoglobin. Red cell survival was not measured in these patients. The responsiveness of cerebral blood flow to carbon dioxide is a putative NO-dependent phenomenon that is related to increased risk of stroke in microvascular disorders. In a much smaller study (23 adult sickle cell patients), there was no association between cerebral CO2 responsiveness and markers of hemolysis (reticulocyte count, serum LDH, and total bilirubin).47

The hypothesis that NO scavenging contributes significantly to the clinical phenotype of SCD is of course best tested by measurements of plasma hemoglobin. Instead the studies cited in this section of our Perspective have used indirect assessments of hemolysis such as reticulocyte counts, serum LDH, and bilirubin and sometimes a “hemolytic index” that entails a combination of these tests. However, in these studies the reticulocyte count is not corrected for the reduction in red count, AST is sometimes used when the ALT is elevated and total LDH is used rather than specific LDH isoenzymes.

The findings described in this section have prompted a paradigm, summarized in Table 1, in which the frequency of several important complications in SCD patients is associated with the degree of hemolysis. Specifically, those with increased hemolysis are predicted to have pulmonary hypertension, leg ulcers, priapism, early death, and possibly stroke, whereas those with relatively less hemolysis are predicted to have pain crises, acute chest syndrome, and osteonecrosis. Diagrams that depict the information in Table 1 have appeared in several reviews17,22,24 and have attracted considerable attention.

### Does plasma NO scavenging contribute to the pathogenesis of SCD?

The numerous studies cited in the 2 previous sections make the case that a higher degree of hemolysis in SCD patients is associated with the presence of pulmonary hypertension, leg ulcers, priapism, and possibly stroke. Even though these associations are statistically significant, differences in reticulocyte counts and LDH values between affected and nonaffected patients are small, do not come close to reaching a bimodal distribution, and may relate in part to other mechanisms such as recovery from “aplastic” crisis or underlying renal disease. Therefore, in any given patient variation in these biologic markers may or may not reflect the degree of hemolysis will have little if any predictive value.

Of more importance is the time-honored principle in medicine that statistically significant associations in no way imply causality.

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**Table 1. Impact of hemolysis on complications in SCD**

<table>
<thead>
<tr>
<th>Hyperhemolysis</th>
<th>Less hemolysis</th>
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<tbody>
<tr>
<td>(Endothelial dysfunction)</td>
<td>(Sickling-induced vaso-occlusion)</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>Pain crisis</td>
</tr>
<tr>
<td>Leg ulcer</td>
<td>Acute chest syndrome</td>
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<tr>
<td>Priapism</td>
<td>Osteonecrosis</td>
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<tr>
<td>? Stroke</td>
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and seldom offer mechanistic insights. Furthermore, it should be noted that few direct measurements of plasma hemoglobin and none of red cell life span have been included in these clinical studies. It seems to us that this hypothesis is based on associations among large datasets with no direct evidence of causality. Causality is weighed by 4 major criteria: temporal relationship, consistency, biologic plausibility, and elimination of confounding variables.\(^{48}\) A very different, but to us equally plausible, view of the correlations noted above is that variation in the degree of hemolysis in SCD patients is secondary to confounding variables associated with development of young irreversible sickle cells,\(^{49}\) endothelial damage, chronic and acute inflammation, hypercoagulation, and others, which are more likely to be present in patients with more severe disease as manifested by more frequent complications. The fact that frequency of severe pain crises does not apparently correlate with degree of hemolysis\(^{20}\) may reflect the fact that pain crisis frequency and severity are more proportionally affected by factors independent of hemolysis that thwart the ability of erythrocytes containing sickle hemoglobin to transit through small vessels and effectively provide oxygen to surrounding tissues. Indeed, the frequency of pain crisis varies directly with the hematocrit.\(^{50}\)

**Comparison between SS disease and PNH**

For us an independent and perhaps stronger argument against the notion of the importance of NO scavenging in SCD comes from a comparison with patients who have much higher plasma hemoglobin levels. Those with PNH have intravascular hemolysis in contrast to SCD patients in whom hemolysis is primarily extravascular. Sickle cell patients virtually never have hemoglobinuria. In contrast, PNH patients commonly have hemoglobinuria with plasma hemoglobin levels at least 10-fold higher than that encountered in SCD patients. Therefore, if NO scavenging from plasma hemoglobin plays a significant role in the pathogenesis of pulmonary hypertension, leg ulcers, stroke, or priapism, these complications should be even more prominent in PNH patients than in those with SCD.

