

## Sickle Cell Disease and Anesthesia

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The hazards of surgery in these patients are not always those which are attendant on conditions suggesting emergency surgery. . . The presence of the basic disease increases the hazard of surgery, and of course, of anesthesia. —In ANESTHESIOLOGY, 1955.<sup>1</sup>

IN October 1902, a “peculiar anomaly in human red blood corpuscles. . . came to notice in the histologic laboratory of the Ohio State University,” Columbus, Ohio. “Examination disclosed the fact that the colored corpuscles in the sample recently drawn by (a) student from his own finger that were elliptical and not circular.”<sup>2</sup> Similar erythrocyte abnormalities were reported in North African Arab subjects shortly afterwards.<sup>3</sup> In November 1910 James B Herrick, M.D. (Professor Of Medicine, Rush Medical College, Chicago, Illinois; 1861–1954) published a detailed case report. This described a patient with jaundice, shortness of breath, lymphadenopathy, dark urine, leg ulcers, epigastria pain, and anemia associated with these same types of “peculiar elongated and sickle-shaped red blood corpuscles.”<sup>4</sup> This classic report was the first unequivocal clinical description in Western scientific literature of sickle cell disease (SCD), a set of closely related hemoglobinopathies that have in common the inheritance of mutant hemoglobin S (fig. 1).

Clinically, SCD is characterized by chronic hemolytic anemia, recurrent episodes of intermittent vasoocclusion and severe pain, progressive organ damage, and a striking variation of expression. In 1927, Hahn and Gillespie noted that the eponymous<sup>5</sup> deformation or sickling of the erythrocytes was induced by deoxygenation and reversed with reoxygenation.<sup>6</sup> The clinical segue was a hypothesis that vasoocclusion was triggered by delayed passage of erythrocytes through the micro-

circulation, leading to a “vicious cycle” of increased sickling, mechanical obstruction to flow, further sickling, vasoocclusion, and infarction.<sup>7</sup> In 1955, the first major review of the anesthetic implications of SCD acknowledged the high incidence of serious and potentially fatal exacerbations of the disease after surgical procedures.<sup>1</sup> The avoidance of factors said to increase erythrocyte sickling and precipitate the vicious cycle<sup>7</sup> has been the traditional foundation of anesthetic management of SCD. The century after the discovery of the peculiar anomaly<sup>2</sup> has seen an immense expansion in the understanding of the complex relationship between these peculiar erythrocytes<sup>4</sup> and the clinical expression of the disease. This article briefly summarizes advances made in understanding of the disease pathophysiology, describes salient clinical features relevant to the anesthesiologist, and reviews data from the perioperative period, emphasizing a new anesthetic approach to this old problem.

### Epidemiology

Sickle cell disease is a hereditary hemoglobinopathy resulting from inheritance of a mutant version of the  $\beta$ -globin gene ( $\beta^A$ ) on chromosome 11, the gene that codes for assembly of the  $\beta$ -globin chains of the protein hemoglobin A. The mutant  $\beta$ -allele ( $\beta^S$ ) codes for the production of the variant hemoglobin, hemoglobin S. The heterozygous carrier state, known as sickle cell trait (SCT), results in production of both hemoglobin A and S and has a predominantly benign clinical picture. Polymorphic restriction endonuclease sites in and around the mutant sickle gene are known as haplotypes. At least four haplotypes of the  $\beta^S$ -allele have been identified in Africa, and a fifth Arabo-Indian or Asian haplotype has been reported in India and the Persian Gulf region.<sup>8–10</sup> The existence of different haplotypes specific to different regions of the world suggests that the sickle gene mutation occurred on multiple occasions in equatorial Africa and south-western Asia.<sup>11–13</sup> As a result of global population shifts, the disease now has worldwide distribution. Large-scale screening of American military conscripts found an incidence of SCD of 0.2% in black recruits and a prevalence of SCT of 8% in black and 0.05–0.08% in nonblack recruits.<sup>14–16</sup> The high inci-

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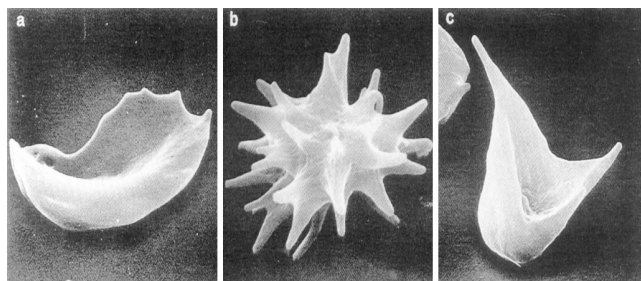


Fig. 1. Deoxygenated sickle cells: a peculiar anomaly in human erythrocytes. Reproduced with permission from: *Sickle Cell Disease: Basic Principles and Clinical Practice*, 1st edition. Edited by Embury SH, Hebble RP, Mohandas N, Steinberg MH. Raven Press, New York, 1994.

dence of the mutant allele in the gene pool has been suggested to be a result of the historical survival advantage heterozygotes have had over hematologically normal individuals when infected by the malarial parasite *Plasmodium falciparum*.<sup>17</sup>

### Genetics

With the exception of early embryonic hemoglobins, hemoglobin consists of two alpha and two nonalpha polypeptide chains, attached to four iron-containing heme complexes.<sup>18</sup> Production of the alpha chains is coded by four alleles, paired on chromosome 16, whereas nonalpha chains are synthesized under the control of two alleles located in the  $\beta$ -gene cluster on chromosome 11. The  $\beta$ -gene cluster is a sequence of genes that encode for the differing nonalpha globin polypeptides of the various hemoglobin types. These chains include epsilon (embryonic hemoglobins), gamma (fetal hemoglobin F), beta (hemoglobin A), and delta (hemoglobin A<sub>2</sub>) chains. The sickle cell gene mutation is a point mutation in the sixth codon of exon 1 in the  $\beta^A$  gene, replacing adenine with thymine (guanine-adenine-guanine  $\rightarrow$  guanine-thymine-guanine).<sup>19</sup> Hemoglobin S therefore differs from normal adult hemoglobin A in the structure of the  $\beta$ -chains.

**Inheritance.** Sickle cell disease can arise from a variety of closely related genotypes. The alleles encoding the  $\beta$ -globin chain display codominant transcription and translation and are inherited following Mendelian laws.<sup>20</sup> The classic, and the most widespread, genotype of SCD is the homozygous state of the mutant allele ( $\beta^S \beta^S$ ), coding exclusively for hemoglobin S production. Heterozygous genotypes coding for hemoglobin S together with other hemoglobin variants or alterations in the regulation of the beta gene expression may result in symptoms of SCD. The most common heterozygous SCD genotypes are sickle cell-hemoglobin C disease (hemoglobin SC -  $\beta^S \beta^C$  Lys) and sickle cell- $\beta$  thalassemia (hemoglobin S $\beta$ ). Roughly 70% of the American SCD population is homozygous for  $\beta^S$ , whereas sickle cell C disease (approximately 20%) and sickle- $\beta$  thalassemia (10%) heterozygotes make up the remainder.<sup>21</sup> Hemoglobin C ( $\beta^C$

glutamic acid $\rightarrow$ lysine), a variant of hemoglobin A common in the African-American population,<sup>22</sup> does not afford the protective clinical effect of hemoglobin A against hemoglobin S.  $\beta$ -thalassemias are a closely related group of hemoglobinopathies arising from a variety of mutations in the effector genes that regulate the expression of the  $\beta$ -gene. These mutations result in absent ( $\beta^0$ -thalassemia) or impaired ( $\beta^+$ -thalassemia) expression of the affected beta allele. Heterozygotes for the  $\beta^S$ -allele and a thalassemia mutation ( $\beta^S \beta^0$ ,  $\beta^S \beta^+$ ) thus have decreased or absent production of hemoglobin A combined with expression of hemoglobin S, leading to symptoms of SCD. Other symptomatic but rare genotypes include sickle cell/hemoglobin D-Punjab (or Los Angeles) ( $\beta^S \beta^{121 \text{ Gln}}$ ), sickle cell/hemoglobin O-Arab ( $\beta^{S121 \text{ Lys}}$ ), and sickle cell/hemoglobin Lepore-Boston ( $\beta^{S\alpha\chi\beta}$ ) diseases.

**Gene Penetration.** The clinical picture of SCD is remarkable for the striking heterogeneity in presentation, progression, and severity. Heterogeneity for the  $\beta$ -allele has the greatest impact on phenotypic expression. As noted, the hemoglobin SA carrier state of SCT is largely asymptomatic. Rare complications include increased susceptibility to heat exhaustion, splenic infarction at altitude or after exercise, and, possibly, an increased incidence of renal tumors. Sickle cell C disease tends to have a milder phenotypic expression than the homozygous SCD because of the ameliorating presence of hemoglobin C. Sickle- $\beta^+$  thalassemia is symptomatic, consequent on impaired production of hemoglobin A, but has a more benign course than the homozygous  $\beta^S \beta^S$  genotype.<sup>21,23,24</sup> The clinical course of sickle  $\beta^0$  thalassemia is comparable to that of the homozygous  $\beta^S \beta^S$  genotype, as minimal or no hemoglobin A is produced.

Although part of the variability of SCD is explained by differing  $\beta$ -alleles, there is remarkable diversity in phenotypic expression within the individual genotypes. Approximately 30% of homozygous S patients have a rapidly progressive disorder leading to widespread vascular damage, early organ failure, and death, 60% have a less devastating clinical course, whereas 10% remain relatively well for much of their life.<sup>25</sup> The synthesis of the hemoglobin tetramer is a multi-step process regulated by numerous genes. The timing, extent, and coordination of gene expression are under tight polygenetic control. Variation in these regulatory genes accounts for some of the variability seen in SCD. Identified genetic factors that alter the phenotypic impact of hemoglobin S include the expression of hemoglobin F, haplotype variation, and the coinheritance of  $\alpha$ -thalassemia.

The markedly increased but extremely variable production of hemoglobin F significantly affects the clinical effects of hemoglobin S. Production of fetal hemoglobin after infancy typically stabilizes at approximately 1% of the total hemoglobin in the general population. In contrast, the African haplotypes commonly express fetal

hemoglobin concentrations of up to 15%, and typical production by the Asian haplotype is even higher at 8–30%.<sup>26</sup> Higher intracellular hemoglobin F concentrations ameliorate the pathologic impact of hemoglobin S on the erythrocyte and are associated with a protective clinical effect.<sup>13,21,24</sup> There are also differences between the haplotypes in the polypeptide sequence of the hemoglobin F  $\gamma$ -chains. An association between the variance in fetal hemoglobin concentrations, the proportion of  $A\gamma$  to  $G\gamma$  polypeptide chains making up hemoglobin F, and the differing haplotypes can explain part of the interhaplotype variation in phenotypic expression.<sup>8,20,25</sup> Compared to the Arab-Indian and African Senegal haplotypes, for example, the African Benin and Central African Republic haplotypes have a higher frequency of organ damage, lower hemoglobin F concentrations, and a preponderance of  $A\gamma$  chains.<sup>8,25</sup> It is unclear whether the identified haplotypes of the  $\beta^S$ -gene directly affect production of fetal hemoglobin or whether they are simply markers of variation in other regulatory genes.

