Anesthesia and Hemoglobinopathies

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Hemoglobinopathies are diseases involving abnormalities of the structure or production of hemoglobin. This group of disorders poses many challenges to the anesthesiologist, both in the questions they raise about basic physiology and in the practical issues of assisting patients through a wide variety of surgical procedures. Hemoglobinopathies may present to the anesthesiologist as the primary cause of a surgical procedure, as an incidental complicating factor of a surgical patient, or with a problem arising from the disease itself. An understanding of the disease process, the potential complicating issues, and the evidence surrounding management principles is key to helping people with this group of diseases. This article reviews the common types of hemoglobinopathies, presents a basic summary of pathophysiology relevant to anesthesia, and outlines current perioperative management.

STRUCTURE AND GENETICS OF HEMOGLOBIN

With the exception of embryonic hemoglobins present in early fetal life, hemoglobin is a tetrameric protein consisting of two alpha (α) and two nonalpha polypeptide chains attached to four iron-containing heme complexes. All normal hemoglobins of adult life contain two α chains, with different types of hemoglobin varying in the structure of the nonalpha chain pairs. These types of chains include epsilon ε (embryonic hemoglobins), gamma γ (fetal hemoglobin F), beta β (hemoglobin A), and delta δ (hemoglobin A2).

Adult red cells contain mixes of hemoglobin A (α2β2, approximately 95%–98%), hemoglobin A2 (α2δ2, about 2%–3%), and hemoglobin F (α2γ2, less than 2%). In the neonate, the predominant hemoglobin is hemoglobin F, with the proportion of
hemoglobin A superseding that of hemoglobin F during early infancy. In adults, hemoglobin F is usually limited to a population of erythrocytes known as F cells.

The alleles coding for the polypeptides are codominant, so chain production is the result of the combined expression of all alleles. Genetic coding for the alpha chains is stored in four codominant alleles paired on chromosome 16. The nonalpha chains are coded by two codominant alleles located in a cluster of beta-genes on chromosome 11, the various genes within this cluster coding for different non-alpha chains. The four hemoglobin polypeptides are thus encoded by six alleles, two nonalpha and four alpha alleles.

HEMOGLOBIN FUNCTION

Most oxygen in the blood is transported by hemoglobin, with only a small proportion in solution in the plasma. Hemoglobin binds and releases oxygen in an elegant and finely controlled manner. At high oxygen concentrations typical in the pulmonary capillaries, oxygen binds to the iron of the heme group in the ferrous Fe\(^{2+}\) state; at low concentrations found in the peripheral circulation, the oxygen is released. The binding of oxygen to the iron of one heme subunit induces a conformational or structural change in the whole hemoglobin molecule, producing an increased affinity for oxygen in the other subunits. The binding of oxygen is thus a cooperative process.

The oxyhemoglobin dissociation curve traces the relationship of the partial pressure of oxygen in the plasma with the affinity and hence saturation of hemoglobin with oxygen. The curve is roughly sigmoid, the abrupt change in hemoglobin affinity between the oxygen tensions in the lungs and the peripheries reflecting the cooperative binding to oxygen. By contrast, a dissociation plot of noncooperative binding would trace a normal hyperbolic curve. The upper portion of the sigmoid curve represents the affinity of hemoglobin at oxygen tensions typical in the lung. The flatter shape of the curve at these tensions reflects that small changes in oxygen tensions in the pulmonary capillaries have little effect on oxygen uptake, because the hemoglobin has a high affinity for oxygen. The steepness of the lower section of the curve represents the rapid release of oxygen that occurs with only a small drop in capillary oxygen pressure.\(^1\)\(^2\)

The oxygen affinity of hemoglobin, and hence the dissociation curve, is affected by several factors. The Bohr effect is the change caused by alterations in hydrogen ion concentration. A right shift in the curve, reflecting a decreased affinity for oxygen, occurs with the increase in hydrogen ion concentration at levels typically present in peripheral tissue. The offloading of oxygen into the tissues is therefore facilitated by this physiologic function. Increases in 2,3-diphosphoglycerate, temperature, or carbon dioxide tension also shift the curve right and promote oxygen release.\(^1\)\(^2\) A left shift reflects an increased affinity and decreased unloading at a given tension.