In fact, PNH patients do have clinical manifestations that are best explained by NO scavenging and that disappear when elevation of plasma hemoglobin is reversed by ecuizumab therapy, which essentially halts intravascular hemolysis.\(^{15}\) Principal among these manifestations are those related to excessive gastrointestinal smooth muscle contractility. Approximately two-thirds of PNH patients have esophageal spasm with tightness of the chest and difficulty swallowing, particularly early in the morning and during hemolytic episodes. Manometric measurements have shown that the peristaltic waves are 10 to 30 times stronger than normal. This symptom is only slightly relieved by exogenous nitrates but is completely eliminated by eculizumab. In addition, many patients with PNH have intermittent abdominal pain lasting for short periods. Some patients are nearly disabled by this and undergo unnecessary surgery in an effort to find its cause. This symptom, when not caused by intraabdominal thrombosis, is completely relieved by eculizumab. As in PNH, NO scavenging is responsible for disordered gastrointestinal motility encountered in patients receiving intravenous solutions of hemoglobin-based blood substitutes.\(^{51}\) These recipients have plasma hemoglobin levels at least 2 orders of magnitude greater than those encountered in SCD patients. In contrast to these recipients and those with PNH, symptoms due to disordered gastrointestinal motility do not occur in SCD.

NO scavenging in PNH patients is also likely to be responsible for clinical manifestations due to arterial spasm. Hill and colleagues\(^{52}\) have reported that 50% of PNH patients had evidence of pulmonary hypertension by cardiac Doppler and 47% had an elevation of N-terminal pro-brain natriuretic peptide, a useful serum marker of this complication.\(^{53}\) Approximately 25% of patients included in this study had evidence of subclinical pulmonary emboli. Eculizumab eliminated the “evidence” of pulmonary hypertension in only half the affected cases, suggesting that hemolysis-associated NO scavenging was not the sole cause of the pulmonary hypertension. In the extensive experience of one of us (W.F.R.), in more than 200 patients with PNH no patient is known to have died of pulmonary hypertension.

Erectile dysfunction (impotence) is a very common, nearly universal, symptom in men with PNH. It responds poorly to sildenafil and related drugs but completely to eculizumab. Priapism is unknown in PNH. Impotence is uncommon in men with SCD unless they suffer from priapism. Thus, disorders of penile erection differ markedly between SCD and PNH. Indeed, a recent study in a transgenic sickle mouse model suggests that priapism is more likely due to excessive accumulation of adenosine and the activation of adenosine A2B receptors in the endothelium of the corpus cavernosum of the penis and no relationship to NO was postulated.\(^{54}\)

Leg ulcers are common in SCD patients but are not encountered in PNH patients except in rare instances of dermal vein thrombosis. Again, if NO scavenging plays a significant role in pathogenesis, one would expect that, because of marked differences in plasma hemoglobin levels, leg ulcers would have an even higher prevalence in PNH than in SCD.

**Therapeutic implications**

If elevated levels of plasma hemoglobin play a critical role in the vasculopathy and survival of patients with SCD, 2 approaches to therapy make sense: treatments that decrease hemolytic rate and those that enhance either the biologic activity or the availability of NO.

In fact, the drug hydroxyurea, an inhibitor of ribonucleotide reductase, has been convincingly shown to lower hemolytic rate in sickle cell patients as documented by increased red cell survival,\(^{55,56}\) elevation of hemoglobin levels, and decreases in reticulocyte counts as well as serum LDH and nonconjugated bilirubin. Accordingly, it is expected that hydroxyurea therapy would also lower plasma hemoglobin levels to a comparable degree. Therefore, according to the NO hypothesis, treatment with hydroxyurea would be expected to lower pulmonary artery blood pressure. Indeed, such was the case in a small study of 5 SCD patients before and during therapy.\(^{57}\) The same group\(^{58}\) then found, in a larger cross-sectional study of 143 patients on hydroxyurea, that the fraction with TRVs above 2.5 m/s was no different from that among 227 patients not on hydroxyurea. Instead of accepting these results as contrary to their theory, the authors postulate that the benefit from hydroxyurea in lowering hemolysis and NO scavenging was somehow offset by a mysterious adverse effect of hydroxyurea because of elevations of Hb F and/or erythropoietin. It is hard to understand why either factor would aggravate pulmonary hypertension in the treated group. Furthermore, we do not understand why the serum erythropoietin would be higher in the treated patients who had higher hemoglobin levels and less hemolysis. In any case, noneziroid “toxic” effects of plasma erythropoietin are seen only with pharmacologic doses of recombinant erythropoietin.
therapy. Moreover, it is hard to understand how the induction of Hb F by hydroxyurea therapy would render patients hypoxic. Patients with 100% hemoglobin F due to homozygous hereditary persistence of fetal hemoglobin do not have hypoxia or pulmonary hypertension, and women with the anomaly have healthy babies. There is no apparent supporting evidence for such an adverse effect of the best drug we have for patients with SCD.