$\alpha$ -thalassemia is a genetic hemoglobinopathy produced by the deletion of one or more of the four genes encoding for the  $\alpha$ -chains.  $\alpha$ -thalassemia-2, characterized by the loss of one gene from each allele, has a high incidence in the SCD population. Coinheritance decreases hemolysis and cell turnover. This is associated with less soft tissue damage and resultant mortality but increased osteonecrosis and bone pain.<sup>24,27</sup>

Although differences in hemoglobin expression can explain part of the variability seen in the disease, there is greater diversity in clinical expression within these groups than between them.<sup>25</sup> The inability to fully explain clinical variance based simply on hemoglobin variance points to the impact of other pleiotropic genes that control secondary pathophysiological events beyond the level of hemoglobin regulation. Polymorphisms at the cellular or physiologic levels, such as the erythrocyte membrane structure and function, erythrocyte adhesiveness, hemoglobin scavenger proteins, heme catabolizing enzymes, nitric oxide generating systems, and assorted inflammatory mediators, undoubtedly modify disease severity.<sup>28,29</sup> The simplicity of the primary genetic defect therefore belies the complexity of the resultant pathophysiology.

### Molecular Biology

The isolated genetic point mutation supplanting adenine with thymine produces a consequent isolated substitution of the amino acid dictated by the new codon. The resultant hemoglobin variant S is distinguished from the normal A by the replacement of the negatively-charged hydrophilic glutamic acid with the nonpolar hydrophobic valine at position six on the 146 amino acid  $\beta$ -chain<sup>30,31</sup> (fig. 2). As a “molecular disease”—a disease originating from a single abnormal molecule—the erythrocyte abnormalities and protean symptoms of SCD must

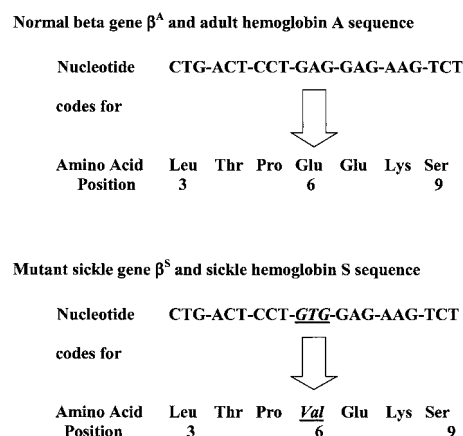


Fig. 2. Normal and sickle mutant gene and amino acid sequences. The point mutation substituting thymine for adenine results in the insertion of neutrally charged valine at position six on the  $\beta$ -globin chain. Nucleotides: A = adenine; C = cytosine; G = guanine; T = thymine. Amino acids: glu = glutamic acid; leu = leucine; lys = lysine; pro = proline; ser = serine; thr = threonine; val = valine.

arise ultimately from the atypical characteristics of hemoglobin S consequent on this solitary change.<sup>32</sup> The loss of the electrical charge by the amino acid substitution has two results of particular clinical significance. First, the absence of the negative charge significantly destabilizes the structure of oxygenated hemoglobin, resulting in accelerated denaturation and breakdown.<sup>33,34</sup> Second, the nonpolar hydrophobic substitute causes a dramatic decrease in the solubility of deoxygenated hemoglobin.<sup>35</sup> The conformational changes of deoxygenation result in a hydrophobic bond forming between the  $\beta^S$ -6 valine of one tetramer and the  $\beta$ -85 phenylalanine and  $\beta$ -88 leucine of an adjacent tetramer, thus generating a nidus of polymerized hemoglobin S. Further aggregation of deoxygenated hemoglobin tetramers forms long helical strands of polymers. Progression of this process generates a critical nucleus to which additional tetramers bind. Polymerization then proceeds in an explosive autocatalytic fashion, causing the hemoglobin to gelate or precipitate out of solution. These two features of hemoglobin S, instability and insolubility, account for the majority of cellular and clinical pathology<sup>28</sup> (fig. 3).

### Biochemistry

The instability of hemoglobin S exposes the erythrocyte cell membrane to the destructive oxidant potential of intracellular iron.<sup>36</sup> Under normal circumstances, the dangers of oxygen and iron are nullified primarily by the structure of hemoglobin. Iron-containing heme is contained within a hydrophobic globin pocket that constrains the reactivity of iron by shielding the heme from most external solutes. Consequently, heme tends to bind reversibly with oxygen in the ferrous ( $Fe^{2+}$ ) state rather than the ferric ( $Fe^{3+}$ ) state. In addition, the heme is



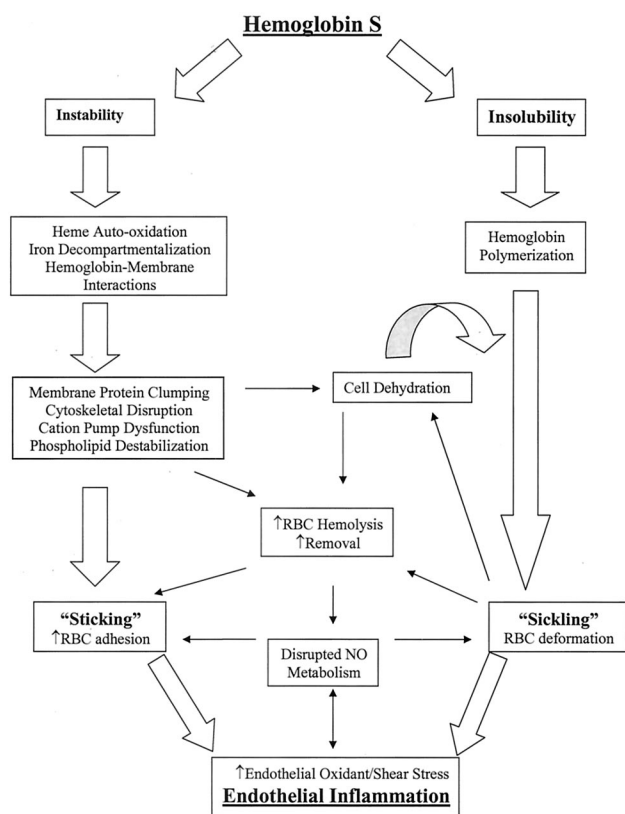


Fig. 3. Cellular consequences of Hemoglobin S. Hemoglobin S is both unstable and insoluble as a result of the loss of the negative charge. The two features act in concert to disrupt the erythrocyte and the surrounding environment.

compartmentalized by a globin coat that separates the iron from potential targets of oxidant damage in the cytosol or membrane.<sup>37</sup> Both these defense mechanisms (checks on the reactivity with oxygen and the separation of heme from targets of oxidant damage) are interrupted by the instability of hemoglobin S.<sup>38</sup> The loss of hemoglobin structural stability increases the rate of globin denaturation and deterioration of the protective hydrophobic shield, increasing oxidation of heme to methemoglobin, the ferric state of heme.<sup>39</sup> Greater iron auto-oxidation in sickled erythrocytes generates superoxide ( $\cdot\text{O}_2^-$ ) and hydrogen peroxide ( $\text{H}_2\text{O}_2^-$ ), leading to the formation of the highly reactive hydroxyl radical ( $\cdot\text{OH}$ ) at approximately double the rate of normal hemoglobin A-containing erythrocytes.<sup>40</sup> Decompartmentalization of iron by globin breakdown provides a synergistic effect, releasing free iron and heme compounds from the protective embrace of globin, thus exposing the cell directly to the deleterious effects of increased oxidant production. Free iron and iron-containing compounds accumulate in the cell membrane, partly because of abnormal interaction between hemoglobin S and membrane phospholipids and proteins. Endogenous oxidant stress is consequently targeted directly to sickle cell membrane structures. Increased membrane-iron compounds result in denaturation and aberrant clustering of membrane

surface proteins, abnormal cation permeability, and the disruption of normal phospholipid membrane asymmetry. The loss of the stabilizing  $\beta 6$  amino acid charge in hemoglobin S therefore disrupts the erythrocyte's globin defenses against the oxidant perils of large quantities of intracellular iron present in the heme.<sup>28,36-40</sup>

Increased cell membrane iron disrupts the transmembrane ion transport pathways, leading to pathologic cell dehydration. Cellular dehydration is essential for the deformation or sickling of the deoxygenated erythrocyte.<sup>28,35</sup> Sickling is caused by widespread polymerization and gelation of hemoglobin S after deoxygenation (fig. 3). Because gelation does not occur instantaneously on deoxygenation, sickling occurs after a delay time required for sufficient intracellular polymerization to deform the cell. The delay time of most cells is greater than the circulation time required to return to the pulmonary capillaries and reoxygenate. Typically, approximately 10% of erythrocytes sickle reversibly, and a further 10% circulate in an irreversibly sickled state.<sup>35</sup> Delay time is extremely sensitive to intracellular hemoglobin concentration because the progress of aggregation and precipitation from solution is catalyzed by the formation of the polymer nuclei that exponentially accelerate gelation. Severe cell dehydration, present in older cells, is required to increase hemoglobin concentration and decrease the delay time to within a single systemic circulation time. Reversible cell sickling exacerbates the process of dehydration, resulting in irreversibly sickled cells that remain deformed throughout the circulation. Sickling is therefore consequent not only on the insolubility of deoxy-hemoglobin S but also on cellular dehydration arising from previous membrane damage secondary to hemoglobin S instability.