Although the oxygen-carrying function of hemoglobin has long been recognized, the role of hemoglobin in the transport and release of nitric oxide has attracted intense study only in recent years. Nitric oxide is a key messenger involved in vasodilation, vascular wall modeling, endothelial activation, platelet aggregation, and leukocyte adhesion.\(^3\)\(^4\) As high-affinity binding to many organic molecules inactivates the physiologic actions of nitric oxide, means of transport of bioactive forms of nitric oxide from the lung to sites of action in the peripheries must exist. Nitric oxide is transported to the peripheries as a variety of nitric oxide products, directly by binding to proteins or indirectly by secondary reactions with oxygen, to form nitrosating species that in turn bind to organic molecules.\(^5\)\(^6\)
Nitric oxide interacts with hemoglobin in a variety of ways: the reversible binding to the heme iron, the irreversible oxidation to nitrate after reaction with bound oxygen, and the formation of S-nitrosothiol hemoglobin.\textsuperscript{7,8} S-Nitrosothiol is a cysteine residue at position 93 on the hemoglobin $\beta$ chain. Because the affinity of this site is affected by the conformational oxygen state of hemoglobin, it has been suggested that this reaction can deliver bioavailable nitric oxide to the peripheries.\textsuperscript{5,8} However, nitric oxide has a short half-life measured in seconds, with many physiologically active metabolites.\textsuperscript{9} Determining the in vivo peripheral delivery and biologic effects of the various metabolites of nitric oxide is therefore technically difficult, and has not yet been definitively delineated. Hemoglobin seems to play a role in the pulmonary uptake and systemic release of nitric oxide, but the precise physiologic mechanisms remain incompletely understood.\textsuperscript{10–12}

The intricate structure of hemoglobin thus allows not only for the uptake, transport, and release of oxygen but also may affect the blood flow, vascular structure, inflammation, coagulation, and cell adhesiveness through nitric oxide signaling mechanisms.

**HEMOGLOBINOPATHIES**

Hemoglobin is a large and complex protein. Several hundred variants have been discovered. Most are benign or are of minimal significance, whereas other variants produce disease or are incompatible with life. Sickle cell disease and the thalassemias are the largest and most significant groups of hemoglobinopathies. Whereas hemoglobinopathies have long been viewed largely within the paradigm of oxygen delivery, more recent views approach these diseases as a broader consequence of oxygen and nitric oxide transport dysfunction.\textsuperscript{13–15} These diseases have a wide range of clinical expression, even between individuals with identical hemoglobin genotypes. Symptoms are therefore a product not simply of the primary genetic defect, but rather of the complex interactions of multiple other genes.\textsuperscript{16}

**Sickle Cell Disease**

Sickle cell disease results from the inheritance of a mutant $\beta$-globin gene that codes for a variant of hemoglobin A called hemoglobin S. Various genotypes produce disease states. Paired inheritance of the mutant gene results in exclusive expression of hemoglobin S and the most severe form of the disease, known as sickle cell anemia. The heterozygous inheritance of a mutant and a normal gene results in the largely benign carrier state, sickle cell trait, with erythrocytes containing hemoglobin S and hemoglobin A. The heterozygous inheritance of the $\beta^s$-allele and a thalassemia mutation that codes for impaired or absent hemoglobin A production also produces symptoms. The coexpression of hemoglobin S and hemoglobin C, a variant of hemoglobin A that does not afford protection against hemoglobin S, also results in a disease phenotype. The coinheritance of hemoglobin S with other rare mutants such as hemoglobin O-Arab, hemoglobin D-Punjab, or hemoglobin Lepore-Boston can also result in disease.\textsuperscript{13} Sickle cell disease is thus a group of disorders with similar genotypes and phenotypes, all characterized by the inheritance of hemoglobin S.