Recently, several therapeutic trials have been carried out with the aim of increasing the biologic activity of NO or its availability in SCD. Sildenafil inhibits phosphodiesterase 5 and therefore enhances the biologic effect of NO on guanylate cyclase. In 2005, oral sildenafil therapy was claimed to benefit a group of 12 SCD patients with reduction in TRV and improvement in a 6-minute walk distance.59 However, a recent large multicenter clinical trial of sildenafil therapy demonstrated no benefit and had to be stopped prematurely because the drug appeared to increase the frequency of pain crises.60

In like manner, a small pilot study of inhalational NO administration to children suffering from sickle cell pain crises suggested that treatment lowered the amount of analgesic therapy.61 However, a recent larger multi-institutional controlled trial of inhalational NO (ClinicalTrials.gov NCT00094887) has revealed no benefit in adults with acute pain crises (D. Weiner, Department of Emergency Medicine, Children’s Hospital, Boston, MA; written communication, February 2010).

As mentioned above, several studies have suggested that plasma arginine levels are low in sickle cell patients, perhaps because of the release of arginase during lysis of red cells. Accordingly, plasma arginine has been proposed as an important source of endogenous NO.19,24 However, a recent trial of oral arginine therapy in sickle cell patients has failed to show any convincing benefit.62

In interpreting these 3 recent negative clinical trials, one might argue, according to the NO hypothesis, enhancing the bioactivity or availability of NO might not ameliorate the clinical manifestations of SCD in the short-term, but that in the future alternate strategies may emerge for safely and effectively enhancing NO activity at sites of sickle vaso-occlusion. However, at this point the prospects for NO-based treatment of SCD do not look promising. We argue that one must also consider that NO levels are either not crucial or are only one of many factors that influence the pathophysiology of SCD. Certainly it is premature to try to define distinct subphenotypes of SCD solely on the basis of postulated effects of hemolysis on NO availability.

Conclusions

We acknowledge and appreciate the energy and ingenuity devoted to these studies of the impact of NO biology on SCD. However, on the basis of what has been published and recently presented at meetings, along with our experience in treating patients with SCD and studying its pathophysiology, we conclude the following:

- There is insufficient evidence from genetic or physiologic studies to define distinct clinical subphenotypes of SCD with particular constellations of symptoms or common mechanisms.
- A significant subset of SCD patients have pulmonary hypertension, but it is usually minor, and confounded by several comorbid conditions including high cardiac output, pulmonary vascular inflammation and occlusion (thrombosis in situ, fat embolism), and left ventricular failure.
- Pulmonary hypertension per se does not appear to be a major cause of death in sickle cell patients.
- Therapies that might enhance the availability of NO to the vasculature have thus far been ineffective and/or toxic. Further studies must be pursued with caution.
- NO scavenging by elevated plasma hemoglobin is unlikely to be a major determinant of complications or life expectancy in sickle cell patients.
- The specter of worsening pulmonary hypertension by hydroxyurea-induced Hb F elevation has not been convincingly documented.

Medical science and certainly medical practice often depend on association studies but association in science can be very risky in deducing causality especially when weak clinical observations are linked to multiple laboratory assessments. P values rarely establish new biologic relationships or clinical principles. Hence, results can be statistically, but not biologically or clinically, significant.

Acknowledgment

We thank Alan N. Schechter for helpful discussions and comments on the manuscript.

Authorship

Contribution: H.F.B. wrote the first draft; D.G.N., G.J.D., R.P.H., O.S.P., W.F.R., and R.E.W. all made extensive revisions; and D.G.N. and H.F.B. coordinated the revisions and prepared the final draft.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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