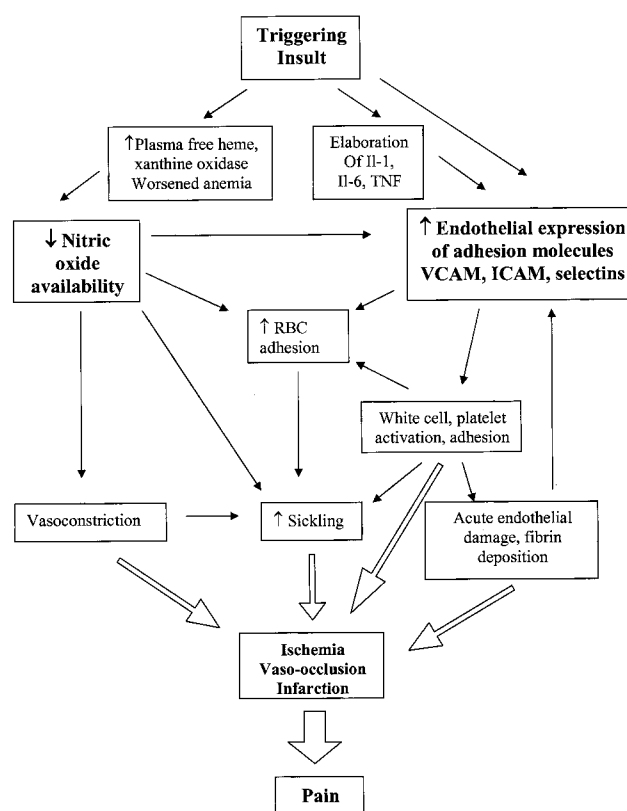
Disruption of the erythrocyte cell membrane results in increased adherence of rigid, iron-laden erythrocytes to the vascular endothelium, exposing the endothelium to increased shear and oxidant stress. Adherence is mediated predominantly by a wide variety of adhesion molecules expressed by the erythrocytes and endothelial cells.<sup>41,42</sup> In addition, structural membrane changes diminish erythrocyte deformity and increase fragility, shortening red cell lifespan, hastening erythrocyte turnover, and increasing the proportion of reticulocytes. This young erythrocyte group expresses increased amounts of adhesive proteins compared with the overall erythrocyte population. High erythrocyte turnover therefore combines with the direct effects of cell membrane changes to produce abnormally adhesive cells. This heightens mechanical and oxidant stress on the vascular endothelium.

Persistent endothelial stress produces chronic vascular inflammation. Evidence suggestive of continuing endothelial inflammation includes up-regulation of endothelial cell adhesion molecules, altered expression of endo-

thelial nitric oxide synthetase, increased baseline leukocyte count, activated coagulation pathways, increased cytokines, and increased numbers of circulating activated endothelial cells in the plasma.<sup>42,43</sup> The vascular endothelium plays a central role as the master regulator of vascular tone, coagulation, fibrinolysis, inflammation, lipid transport, and permeability.<sup>44,45</sup> More long-term functions regulated by the endothelium include the control of intimal growth and vascular architecture. Damage to the endothelium or disruption of normal functioning therefore has widespread consequences for vascular homeostasis.

An additional source of endothelium functional disruption is impairment of nitric oxide (NO) signaling pathways. NO is a key modulator of vasodilation, vascular wall modeling, endothelial activation, platelet aggregation, leukocyte adhesion, and hemoglobin polymerization.<sup>46</sup> NO is thought to be delivered from the pulmonary vascular bed to peripheral microvasculature bound to intracellular hemoglobin as S-nitroso-hemoglobin.<sup>47</sup> Decrease in peripheral oxygen tension causes an allosteric structural transformation of hemoglobin, triggering release of bioavailable NO. However, extracellular oxygenated hemoglobin binds avidly to NO, converting NO to nitrate, whereas free deoxy-hemoglobin binds NO strongly as heme-nitrosyl-hemoglobin.<sup>29,48,49</sup> In a fashion similar to the regulation of oxygen binding, compartmentalization of hemoglobin is essential to constrain and control the reactivity of hemoglobin. Confinement of hemoglobin within the red cell sequesters hemoglobin from NO, diminishing the binding of NO by diffusion limitation while allowing for the release of NO by the conformational shift. Cell-free plasma hemoglobin therefore scavenges and inactivates NO, whereas intracellular hemoglobin packages and stabilizes NO for delivery. In SCD, the balance between these antagonistic properties is disrupted. The aggravated intravascular hemolysis of sickle erythrocytes increases free plasma heme complexes, scavenging NO and diminishing bioavailability. Anemia and diminished erythrocyte mass limits the quantity of intracellular hemoglobin available for physiologic transport of NO to the tissues. Although the precise significance and degree of NO physiologic disturbance in SCD remains incompletely understood, decreased NO bioavailability probably plays a key role in the development and exacerbation of endothelial inflammation and dysfunction.<sup>29,47-49,50,51</sup>

The biochemical consequences of hemoglobin S therefore extend well beyond the structure or shape of the erythrocyte. The entire vascular milieu of the sickle erythrocyte is drastically altered. It is these widespread and diverse biochemical changes, rather than simply isolated alterations in erythrocyte characteristics, that produce the clinical features of SCD.



**Fig. 4. Pathophysiological model of vasoocclusive crisis.** Vasoocclusion arises from acute disruptions to the chronically disturbed erythrocyte environment. Activation of the endothelium is modulated by elaboration of interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor (TNF). This leads to endothelial expression of molecules such as Vascular Cell Adhesion Molecule 1 (VCAM), Intercellular Adhesion Molecule 1 (ICAM), P-selectin, and E-selectin. Interruption to the balance of vasodilation and vasoconstriction, combined with changes in the procoagulant and anticoagulant equilibrium, trigger vascular stasis. Erythrocytes are trapped in the microcirculation, deoxygenate, and sickle, worsening ischemia and infarction. Ischemia and infarction are generally accepted as key precipitants of pain crises.

### Vasoocclusion

The clinical hallmark of SCD is intermittent, recurrent, acute episodes of severe pain, known as vasoocclusive crises (VOC) or pain crises. It is generally accepted that ongoing acute ischemia, vasoocclusion, and infarction are the central causes of pain, although nociceptive pathways and changes have not been extensively studied. Although the precise pathophysiology of VOC is incompletely characterized, acute changes in the endothelial regulation of flow and hemostasis are thought to be the key steps in the initiation and progression of vasoocclusion (fig. 4).

Activation of the vascular endothelium involves the increased endothelial expression of adhesion molecules, stimulating the binding of neutrophils and the release of proteolytic enzymes.<sup>41,42,51</sup> Endothelial activation is triggered by insults such as infection, surgical stress, or, possibly, subclinical episodes of recurrent microvascular

ischemia-reperfusion.<sup>52</sup> Endothelial activation may be induced directly or *via* the elaboration of inflammatory cytokines and mediators by monocytes and macrophages. Platelet activation and aggregation, as well as fibrin deposition on areas of endothelial damage, may be additional early pathophysiological mechanisms during the development of VOC. Expression of adhesion molecules increases erythrocyte endothelial adhesion (and possibly impairs flow) sufficiently to allow microvascular sickling. The triggering event therefore impacts primarily on the endothelium, shifting the procoagulant and anticoagulant balance of the circulation towards hemostasis. The abnormal response to stressors seen in SCD is the result of the acute exacerbations of chronically deranged endothelial biology and physiology.

An alternative initiation route of vasoocclusion may follow impairment of the usual counterregulatory balances that inhibit endothelial activation and up-regulation of adhesive molecules. Increased hemolysis, such as occurs after a hemolytic transfusion reaction or during infection, may acutely increase NO scavenging by free heme and decrease the bioavailability of NO to the endothelium.<sup>29,47</sup> The release of xanthine oxidase from the liver into the circulation has also been suggested as a trigger mechanism of vasoocclusion.<sup>49</sup> Xanthine oxidase binds avidly to vessel luminal walls, and catalytically consumes NO *via* superoxide-dependant pathways, exacerbating the lack of bioactive NO. This might diminish the inhibitory effects of NO on the endothelial expression of adhesion molecules, leukocyte adhesion, and platelet activation. In addition, disrupted NO transport impairs endothelial balance of vasodilation and constriction, leading to vasoconstriction and tissue ischemia. Severe impediments to microvascular flow may ultimately result in the trapping of erythrocyte in the microcirculation, sickling, further vascular obstruction, continuing ischemia, and infarction.

The VOC is therefore an intricate pathophysiological process thought to involve vasoconstriction, leukocyte adhesion and migration, platelet activation and adhesion, and coagulation. The considerable weight of evidence indicating the central role of endothelial and vascular dysfunction arises not only from the extensive biochemical, animal, and clinical data on SCD but also from related data on the role of inflammation in other vascular disorders such as unstable coronary angina and atherosclerosis.<sup>53,54</sup> Although the precise significance and interaction of these various mechanisms remains to be defined, VOC is clearly more than a simple case of "log jamming" of the microvasculature by sickled cells.

Given the historical emphasis on the hypothesis of erythrocyte sickling as the dominant initiating event of VOC, the details of some longstanding clinical observations on the effect of hypoxia are of particular interest to the anesthesiologist. During a study of the effects of hypobaric hypoxia on American airmen with SCT pub-

lished in 1946 a volunteer with a clinical diagnosis of SCD was exposed to decompression to 411 mm Hg for 30 min.<sup>55</sup> Despite a reported arterial oxygen saturation of 74%, the subject tolerated the hypoxemia "even better than . . . control subjects." Following on this observation, another study reported in 1958 on oxygen transport physiology in SCD, using 17 subjects with sickle diagnosis confirmed by electrophoresis.<sup>56</sup> The subjects inhaled hypoxic gas mixtures ranging from 8.9 to 16% of inspired oxygen for 30 min. Prolonged induced hypoxemia of  $33.1 \pm 6.9$  mm Hg (mean  $\pm$  SD) arterial oxygen tension, with arterial hemoglobin oxygen saturation of  $62.4 \pm 3.5\%$  "resulted in no discernible acute or chronic symptomatology." More recently, three series described a total of 37 cases of occlusive orthopedic tourniquet use for patients with SCD.<sup>57–59</sup> There were no cases of ACS and only one episode of bony pain,<sup>59</sup> with a causal relationship to tourniquet use not established. Prolonged survival with coexistent SCD and cyanotic heart disease has been reported,<sup>60–64</sup> whereas people with the end stages of sickle cell lung disease survive with chronic baseline hypoxemia.<sup>56,65,66</sup> Severe global and regional hypoxia, and presumably by extension increased erythrocyte sickling, does not therefore invariably produce a pain crisis.

In contrast, ascents to altitude and prolonged aircraft flights of several hours' duration are well-documented triggers of acute SCD-specific complications.<sup>67–71</sup> Prolonged exposure to acute moderate hypoxia therefore appears to induce symptoms. Ascent to altitude imposes an adaptive pressure on the body's oxygen-delivery systems. The vascular endothelium, which regulates blood flow, is a central component of the oxygen delivery chain. Pathology induced by high altitude arises when the degree of hypoxic stress exceeds the body's adaptive capacity. Endothelial dysfunction is thought to be the origin of high-altitude pulmonary and cerebral edema, as well as acute mountain sickness.<sup>72</sup> Ascent to altitude may therefore place an adaptive strain on the vascular endothelium, an interface in SCD that may be vulnerable to inflammatory damage during hypoxic stress.<sup>43,52</sup> A speculative explanation for these paradoxical clinical observations would therefore support the concept that changes in the erythrocyte environment, rather than simply an isolated acute increase in erythrocyte sickling, are needed to trigger acute symptoms.