Approximately 8% of African Americans are heterozygous and have sickle cell trait, and roughly 1 in 600 has some form of sickle cell disease.\textsuperscript{17} The carrier state of sickle cell trait provides some protection against severe forms of malaria, believed to be the reason for the evolutionary persistence and high incidence of the mutant allele.\textsuperscript{18} There are believed to have been at least five separate spontaneous mutations of the allele occurring in human history, four in Africa and one in south-east Asia, areas where malaria has historically been prevalent.\textsuperscript{19} The African mutations are common in
equatorial Africa, the eastern Mediterranean littoral, and western Saudi Arabia, whereas the Asian mutation is prevalent in the Gulf region and parts of India. With global migration, these mutations are now distributed worldwide.

The point mutation of a single nucleotide substitution, guanine-adenine-guanine for guanine-thymine-guanine, results in the substitution of the negatively charged glutamic acid by the nonpolar valine in the $\beta$ chain. This has at least three interrelated effects on hemoglobin function: the hemoglobin S molecule is unstable and degrades more rapidly, the deoxygenated form is insoluble and precipitates out of solution in the cytosol, and, indirectly, the expression of hemoglobin F is upregulated.

The instability of hemoglobin is associated with widespread vascular inflammation, related to the release of iron and disturbances in nitric oxide physiology. In the intact hemoglobin molecule, the iron-containing heme moieties are contained within a hydrophobic pocket formed by the polypeptide chains. This constrains the reactivity of iron with oxygen, allowing for reversible binding in the ferrous Fe$^{2+}$ form rather than in the ferric Fe$^{3+}$ form. The accelerated disintegration of hemoglobin releases the iron moieties from this protective encasing, exposing the cell membrane to oxidative damage from the iron. Subsequent hemolysis releases free iron into the circulation, both consuming free nitric oxide and exposing the vascular endothelium to oxidant damage. Loss of intracellular intact hemoglobin may also impair normal physiologic transport of nitric oxide within the erythrocyte. People with sickle cell disease may, therefore, be in a chronic state of nitric oxide deficiency based on impaired nitric oxide transport and increased scavenging of nitric oxide by free plasma iron. This contributes to a chronic inflammatory vasculopathy.

The second and associated consequence is the insolubility of the deoxygenated hemoglobin. Hemoglobin is normally in solution in the cytosol. On deoxygenation, hemoglobin S tends to crystallize and precipitate out of solution into a gel. The precipitation and polymerization of hemoglobin deforms the cell; the distortions include the characteristic “sickle” shape that gives the disease its name. This process is time dependent, with most red cells transiting the circulation and reoxygenating before widespread precipitation and cell deformation occurs. Only a small proportion of cells sickle reversibly during normal circulation. The polymerization process is exquisitely sensitive to the concentration of the hemoglobin. Extensive cell membrane damage associated with the accelerated hemoglobin breakdown results in pathologic cell dehydration and consequently an increased intracellular hemoglobin concentration. As a terminal result in the accelerated aging process, concentration increases to the point whereby a small proportion of pathologically dehydrated cells sickle reversibly, before deteriorating to an irreversibly sickled state. Cell sickling results therefore not just from the insolubility of deoxyhemoglobin S but also from the pathologic cellular dehydration due to membrane damage associated with the breakdown of the unstable hemoglobin S. There is therefore no specific hemoglobin oxygen saturation at which sickle cells universally start to sickle but rather a spectrum of responses related to cell membrane health. The responses range from cells that do not sickle during the physiological circulation time, to cells that circulate in a permanent and irreversible sickled state, irrespective of oxygenation.

A third associated effect on hemoglobin is an increased expression of hemoglobin F, which has a protective effect. Compared with the African haplotypes, the Asian mutation has a more benign course associated with high levels of hemoglobin F.

**Clinical Picture**

Sickle cell disease is characterized clinically by a shortened life span, chronic hemolytic anemia, extensive vascular disease, progressive end organ damage, and acute
The two most common acute complications are pain crises and acute chest syndrome. Pain crises or vaso-occlusive crises can loosely be defined as an acute episode of pain not attributable to pathology other than sickle cell disease. Bone pain most commonly presents following marrow infarction of the lumbar spine, femoral shaft, or knee, is often present in multiple areas, and is sometimes symmetrically distributed. Abdominal pain may arise from gastrointestinal dysfunction, splenic or liver infarction, or be referred from the ribs. The acute chest syndrome is an acute lung injury specific to sickle cell disease, although overlap with other pulmonary syndromes may occur. The syndrome consists of a new pulmonary infiltrate involving at least one lung segment on chest radiography, together with chest pain, fever of greater than 38.5°C, tachypnea, wheezing, or cough. Three probable precipitants of the syndrome include pulmonary infection, bone marrow fat embolism following a pain crisis, and occasionally pulmonary sequestration and entrapment of erythrocytes leading to lung injury and infarction.

In attempting to tease out the relative contributions of the insolubility and instability of hemoglobin S to the end clinical picture, a comparison with other diseases yields some interesting insights. The thalassemias are a group of hemoglobinopathies that are also characterized by accelerated breakdown of hemoglobin, heightened oxidative stress, nitric oxide disruption, and widespread vascular damage. Clinical features common to sickle cell disease and the thalassemias include a chronic hemolytic anemia, pulmonary damage, stroke, arterial occlusion, leg ulcers, and shortened life expectancy. Other hereditary chronic hemolytic anemias, such as hereditary spherocytosis, also develop vascular damage and similar complications associated with marked hemolysis. Much of the clinical picture of sickle cell disease also found in other hemoglobinopathies or hemolytic diseases may be accounted for by the instability and breakdown of the hemoglobin.

By contrast, the pathognomic features of sickle cell disease, the pain crisis and some types of acute chest syndrome, might be related to the unique feature of hemoglobin S: the insolubility and polymerization of the deoxygenated molecule. Experimental and observational studies also provide some interesting data. Experimental exposure to acute severe hypoxia does not seem to trigger pain crises or pulmonary problems. One study exposed 17 subjects to hypoxic gas mixes, and induced hypoxemia of 33.1 ± 6.9 mmHg and arterial oxygen saturation of 62.4% ± 3.5% (mean and standard deviation). Despite this severe hypoxemia, there were no acute complications. Other small early studies exposed a total of five people with symptoms of sickle cell disease to hypoxia, without significant problems. The uneventful use of occlusive arterial orthopedic tourniquets has been described in series totaling 37 patients. Prolonged survival with coexisting cyanotic heart disease and right-to-left communication, such as tetralogy of Fallot, is possible. As some symptom complexes of sickle cell disease are unique to the disease, the unique feature of hemoglobin S presumably plays a significant role in the pathology. However, these studies suggest that hemoglobin polymerization and cell sickling are not the sole precipitants of complications.

**Perioperative Management**

Management of sickle cell disease includes the confirmation of a preoperative diagnosis, a clinical assessment, anesthetic management appropriate to the procedure and clinical status of the patient, and the prevention and management of postoperative complications. The quoted incidence of complications varies widely, and may relate to the type of procedure, disease activity and severity, patient age, and preexisting organ dysfunction. A retrospective study of 1079 procedures noted an incidence...
of acute sickle cell exacerbations of 0% for tonsillectomy, 2.9% for hip surgery, 3.9% for myringotomy, 7.8% for intra-abdominal nonobstetric surgery, 16.9% for cesarean section and hysterectomy, and 18.6% for dilation and curettage.\textsuperscript{39}

**Preoperative Assessment and Workup**

The appropriate preoperative screening for sickle cell disease is unclear. In the United States and parts of Western Europe, neonatal screening for hemoglobinopathies is widespread. Most patients or families in these parts of the world will know if they or their children have the disease. For patients from countries with a higher incidence of sickle cell disease but no universal screening, such as tropical African countries, the Caribbean, or some Mediterranean countries, the decision to request a screening test in younger children is ill defined. Children who reach the age of 10 years and have no symptoms are unlikely to have a clinically severe form of the disease that manifests for the first time in the perioperative period. Reports of universal or targeted preoperative screening programs including younger children have noted zero or clinically insignificant detection rates.\textsuperscript{40–43}