### *Clinical Features*

The clinical picture of SCD is one of evolving organ damage punctuated by intermittent periods of severe pain and pulmonary complications. The severity and progression of the disease is remarkably varied, with some patients experiencing a relatively indolent course and others suffering early organ dysfunction and death (table 1). Pulmonary and neurologic disease are the leading causes of morbidity and mortality.<sup>21</sup> Chronic renal

**Table 1. Clinical Features of Sickle Cell Disease**

Complication	Features
Neurological	
Pain crisis	Occurs in >70% of patients
Stroke	10% of children; subclinical microvascular occlusion in ≈20%. Cause of >20% deaths.
Proliferative retinopathy	50% of SC adults; rare in SS homozygotes
Peripheral neuropathy	Unusual complication
Chronic pain syndrome	A small subset of patients
Pulmonary	
Acute Chest Syndrome	Occurs in 40% of patients; mortality rate of 1.1% for children and 4.8% for adults.
Airway hyperreactivity	35% of children
Restrictive lung disease	10–15% of patients
Genitourinary	
Hyposthenuria	Nocturnal enuresis not a sensitive predictor
Chronic renal insufficiency	Present in 5–20% of adults
Urinary tract infection	Increased incidence; may trigger ACS
Priapism	10–40% of men
Pregnancy	Probable increased incidence of obstetrical complications, increased incidence of VOC
Gastrointestinal	
Cholelithiasis	Up to 70% of adults
Liver disease	Viral hepatitis from transfusion in up to 10% of adults. Liver failure <2%.
Dyspepsia	Mucosal ischemia, rather than increased acid production, is thought to be the cause. Reflux is not a complication of SCD.
Hematological	
Hemolytic anemia	Typical baseline hemoglobin levels are 6–9 g/dl in SS disease, higher in SC disease and Arab phenotype.
Acute aplastic anemia	Parvovirus B19 infections trigger acute severe exacerbations of anemia
Splenic enlargement/fibrosis	Less affected: SC disease, Arab haplotype
Orthopedic	
Osteonecrosis	Up to 50% of adults
Osteomyelitis	Salmonella and <i>Staphylococcus aureus</i> are commonest pathogens.
Dactylitis	Early onset is a marker of disease severity
Vascular	
Leg ulcers	20% of SS adults; rare in SC disease
Immunological	
Immune dysfunction	Increased susceptibility to infections
Erythrocyte auto/alloimmunization	Increased incidence of transfusion
Hemolytic transfusion reactions	Alloimmunization

ACS = acute chest syndrome; SCD = sickle cell disease; SS = patients homozygous for hemoglobin S; VOC = vasoocclusive crisis.

failure is an additional significant cause of morbidity and early mortality. Many deaths are not attributable to overt chronic organ failure but occur during an acute episode of pain, respiratory compromise, stroke, or a combination of these events.

Pain crises or VOC can loosely be defined as an acute episode of pain not attributable to pathology other than SCD. A study of 183 crises in 118 patients noted that the lumbar spine (49%), abdomen (32%), femoral shaft (30%), and knee (21%) were the most common sites of bone pain.<sup>73</sup> Bone pain was often present in multiple areas and was symmetrically distributed. More than half of VOC occurred in the absence of identifiable triggering events. Patients perceived skin cooling (34%), emotional stress (10%), physical exertion (7%), and alcohol consumption (4%) as triggers of the remaining episodes. Bone pain is thought to arise from cortical infarction or from marrow infarction that produces cortical pressure as a result of inflammation and edema.<sup>74,75</sup> Abdominal pain, commonly associated with abdominal distention, may arise from bowel dysfunction, organ infarction, or be referred from the ribs. The average rate of VOC in the

SS genotype is 0.8 per patient-year; people having SC and  $S\beta^+$ -thalassemia genotypes have lower incidences of pain than those having SS and  $S\beta^0$ -thalassemia genotypes.<sup>24</sup> Although 1% of patients have more than six episodes a year, 39% have none.

The acute chest syndrome (ACS), an acute pneumonia-like complication of SCD, is defined on the basis of the finding of a new pulmonary infiltrate involving at least one complete lung segment on chest radiograph, consistent with alveolar consolidation, but excluding atelectasis. An additional diagnostic feature includes chest pain, pyrexia greater than 38.5°C, tachypnea, wheezing, or cough.<sup>76–78</sup> Precipitants include a variety of infectious pathogens, fat embolism after bone marrow infarction, pulmonary infarction and surgical procedures. The typical duration of hospitalization for ACS in the United States is 11 days.

In addition to ACS, SCD causes chronic progressive lung damage. This disease state may be a persistent inflammatory process, expressing initially as lower airway obstruction and airway hyperreactivity in children and adolescents and evolving to fibrosis and a progres-



sive restrictive defect in later stages.<sup>79</sup> Progressive vasculopathy, decreased vital capacity and total lung capacity, decreased membrane diffusing capacity, pulmonary hypertension, and right-sided cardiac hypertrophy develop with end-stage restrictive disease, pulmonary fibrosis, and severe hypoxemia.<sup>65,80</sup> Progression of lung disease is associated with, and is probably hastened by, recurrent attacks of ACS.

Stroke, a devastating complication of SCD, may be infarctive or hemorrhagic in origin.<sup>81</sup> Hemorrhagic stroke is most frequently seen in the third decade of life, whereas infarctive stroke tends to occur in adolescence or in later adult life. Hemorrhage may arise from ruptured of chronically damaged and weakened arteries,<sup>82</sup> whereas infarction may be secondary to intimal hyperplasia and progressive occlusion of large and small arteries.<sup>83</sup> Stroke is therefore typically consequent on arterial disease rather than arising primarily from venous sickling and thrombosis. Strokes may also be precipitated by ACS, possibly by acute hypoxemia or fat embolism.<sup>77,78</sup>

Nephropathies attributable to SCD include glomerular disease and papillary necrosis.<sup>84</sup> Papillary necrosis commonly presents as painful gross hematuria, whereas glomerular lesions present with varying degrees of hematuria and proteinuria. Hyposthenuria, the inability to concentrate urine to a specific gravity greater than 1.010, is the first clinical expression of defective medullary tonicity. Vasopressin generation and urinary diluting capacity is unchanged. Glomerular filtration rate is increased in children but decreases during adolescence and adulthood. Proteinuria, which may be indicative of progressive glomerulopathy, develops in 20–30% of adults. The most common glomerular changes are glomerulomegaly with hypercellularity and glomerulosclerosis. Chronic renal failure, usually secondary to glomerulosclerosis, typically develops during the third or fourth decade of life.

### *Perioperative Epidemiology*

Although sickle cell trait does not cause a marked increase in perioperative morbidity or mortality,<sup>85,86</sup> SCD patients have a high incidence of perioperative problems. Perioperative complications can be specific to SCD or nonspecific. SCD-specific complications, or “sickle events,” include pain crisis and ACS and occur with a high frequency in the perioperative period. Complications related to SCD include an increased incidence of erythrocyte alloimmunization and transfusion reactions consequent on perioperative transfusion. Nonspecific complications include fever, infection, bleeding, thrombosis, embolism, and death from causes other than SCD. Opinion is divided as to whether SCD patients are at greater risk of developing these nonspecific complications than the general population.<sup>87,88</sup>

**Table 2. Predictors of Postoperative Complications**

Predictors of Postoperative SCD complications
<ul style="list-style-type: none"> <li>• Type of surgical procedure—Low, moderate or high risk</li> <li>• Increased age—Associated with disease progression</li> <li>• Frequency of recent complications—Current activity of disease state</li> <li>• Hospitalization—Marker of disease severity</li> <li>• Temporal clustering of ACS—Progression of lung disease</li> <li>• Abnormal lung fields on radiograph—Evidence of sickle chronic lung disease</li> <li>• Pregnancy—Increased risk of maternal complications</li> <li>• Pre-existing infection—Triggering agent for ACS</li> <li>• Haplotype—African haplotypes have more severe disease than the Asian haplotype</li> </ul>

Low-risk surgical procedures include minor procedures such as inguinal hernia repair or extremity surgeries. Moderate risk procedures include more invasive interventions such as intra-abdominal operations, while high-risk events include intracranial and intrathoracic procedures.

ACS = acute chest syndrome; SCD = sickle cell disease.

### *Preoperative Assessment*

Preoperative assessment should aim to determine the risk of perioperative SCD complications and organ dysfunction with the intention of preventing or anticipating these problems. Each individual's risk is related to the interaction of numerous variables including type of operative procedure, disease activity, patient details, and organ dysfunction consequent on disease progression (table 2). Attention should therefore be directed to recent acute exacerbations of the disease, as well as to chronic organ damage as a result of disease progression.

There is a wide variation in the incidence of SCD events after different surgical procedures. In 1995 Koshy *et al.* published a decade-long retrospective review of 1079 procedures.<sup>87</sup> This found that cholecystectomy, splenectomy, dilation and curettage, caesarean section, hysterectomy, tonsillectomy and adenoidectomy, myringotomy, and orthopedic prosthetic surgery were the most frequently performed procedures. The rates of SCD events in patients with SS disease were 0% for tonsillectomy and adenoidectomy, 2.9% for hip surgery, 3.9% for myringotomy, 7.8% for nonobstetrical intraabdominal surgery, 16.9% for caesarean section and hysterectomy, and 18.6% for dilation and curettage. As the study was a retrospective observational study, the findings should be interpreted within the limitations of study design. The study did not control for management techniques or patient characteristics that may significantly have affected the complication rate. Nevertheless, this study suggests that the type of procedure is a significant predictor of SCD-specific complications.

The pattern of acute exacerbations of SCD gives an indication of disease activity and severity. Pain crisis typically occurs in chronological clusters interspersed with symptom-free periods.<sup>25</sup> Although many patients with frequent pain do not seek hospital treatment,<sup>24</sup> frequent hospitalizations or an increased number of hospitalizations in the year before surgery are significant



independent predictors of perioperative VOC.<sup>88,89</sup> A history of pulmonary disease is a significant independent predictor of perioperative SCD-specific events.<sup>88</sup> The frequency and severity of recent acute SCD exacerbations are therefore indicators of increased perioperative risk.

Additional patient characteristics may alter risk for perioperative sickle events. Increased age is independently associated with an increased perioperative incidence of pain crises and ACS. Pregnant patients may have increased SCD-specific perioperative morbidity.<sup>90</sup> As minor urinary or respiratory tract infections are closely associated with the development of ACS,<sup>78</sup> pre-existing infections presumably increase the risk of perioperative sickle events. Homozygous SS patients tend to have a more aggressive form of the disease, but SCD-related complication rates are similar for SC and SS patients undergoing abdominal and orthopedic procedures.<sup>87</sup> The Arab haplotype, which has a more benign clinical course than African haplotypes, probably has a lower incidence of perioperative complications. The relative proportions of hemoglobins F and S and the specific African haplotype are not sufficiently sensitive predictors of perioperative risk to warrant routine preoperative laboratory investigation. Although a baseline hematocrit is important to assess the severity of anemia, steady state hemoglobin concentration is not generally predictive of postoperative SCD-specific complications. Increased age, pregnancy, and infection are therefore the best additional risk predictors.

Organ failure is a significant cause of perioperative mortality. Koshy *et al.* noted an overall 30-day mortality of 1.1%.<sup>87</sup> Transfusion reaction or surgical procedure was thought to account for three deaths (0.3%). The remaining nine deaths (0.8%) occurred secondary to comorbid medical conditions and SCD-related multiorgan failure. The mean age at death was  $27.4 \pm 10.4$  yr, with no deaths reported in patients younger than 14 yr of age. In addition to establishing the nature and frequency of acute SCD exacerbations, the clinician should therefore estimate the presence and extent of organ damage or dysfunction. Early onset of dactylitis (swelling of the small bones of the hand) is an early indicator in children of future disease severity.<sup>91</sup> Because SCD produces progressive organ damage, older patients will tend to have a greater degree of dysfunction. Vascular damage in the lungs, kidneys, and brain may be difficult to detect clinically until the effects of end-organ damage become evident. Pain crises, ACS, stroke, and renal failure, however, are not sensitive indicators of vascular damage.<sup>21,25,92</sup> The clinician should consequently be alert to the existence of silent or cryptic pulmonary, renal, or neurologic vasculopathy that may be unmasked in the surgical patient.

A preoperative evaluation of pulmonary damage is essential to establish pulmonary function, to predict

perioperative risk of sickle events, and as a useful marker of disease progression. Temporal clustering of ACS episodes commonly signifies progression to clinically significant lung disease.<sup>67</sup> Chest radiograph, hemoglobin oxygen saturation, and lung function tests may delineate the degree of pulmonary pathology. A recent chest radiograph is an inexpensive and easily available screening investigation that provides valuable insight into disease progression. Abnormal chest radiograph, but not lower hemoglobin oxygen saturation, was associated with longer hospital stay after cholecystectomy.<sup>89</sup> A history of increasing or paroxysmal dyspnea or significant abnormalities on chest radiograph may indicate the need for pulmonary function tests to rule out reactive airway disease or establish the extent of restrictive lung disease.

An assessment of renal pathology is an additional important preoperative objective. Sickle patients have significantly lower blood pressure than the general population, consistent with chronic anemia, but superimposed hypertension may arise from renal failure.<sup>84</sup> Plasma urea and creatinine concentrations and urine dipstick screening for proteinuria or occult urinary tract infection are useful and inexpensive screening tools. Plasma creatinine concentrations are typically lower than population controls in the early stages of the disease, but progression of glomerular damage results in worsening proteinuria and rising creatinine.

Psychiatric problems, seizures, poor school performance, and developmental retardation may be markers of insidious neurologic vascular damage and cerebral infarction.<sup>93</sup> Silent infarction is predictive of increased risk of subsequent stroke.<sup>94</sup> Although preoperative neurologic imaging should not be considered a routine investigation, a suggestive history may indicate a neurology consultation and further investigations.

Preoperative history and examination should therefore establish the frequency, pattern, and severity of recent SCD events and the presence and degree of organ damage, particularly in the lungs, kidneys, and brain. A guideline for investigations that should be considered routine for all but minor procedures would include a recent hematocrit, plasma urea and creatinine, urine dipstick, and chest radiograph (table 3).

### *Perioperative Management*

The broad clinical spectrum of SCD makes it difficult to establish definitive management protocols for the entire population. Although the quality of recent perioperative clinical studies has improved, there remain many unanswered questions regarding the ideal management. The anesthesiologist should therefore adapt the general guidelines of this review according to specifics of patient and procedure.

**Erythrocyte Transfusion.** Potential indications for erythrocyte cell transfusion include the prevention or

**Table 3. Use of Preoperative Investigations**

Investigation	Comments
Routine/low threshold	Useful for preoperative screening
Hematocrit	Typical baseline hematocrit 15–30%
Plasma urea/creatinine	Baseline lower than general population if no proteinuria Incidence of creatinine >1.5 mg/dL is 4–5%
Urine dipstick	Hematuria, proteinuria in 12% children, 25% adults Screen for occult infection
Pulse oximetry	Hemoglobin oxygen saturation <90% in 2–4% of patients
Chest radiograph	Surgical population—abnormal lung fields 10–15% Subtle, diffuse interstitial fibrosis in early stages of restrictive disease, progressing to pulmonary fibrosis Calcified spleen, marrow; renal osteodystrophy
As Indicated	
Blood Crossmatch	Screen for prior antibodies Extended crossmatch for E, C, K groups
Pulmonary Function Tests	If severe pathology, paroxysmal dyspnea
Arterial Blood Gas	If indicated by pulmonary pathology
Electrocardiogram	Right ventricular strain with severe lung disease
Liver function tests	Abnormal viral serology
Guaiac Stool	May indicate mucosal ischemia
Neurological Imaging	Consider if developmental retardation

treatment of SCD complications and the correction of anemia and replacement of blood loss.

**Prevention of Complications.** The rationale for prophylactic erythrocyte transfusion is the assumption that

the “dilution” of sickle cells with normal erythrocytes will decrease the incidence of perioperative SCD-specific complications. Conclusions from early reports, the subject of a previous extensive anesthetic review,<sup>95</sup> are restricted by limitations in the design of these studies. Some authors have concluded that transfusion prevents SCD-specific complications, whereas others have questioned the practice. A further area of early controversy was the degree of hemoglobin S dilution required to achieve significant prophylaxis. Subsequent clinical studies and a broader understanding of SCD pathophysiology have contributed to an evolving and clearer picture of the role of preemptive erythrocyte transfusion (table 4).

A retrospective observational study reported by Griffin and Buchanan in 1993 examined outcomes in children undergoing 66 surgical procedures without preoperative transfusion.<sup>96</sup> There was only one episode of ACS and no pain crises after 46 minor procedures. The authors concluded that any potential benefit from transfusion would therefore be low and the risks of transfusion were not justified for minor procedures.

The retrospective study of 1,079 procedures by Koshy *et al.* also examined the effects of transfusion.<sup>87</sup> This found that perioperative transfusion was associated with a lower rate of SCD-related complications in hemoglobin SS patients undergoing low-risk procedures, with crude rates of 4.8% with transfusion and 12.9% without transfusion. The discrepancy between this outcome and that reported by Griffins *et al.*<sup>96</sup> may be attributable to differing populations. The latter study included adult patients who have a higher perioperative complication rate, presumably as a result of disease progression, whereas the

**Table 4. Outcomes from Recent Studies of Perioperative Blood Transfusion**

Reference	Study Details	Categories	R-XTF	R-TF	NR-TF	NR-NTF
Griffin, 1993 (89)	Retrospective, non-randomized, 66 children	Minor procedures Complications Other procedures Complications				46 2% 20 5%
Koshy, 1995 (80)	Retrospective, non-randomized, 1079 adults, children. Low and moderate risk surgical procedures	Hb SS-Low risk Complications SS-Moderate risk Complications Hb SS-High risk Complications			248 (4.8%) 390 (7.9%) 12 (16.7%)	145 (12.9%) 43 (4.7%) 0–
Vichinsky, 1995 (81)	Prospective, randomized. 604 assorted procedures	Procedures Complications Transfusion complications	303 15% 14%	301 15% 7%		
Haberkern, 1995 (82)	Prospective, randomized, nonrandomized, 364 patients	Cholecystectomies Complications Transfusion complications	110 (12%) 15% 15%	120 (19%) 8% 8%	97 (18%) 9% 3%	37 (32%) 3% 21%
Vichinsky, 1999 (90)	Prospective, randomized, nonrandomized groups. 138 procedures	Orthopedic Procedures ACS Transfusion Complications	34 21% 24%	40 8% 15%	24 3% 15%	40 21% 15%

Vichinsky's 1999 data for the randomized nontransfusion group are reported in the nonrandomized nontransfusion column. Complications refer to sickle cell disease specific complications such as pain crises or acute chest syndrome.

ACS = acute chest syndrome; Hb SS = patients homozygous for hemoglobin S; NR-NTF = nonrandomized nontransfusion; NR-TF = nonrandomized conservative or aggressive transfusion; R-TF = randomized conservative transfusion; R-XTF = randomized aggressive transfusion.

former study examined outcomes solely in children. Koshy *et al.* found no significant association between transfusion and SCD complication rates after moderate risk procedures, with rates of 4.7% without transfusion and 7.9% with transfusion. In a smaller group of hemoglobin SC patients, preoperative transfusion was beneficial for both low and moderate surgical risk levels. The differing outcome in the hemoglobin SS population between low and moderate risk procedures may be a consequence of the retrospective, nonrandomized nature of this study. The type of procedure is only one of a number of factors affecting the incidence of postoperative complications. The report did not control for confounding variables such as disease severity, disease activity, patient characteristics, or changing anesthetic and surgical practices over the decade the study examined. The findings should therefore be interpreted cautiously within the limitations of the study and in the context of complementary studies and the evolving understanding of SCD.

In 1995 Vichinsky *et al.* published the results of a prospective randomized trial that examined target goals for transfusion for 604 surgical procedures.<sup>88</sup> This study compared an aggressive transfusion regimen, designed to decrease the hemoglobin S concentration to less than 30%, with a conservative regimen, designed to increase the hemoglobin concentration to 10 g/dl. Aggressive transfusion techniques included exchange transfusion or serial transfusions, whereas the conservative technique involved simple perioperative transfusion. The surgical categories were predominantly low or intermediate risk.<sup>97</sup> The incidence of perioperative SCD-specific complications, approximately 15%, was similar in both groups. The incidence of transfusion-related complications was higher in the aggressive transfusion group (14%) than the conservative transfusion group (7%). This study clearly demonstrated that a conservative transfusion regimen had fewer complications than, but similar efficacy to, an aggressive regimen. As the study did not have a nontransfusion arm, however, the value of prophylactic transfusion was not examined.

In 1997 Haberkern *et al.* published the results of a study of 364 patients undergoing cholecystectomy.<sup>89</sup> This study compared 110 patients randomized to aggressive transfusion, 120 patients randomized to conservative transfusion, 37 patients nonrandomized to nontransfusion, and 97 patients nonrandomized to transfusion. This confirmed the previous findings of Vichinsky *et al.*<sup>88</sup> of no improved prophylactic benefit from an aggressive transfusion compared with conservative transfusion. The incidence of sickle events was higher in the nonrandomized, nontransfusion group (32%) compared with the combined transfusion group total (19%). The nontransfusion group patients were more likely to be female, smokers, and more than 20 yr old, whereas indications for nonrandomization included physician dis-

cretion, patient refusal, or recent transfusion. There is therefore potential bias for disease severity or activity in the small nontransfusion group. Consequently, this apparent effect should be interpreted with caution.

A 1999 report by Vichinsky *et al.* examined 138 orthopedic surgical procedures.<sup>98</sup> Groups were prospectively randomized to aggressive transfusion ( $n = 34$ ), conservative transfusion ( $n = 40$ ), or no transfusion ( $n = 24$ ). Another nonrandomized group included nontransfused patients ( $n = 40$ ). The previous finding<sup>88,89</sup> that a reduction of hemoglobin S to 30% did not confer greater prophylaxis than achieving a hematocrit of 30% was confirmed. There was no difference in the general complication rates across the four groups except in the occurrence of ACS. This occurred in 21% of case in the aggressive transfusion and randomized nontransfusion groups, 8% in the conservative transfusion group, and 3% in the nonrandomized nontransfusion group. The study did not detect a prophylactic effect from preoperative transfusion.

Cardiopulmonary bypass has been performed on SCD and SCT patients using various aggressive transfusion strategies before or during bypass, designed to decrease the proportion of hemoglobin S. There is a lack of definitive control data to validate the need for these techniques. In more recent series, a total of 28 SCT patients tolerated bypass without alterations to standard protocol.<sup>99,100</sup> Transfusion was avoided where possible. Preventative transfusion therefore does not appear to be necessary for SCT patients. Case reports note successful hypothermic bypass without preoperative transfusion in four patients with SCD (two with a blood prime and two who did not receive any transfusion before or during bypass).<sup>100,101</sup> Bypass without transfusion is feasible in SCD although there are inadequate data to accurately quantify the risks. Similarly, neurosurgery has traditionally been performed only after aggressive transfusion practices, but the need for this practice has never been tested by control comparisons.<sup>102</sup> More recently, there have been various reports of successful outcomes with conservative transfusion practices.<sup>102</sup>

Additional information emerging from these and other studies established red cell alloimmunization, the development of non-ABO erythrocyte antibodies, as a significant complication of transfusion in the SCD population.<sup>87-89,98,103-105</sup> The incidence of alloimmunization in the SCD population varies from 8 to 50%, increasing sharply with the number of transfusions.<sup>103</sup> Delayed transfusion reactions, characterized variously by fulminant hemolysis, development of new antibodies, and diminished survival of transfused cells, also occur with an increased incidence in SCD patients. As SCD patients often require lifesaving transfusion of blood for acute anemia or intraoperative hemorrhage or for chronic therapeutic strategies, difficulty with cross matching as a result of alloimmunization is a serious problem. Alloan-



**Table 5. Guidelines for the use of Perioperative Prophylactic Erythrocyte Transfusion**

<i>Transfusion goal</i>	Low perioperative	Moderate perioperative	High perioperative	Uncomplicated Pain	Severe ACS
Hematocrit of 30%	Not Indicated	May be beneficial	May be beneficial	Not indicated	Reduces hypoxemia
Hemoglobin S <30%	Not indicated	Not Indicated	May not be Indicated	Not indicated	Reduces hypoxemia

An individualized assessment of patient risk should be based on a synthesis of factors outlined in the text. Prophylactic transfusion is of potential benefit in moderate and high-risk cases, but the efficacy has not been clearly demonstrated by a randomized trial. The efficacy of pre-emptive transfusion therefore remains controversial. The use of transfusion for mild cases of acute chest syndrome is unclear, although transfusion in severe cases improves arterial oxygenation. The role of exchange transfusion versus simple transfusion for relief of severe hypoxia in acute chest syndrome is unclear. Extended cross matching for E, C and K antigens decreases alloimmunization.

tibodies are formed most commonly against the Rhesus, Kell, and Lewis antigen groups.<sup>106,107</sup> Immune dysregulation consequent on splenic atrophy, disruption to erythrocyte membrane protein structures, or chronic endothelial inflammation may contribute to the high incidence of immunization abnormalities.<sup>107</sup> Extensive antigen cross matching decreases the rate of alloimmunization from 7% to 1%.<sup>77</sup> Transfusion has been reported to precipitate stroke, pain crises and acute pulmonary deterioration. Infection, particularly with hepatitis C, is an additional complication.<sup>103</sup> More recent reports therefore emphasize the high incidence of serious transfusion complications in the SCD population.

Based on these recent studies, some guidelines for transfusion can be outlined (table 5). An assessment of the patient's complication risk should be made based on predictive factors (tables 1 and 2). For patients at low risk, any potential benefit derived from transfusion would be minimal and offset by a high incidence of complications. Erythrocyte transfusion is therefore not indicated. For patients at moderate or high risk, potential benefit of transfusion might be expected to be greater. If undertaken in situations of moderate risk, transfusion should aim for a hematocrit of 30% rather than aim to achieve a target dilution of hemoglobin S. A rough guideline for the timing of prophylactic transfusion would be a convenient time from the immediate preoperative period to up to a week before scheduled surgery. Although there are limited data for transfusion practices for cardiopulmonary bypass or neurosurgery, there is no conclusive evidence to demonstrate that a particular concentration of hemoglobin S is beneficial. These procedures can apparently be performed with simple transfusion, if transfusion is indeed indicated.

Extended phenotype matching for E, C, and K groups minimizes erythrocyte alloimmunization and autoimmunization.<sup>78,108,109</sup> As erythrocyte alloimmunization is a significant problem in the SCD population, routine phenotype matching of these antigen groups is recommended. Prestorage leukocyte-reduction of erythrocyte units reduces the incidence of human leukocyte antigen alloimmunization, febrile nonhemolytic transfusion reactions, and cytomegalovirus transmission. However, this precaution is not standard for perioperative transfusion

of SCD patients, as recent clinical trials in the general population failed to show significant patient benefit.<sup>110</sup>

The laboratory and clinical data on prophylactic perioperative transfusion remains incomplete. It is unclear whether acute modification of one component of a chronically deranged hemostatic system by the dilution of sickle erythrocytes will affect the complex pathophysiology of acute vasoocclusion. Although widely practiced, prophylactic erythrocyte transfusion remains a treatment with appreciable complications whose potential benefits have not been clearly demonstrated by a prospective, randomized clinical trial.

**Improvement of Oxygen Delivery.** Transfusion is indicated to correct severe anemia or replace significant blood loss. Given the wide variation in the clinical picture of SCD, a general hemoglobin concentration at which transfusion should be initiated cannot be specified. Rather, the decision of when to transfuse for hemorrhage should be based on an individualized assessment of the patient's oxygen delivery and the surgical circumstances. Oxygen delivery may be impaired consequent on obstructive or restrictive lung disease, ventilation-perfusion mismatch, vascular damage, abnormal microvascular rheology, peripheral arteriovenous shunting, and disturbed NO transport.<sup>35,47,66,111</sup> Chronic compensatory mechanisms, however, include increased minute ventilation, increased cardiac stroke volume, decreased peripheral vascular resistance, increased 2,3-diphosphoglycerate, periodic microcirculatory flow, and a decreased hematocrit that compensates for abnormal rheology, and possibly increased plasma volume and heightened NO production.<sup>35,47,49,112,113</sup> These chronic adaptations may allow the SCD population to tolerate greater anemia than a population with normal baseline hematocrit. Sick cell hemoglobin results in a right shift of the oxygen-dissociation curve, largely as a result of polymer formation.<sup>35</sup> A calculation of hemoglobin S oxygen saturation from arterial blood gas, using standard hemoglobin A normograms, will therefore tend to overestimate the true saturation.<sup>114</sup> Pulse oximetry tends to underestimate true hemoglobin S saturation by about 2% because of the high concentration of coexisting methemoglobin.<sup>114</sup> Induced hypotension to reduce blood loss and autologous transfusion to avoid foreign antigen ex-

posure have been reported in neurosurgical and orthopedic patients.<sup>115-121</sup>

**Oxygenation.** Although hypoxia is widely stated to be a precipitant of perioperative SCD-specific complications, there are no clinical data in the anesthetic and surgical literature to demonstrate that hypoxia precipitates perioperative sickle events. The clinical effects of hypoxia have been noted previously in this review. Early reports of postoperative complications attributed to hypoxemia<sup>122-125</sup> do not conclusively show hypoxia as the precipitant. Perioperative SCD-specific complications continue to occur with a high incidence despite avoidance of hypoxia. Prolonged oxygen supplementation depresses erythropoiesis in a population with a chronic hemolytic anemia,<sup>126-128</sup> whereas abrupt withdrawal of prolonged oxygen supplementation has been anecdotally reported to trigger VOC.<sup>128</sup> Although maintenance of adequate oxygenation is the fundamental aim of anesthetic care, there seems to be little rationale to the avoidance of appropriate preoperative anxiolytic medication, the use of intraoperative hyperoxygenation, or prolonged postoperative supplemental oxygen beyond that which is needed to achieve this basic goal.

**Hydration.** Dehydration has been suggested as a cause of perioperative complications, largely because intracellular dehydration increases hemoglobin concentration and sickling *in vitro*.<sup>129</sup> There is a lack of definitive clinical evidence to confirm this assumed causal association. Alcohol binges, ascents to altitude, and prolonged airline flights are apparent precipitants of acute SCD complications,<sup>23,67-71</sup> but the role of dehydration in these possible triggers is unclear. The hypertonic environment of the renal medulla, which may increase erythrocyte adhesion and sickling, is thought to play a role in the development of renal lesions in the SCD and SCT populations, but these are chronic rather than acute complications. Water deprivation,<sup>60,61</sup> diuretics,<sup>61,118,119,130</sup> and hypertonic contrast media<sup>118</sup> have been employed in cardiac and neurosurgical patients without triggering sickle events, although marked dehydration was not induced in these cases. No study has assessed perioperative fluid balance in SCD patients, and perioperative sickle events occur commonly despite generous hydration. It is unclear therefore whether mild dehydration precipitates SCD complications. Patients with renal concentrating defects may be slightly more susceptible to perioperative dehydration, whereas those with renal impairment may be unable to tolerate excess fluid load. Although hyposthenuria and dehydration may theoretically be more of a concern in children, recommended pediatric fasting times are shorter than those of recommended adult fasting times. Preoperative dehydration may therefore not be a significant preoperative concern in practice. Modification of fluid management based on significant renal pathology is indicated, but there are no conclusive clinical data to support prophylactic

modification of standard fluid management to prevent perioperative sickle events.

**Thermoregulation.** Although hypothermia would tend to retard sickling because of a left shift of the oxygen dissociation curve, hypothermia is often identified as a precipitant of perioperative SCD complications. The basis of this suggestion is retrospective accounts by SCD patients that suggest skin chilling as a precipitant of pain crises occurring in nonhospital settings.<sup>13,73,131-134</sup> There are no case reports documenting perioperative hypothermia as a cause of perioperative VOC. Exaggerated reflex vasoconstriction and shunting of blood from the bone marrow in response to skin cooling has been suggested to be the mechanism of hypothermia-induced VOC.<sup>135</sup> As anesthetic drugs alter thermoregulatory vasoconstriction,<sup>136</sup> the role of this possible mechanism in the anesthetized patient is unclear. Because neurosurgical or cardiopulmonary procedures for which induced hypothermia is indicated are performed under deep anesthesia, hypothermia may presumably be induced without undue risk of VOC. Reports suggest that hypothermia can be induced uneventfully in SCD patients during cardiopulmonary bypass.<sup>100,101</sup> In general, however, avoidance of patient hypothermia is a basic objective for most anesthetics. Maintenance of normothermia is therefore the basis of care for SCD patients, as it is for the general patient population.

Postoperative temperature spikes are commonly the result of resetting of the thermoregulatory set point in the surgical patient. Postoperative pyrexia occurs in 6-25% of SCD patients.<sup>87-89</sup> The observation that military recruits with SCT have a higher incidence of sudden death during physical training in hot environments than the general population underlies the assumption that patients with SCD are at increased risk from hyperthermia.<sup>137</sup> Although pyrexia is a feature of sickle complications and infection may trigger sickle events, there is no definitive clinical evidence to suggest that hyperthermia *per se* triggers SCD complications. Provided that infection or incipient SCD complications are excluded, postoperative pyrexia should therefore be managed as in the general patient population.

**Acid-base Regulation.** Because acidosis hastens erythrocyte deformation on exposure to hypoxia,<sup>6,129</sup> acidemia has widely been suggested to be a precipitant of perioperative SCD complications. Clinical evidence of acidemia as a precipitant of perioperative SCD complications is lacking. Experimental administration of ammonium chloride for several days resulted in pain crisis in one subject,<sup>138</sup> but short periods of acidemia without adverse effect have been reported.<sup>139</sup> Bicarbonate alkalization has not been shown to be effective in preventing perioperative pain crises.<sup>140</sup> Because acidosis in a clinical setting is usually secondary to a pathophysiological process, it is difficult to separate the role of acidemia from that of the underlying problem. It seems unlikely

that minor fluctuations in acid-base status are the primary trigger of complications.

**Anesthetic Technique.** The impact of anesthetic technique on SCD complications has been the source of some controversy. Koshy *et al.* noted an apparent association between the use of regional anesthesia and postoperative complications in their review of 1,079 anesthetics.<sup>87</sup> The incidence of SCD-specific complications was higher after regional anesthesia than after general anesthesia (14.3% *versus* 6.9%, low risk procedures; 23.5% *versus* 6.6%, moderate risk procedures). A similar pattern was noted for the incidence of fever and infection. However, this study did not control for the effect of obstetric procedures. As regional anesthesia is commonly used for these procedures, the authors pointed out that the apparent effect might simply reflect an association with the higher complication rates of obstetric interventions. The potential tendency of clinicians to use regional techniques for sicker patients introduces another possible selection bias, further limiting the interpretation of this nonrandomized, observational study.

Other smaller studies did not find an adverse effect of regional anesthesia. A retrospective study of 69 general anesthetics and 43 regional anesthetics noted no effect from the choice of anesthetic technique.<sup>141</sup> There was no correlation between the use of perioperative epidural

anesthesia-analgesia and postoperative complications in a 1997 study of 364 cholecystectomies.<sup>89</sup> A 1994 retrospective observational study of 11 pain crises in nine children noted that epidural analgesia was safe and effective in treating pain.<sup>142</sup> Oxygenation improved markedly with epidural use, a result that was attributed to relief of pain-induced respiratory splinting or opioid respiratory depression. Interestingly, epidural analgesia was effective in controlling severe pain that was previously unresponsive to high dose opioid therapy. This may simply reflect more effective blocking of nociceptive pathways. If vasoconstriction is a key component of pain crises, however, more effective analgesia with a regional technique may reflect the vasodilatory effects of regional anesthesia. The use of regional anesthesia therefore does not appear to be contraindicated in SCD and may provide a useful means of pain control with significant advantages over intravenous analgesics.

#### *Postoperative Management*

Basic supportive care, including adequate analgesia, incentive spirometry, early mobilization, and oxygen supplementation as needed to prevent hypoxemia, is the mainstay of postoperative management (table 6).

**Outpatient Surgery.** As the incidence of SCD complications is low after minor procedures, outpatient surgery

**Table 6. Guidelines for Management**

Management Issue	Guideline
<b>Preoperative</b>	
History and examination	Establish organ damage, risk factors (tables 1 and 2)
Investigations	Investigations as indicated by patient and procedure (table 3)
Consider prophylactic transfusion	Transfusion guidelines (table 5)
	Crossmatch for Rhesus, Kell, and Lewis antigens, alloantibodies
Preoperative fast	Standard protocol
<b>Intraoperative</b>	
Hydration	Modify according to renal pathology
Oxygenation	Modify according to organ pathology
Thermoregulation	Normothermia; hypothermia if indicated under deep anesthesia
Acid-base balance	Standard anesthetic care
Transfusion	As indicated by hemorrhage and organ pathology
Anesthetic technique	As indicated by procedure
<b>Postoperative</b>	
Basic care	Early mobilization, pulmonary toilet, effective analgesia
	Supplemental oxygen as required
	Discharge with follow-up care available
Pain crisis	Pain scoring
	Early effective analgesia—opioids
	Adjuvant analgesics—nonsteroidal antiinflammatory drugs, acetaminophen
	Consider regional analgesia, incentive spirometry
	Pulmonary monitoring
	Psychological support
	Steroids—possible benefit
Acute Chest Syndrome	Oxygen
	Bronchodilators, incentive spirometry
	Effective analgesia
	Consider broad-spectrum antibiotics
	Transfusion for severe hypoxemia, anemia
	Mechanical ventilation for respiratory failure
	Steroids, nitric oxide—possible benefit



seems a reasonable option for selected patients. The usual considerations of outpatient discharge, including the individual's baseline health, procedure risk, and rapid access to medical help should the need arise, should apply.

**Pain Crisis.** Postoperative VOC may result in excruciating pain. Analgesia should be prompt and effective, using pain analog scoring scales to monitor efficacy. Opioids such as morphine, hydromorphone, meperidine, or fentanyl are the mainstays of severe pain treatment.<sup>143</sup> A baseline therapeutic concentration, supplemented by "breakthrough" analgesia as required, should be achieved. Patient-controlled analgesia, on a background infusion if required, is the management of choice, whereas scheduled doses with supplementation as needed are a less effective option.<sup>144</sup> A fentanyl patch may help establish steady baseline analgesia. Although meperidine is not contraindicated, caution should be exercised about accumulation of the epileptogenic, renally excreted metabolite normeperidine, particularly in patients with renal impairment or seizure foci.<sup>145</sup>

Acetaminophen and nonsteroidal antiinflammatory drugs are useful adjunct analgesics; antiinflammatory agents may be particularly effective for bone cortex pain arising from pressure from edematous infarcted marrow. Epidural anesthesia, if feasible, can provide excellent analgesia and possibly reduce pulmonary complications.<sup>142</sup> Incentive spirometry may also help reduce splinting and atelectasis resulting from thoracic bone pain.<sup>146</sup> The ACS, precipitated by fat embolism from infarcted marrow, is a significant complication of pain crises.<sup>78</sup> Daily monitoring for acute pulmonary disease has consequently been recommended as a precaution during pain crises. Corticosteroids decrease analgesic requirements for bone pain but may result in a higher relapse rate.<sup>147</sup> Supplemental oxygen does not affect pain duration or analgesic use.<sup>148</sup> Liberal hydration is commonly practiced, although the benefit of hydration beyond daily maintenance requirements has not been established.<sup>149</sup>

As many patients have required opioids on multiple occasions for pain relief, drug tolerance may produce difficulty in achieving adequate analgesic effect. Patients may require high doses to achieve therapeutic concentrations; adjuvant analgesics and techniques are helpful in achieving relief and decreasing side effects. Although a small subset of the SCD population may have problems with addiction, physiologic tolerance to drug effect should not be inappropriately confused with psychological drug dependency. The clinician should appreciate that pain crises do not simply represent a period of acute discomfort but rather the exacerbation of a chronic, debilitating, and progressive illness.<sup>143</sup> People with SCD understandably have a high incidence of psychological distress.<sup>150</sup> Empathy, support, and simple human kind-

ness are essential for proper relief and care during a potentially extremely distressing situation.

Although erythrocyte transfusion is not indicated for uncomplicated crises,<sup>151</sup> the intriguing use of plasma transfusion has been reported. One study of 17 pain crises noted that fresh frozen plasma transfusion appeared to rapidly diminish the severity and duration of pain in 15 cases.<sup>152</sup> Other case reports note the apparent reversal of multiorgan failure associated with SCD by plasma exchange transfusion.<sup>153-155</sup> Although these findings may be related simply to improved perfusion consequent on intravascular volume expansion, disruption of plasma-transported mediators might explain these striking results.<sup>152,156</sup> These observations would be consistent with the percept of VOC as an acute inflammatory problem.<sup>47,48</sup>

**Acute Chest Syndrome.** The ACS, on average, developed 3 days after surgery and lasted 8 days in a study of 604 patients.<sup>88</sup> Two deaths occurred in approximately 60 episodes, both in patients with preexisting pulmonary pathology. Early incentive spirometry, bronchodilator therapy, supplemental oxygen, adequate analgesia, and broad-spectrum antibiotics are recommended to lessen the progression of ACS.<sup>78</sup> Blood transfusion improves oxygenation in severe anemia and hypoxemia.<sup>50,78</sup> The role of transfusion in less severe cases and the efficacy of exchange transfusion compared with simple transfusion are unclear. Preliminary reports suggest that nitric oxide and corticosteroids may improve outcome.<sup>157-159</sup> Outcomes after mechanical ventilation for respiratory failure are usually good.<sup>78</sup>

#### *Specific Surgical Procedures*

The complications of SCD necessitate a variety of surgical procedures. Typically these operations are to repair organ damage arising from SCD, although SCD can mimic or exacerbate surgical disease states.

**Cholecystectomy.** High erythrocyte turnover and hyperbilirubinemia is associated with an incidence of cholelithiasis estimated as high as 70% in the adult population.<sup>160</sup> Cholecystectomy is the most frequent surgical procedure performed in SCD patients, with an approximate incidence of perioperative SCD events of 10-20%.<sup>87,89</sup> As laparoscopic surgery decreases hospital stay without increasing SCD complications, this technique is recommended over open cholecystectomy.<sup>89</sup>

**Obstetrics.** Parturients with SCD have an increased incidence of spontaneous abortion, intrauterine growth restriction, antepartum hospitalization, premature labor, and postpartum infection.<sup>161,162</sup> Parturients homozygous for hemoglobin S have a higher complication rate than hemoglobin SC heterozygotes, whereas pregnancy outcome is unaffected by SCT.<sup>163</sup> The incidence of pain crises increases with the progression of pregnancy, peaking during the third trimester.<sup>164</sup> Pain crises do not appear to compromise umbilical blood flow,<sup>165</sup> and the

incidence of intrapartum pain crises is not predictive of fetal outcome. Pregnancy outcome is improved with good obstetric and medical management, allowing women with SCD to bear children without significant undue risk.

Obstetrical procedures are common in SCD parturients due to the increased incidence of pregnancy complications. Epidural analgesia has been described to treat the unusual occurrence of a VOC during labor,<sup>166</sup> and the use of epidurals for labor analgesia is not contraindicated. The incidence of SCD complications has been reported as 14–19% after dilation and curettage and 11–17% after caesarean section or hysterectomy.<sup>87</sup> Neonates do not develop SCD symptoms; their predominant hemoglobin, fetal hemoglobin, contains  $\gamma$ -chains rather than the mutant  $\beta^S$ -chain.

**Orthopedics.** Orthopedic disease affects a substantial proportion of SCD patients.<sup>98,167</sup> Common orthopedic procedures reported include drainage of bone infections, joint replacement, and correction of musculoskeletal deformities. Occlusive orthopedic tourniquets are not contraindicated by SCD.<sup>57,58,59</sup> The reported rate of sickle events after hip surgery ranges to 19%.<sup>98</sup> Fat embolism may mimic or trigger ACS, with pulmonary events a prominent cause of death in the orthopedic population.

**Neurosurgery.** The commonest indication for SCD neuroanesthesia is intracerebral aneurysm ablation, typically reported for patients with homozygous hemoglobin S disease.<sup>102</sup> The peak incidence of intracranial hemorrhage occurs during the third decade of life,<sup>81</sup> corresponding with the typical age distribution of SCD neurosurgical patients.<sup>102</sup> Evaluation of the safety of neuroanesthetic techniques such as hyperventilation, forced diuresis, and manipulation of arterial blood pressure manipulation is limited by the extensive use of previous exchange transfusion in this patient population. Hyperventilation to an end-tidal carbon dioxide range of 25–30 mm Hg has, however, been commonly employed.<sup>102</sup> Intrathecal drainage averts the need for aggressive diuresis to optimize surgical conditions, although mannitol and urea have been used without incident.<sup>102,117,118,129</sup> Isoflurane, sodium nitroprusside, nitroglycerine, trimethaphan camsylate, propofol, and fentanyl have been utilized for hemodynamic control. Central venous and pulmonary artery pressures have occasionally been monitored, but most management accounts do not report this level of invasive monitoring. Aneurysm ablation by endovascular coil placement is possible,<sup>102,168</sup> and the use of nonionic radiologic contrast dyes appears to be safe in SCD patients.<sup>169,170</sup> Published outcomes of aneurysm repair using a variety of techniques have predominantly been favorable.

**Cardiopulmonary Bypass.** Cardiopulmonary bypass has been performed in patients with hemoglobin SA, SC, SB, and SS phenotypes.<sup>60–64,171,172</sup> Abnormal cardiac

physiology is usually secondary to chronic anemia, advanced pulmonary pathology, or coexistent structural cardiac abnormalities, rather than a specific SCD-induced cardiomyopathy.<sup>173</sup> Large vessel coronary arteriosclerosis is not a complication of SCD. Cardiac surgery is therefore usually indicated by coexistent pathologies rather than by SCD *per se*. Indications for cardiopulmonary bypass have included valve and congenital defect repairs, pulmonary thrombectomy, and coronary artery bypass. Prosthetic valves were not associated with excessive hemolysis in SCD<sup>171</sup> or SCT<sup>172</sup> patients.

Systemic hypothermia, aortic cross clamping, acidosis, low flow states, and cold cardioplegia during bypass have variously been suggested as potential precipitants of pain crises. However, bypass takes place under conditions of deep anesthesia, hemodilution, and profound anticoagulation designed to minimize these physiologic insults. Conceptually, complications of SCD would probably be triggered by the large postbypass inflammatory response<sup>45</sup> rather than by the mechanics of erythrocyte sickling in the bypass circuit. Case reports demonstrate that hypothermic bypass without previous transfusion is feasible for SCD patients<sup>100,101</sup> but do not clearly define the best way of performing this type of surgery. In the absence of definitive data, the general guidelines in this review are suggested to assess patient risk and choose an appropriate strategy.

### *Therapeutic Approaches*

Despite the complex pathophysiology and diverse clinical picture, considerable progress has been made in the understanding and management of SCD. In the United States, the mean age at death is approximately 42 yr for men and 48 yr for women homozygous for hemoglobin S; during the 1960s it was considered unusual for patients to reach adulthood.<sup>21</sup> Longevity appears to have been steadily improving in association with general improvements in health care and living standards. Successful therapies to minimize or prevent complications include folate supplementation to diminish coexisting anemia and penicillin or vaccine prophylaxis to decrease streptococcal infection.<sup>174</sup> Orally administered hydroxyurea decreases pain episodes, pulmonary events, and hospitalizations,<sup>175</sup> probably by increasing fetal hemoglobin, reducing expression of adhesion molecules, and improving NO delivery. Chronic transfusions reduce the occurrence of stroke and may also reduce sickle events, growth failure, and splenic dysfunction.<sup>176</sup> Angiotensin-converting enzyme inhibitors diminish proteinuria and may slow progression of renal disease, probably by improving regulation of glomerular blood flow.<sup>177</sup> The understanding and management of pain crises and ACS have improved considerably in the past decades. Alone or in combination, these treatments can help to further reduce SCD morbidity and mortality.

Future therapies offer the hope of improved palliation

and even the riveting possibility of a cure. A promising new therapy for sickle events is the use of inhaled NO, first suggested by Head *et al.*<sup>178</sup> Other potential therapies include cellular rehydrating medications, antiadhesion agents, antioxidant therapy, and antithrombotic treatments.

Bone marrow transplant is potentially curative, but donor-host matching and the toxic effects of myeloablation currently severely limit stem-cell transplant. Improved transplant management and the use of unrelated donors may extend the use of this treatment.<sup>179</sup> A recent study, however, holds the greatest promise for SCD therapy. Using a viral vector based on the human immunodeficiency virus, a construct of the  $\beta^A$  and  $\alpha$ -globin genes was inserted into stem cells of transgenic mice with sickle cell disorders, curing the disease.<sup>180</sup> Ironically, as the acquired immunodeficiency syndrome devastates humankind, the retrovirus may hold the key to ending another debilitating scourge. Current objectives for introducing this cure to humans include a means of preventing *in vivo* retroviral replication and bone marrow reconstitution with altered stem cells without toxic myeloablation regimes. Some hundred years after the discovery of the "peculiar anomaly in human red blood corpuscles,"<sup>2</sup> gene therapy offers the electrifying potential of a cure for the disease.<sup>180</sup>

## Conclusion

The intervening decades since the ANESTHESIOLOGY review of 1955<sup>1</sup> have seen a vast expansion in the knowledge of the pathophysiology and perioperative epidemiology of SCD. The initial approach to anesthetic management was based on the assumption that hemoglobin polymerization and erythrocyte sickling are the dominant pathophysiological derangements. Although it would be extreme to dismiss the deformed erythrocyte as a red herring in anesthetic management, it is now abundantly clear that the problem extends well beyond the mechanics of sickling. Rather than purely a consequence of hemoglobin insolubility because of a defect in the globin, cellular pathology arises largely from hemoglobin instability causing disruption to the heme. Hemoglobin S produces a problem of erythrocyte "sticking," instead of simply erythrocyte "sickling." Adhesion, hemolysis, and deformation are interlinked, together leading to profound disruption of vascular function. Disease symptoms stem predominantly from chronic endothelial damage rather than from acute erythrocyte deformation. Although sickling of erythrocytes is inextricably linked to pathophysiology, the clinical picture is that of a chronic inflammatory vascular disease. The anesthesiologist should therefore approach SCD as a problem of broad vascular dysfunction, not simply as a complication of isolated venous sickling.

Although early studies of sickle cell disease noted perioperative morbidity and mortality greater than 50%, perioperative mortality has diminished steadily in concert with overall improvements in anesthetic care. Against this background of improving general anesthetic standards, the understanding of the benefits, risks and subtleties of anesthetic approaches to SCD in particular has increased considerably. Traditional management of SCD has involved profound alterations to the basic handling of oxygenation, hydration, acid-base physiology, thermoregulation, and blood transfusion. This approach has been based on an incomplete pathophysiological construct, combined with extrapolations from clinical situations that are not necessarily analogous to the perioperative period. Although a reductionist approach has undeniable value to the practice of anesthesia, the limitations of this method in a disease as intricate as the sickle hemoglobinopathy must be appreciated. In the absence of controlled outcome data or a definitive understanding of the pathophysiology of this complex disease, major deviations from standard anesthetic care must be made with caution. Almost a half-century after anesthetic attention was first directed to this challenging disease, the fundamental of management remains meticulous observation and vigilance of the basic principles of safe anesthesia.

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