For those with established disease, the history and examination should identify the frequency, pattern, and severity of recent sickle exacerbations, and the presence and extent of organ damage.\textsuperscript{13} The lungs, kidneys, and brain are most commonly affected. Additional investigations may be indicated based on an assessment of the patient’s disease severity and the planned procedure. A hemoglobin level, a chest radiograph, and urine dipstick are inexpensive investigations that are easily obtained. Pulmonary function tests, arterial blood gas, electrocardiogram, or neurologic imaging may be indicated in more severe individual cases. Although the expression of hemoglobin S and hemoglobin F vary widely, there is little practical clinical use in determining hemoglobin S levels preoperatively.\textsuperscript{13}

**Hydration**

Perioperative hydration is often suggested as an important issue in sickle cell disease. This assumption is based on the fact that hemoglobin polymerization is closely related to intracellular concentration,\textsuperscript{22,44} blood containing hemoglobin S has greater viscosity than hemoglobin A, the presence of urine-concentrating defects in many sicklers, and published statements that dehydration causes acute complications. However, as noted previously, pathologic cellular dehydration is produced by cell membrane damage,\textsuperscript{21,22} not passive osmotic gradients. Whether minor alterations in intravascular volume significantly alter intracellular hydration, whether this alters sickling rates in vivo, and if so, whether this is of clinical relevance, is unclear. Most sicklers are anemic with stable hemoglobin levels in the range of 5 to 10 g/dL.\textsuperscript{25} At this level, blood viscosity as measured in vitro is actually less than or similar to normal hemoglobin A blood. To achieve in vivo hemoconcentration to levels at which the in vitro measurement of sickle erythrocyte viscosity starts to increase exponentially would require profound dehydration not typically seen in surgical patients. The relevance of mild concentrating defects to perioperative fluid management has not been studied.

Dehydration is suggested as a cause of acute complications, but there is a paucity of clinical accounts to clearly substantiate this statement.\textsuperscript{13,14} In recent years, preoperative fasting guidelines have been shortened to allow for oral intake of clear fluid up to 2 hours preoperatively. There is also an increased awareness of the complications of invasive intravascular monitoring, such as central line infection. Whereas the clinical effects of fluid shifts in the sickle cell population have not been studied, there is a lack of evidence to support admission for intravenous hydration during preoperative
fasting, aggressive hydration, or invasive monitoring beyond that appropriate for the surgical procedure and the degree of renal dysfunction.

**Transfusion**

Erythrocyte transfusion may be indicated to augment oxygen-carrying capacity, or to prevent acute exacerbations of sickle cell disease. Sickle cell disease is characterized by chronic anemia, increased minute ventilation, increased cardiac output, decreased peripheral vascular resistance, and increased 2,3-diphosphoglycerate. Hemoglobin levels are typically in the range of 5 to 10 g/dL, although values are somewhat higher in sickle cell-hemoglobin C disease. Replacement of blood loss should be individualized based on a patient’s baseline hematocrit, end organ pathology, and surgical losses. Autologous transfusion and the use of cell-saver blood have been reported in case literature.

The efficacy of transfusion to dilute the sickle cells and prevent acute exacerbations remains controversial. A prospective randomized trial involving 604 patients compared the use of an aggressive transfusion protocol designed to reduce the proportion of hemoglobin S to less than 30% with one designed to achieve a hematocrit of 30%. There was no significant difference in postoperative sickle exacerbations. The group that received more transfusions due to the aggressive protocol had a higher incidence of transfusion complications such as alloimmunization, the development of new non-ABO antibodies. This result suggested that aggressive transfusion protocols to dilute hemoglobin S were no more effective than the correction of anemia in preventing complications. However, there are no prospective randomized trials comparing outcome following transfusion with no transfusion. Two retrospective studies of children undergoing minor procedures without transfusion found low rates of acute sickle complications. The investigators concluded that transfusion could be avoided in low-risk cases. By contrast, another retrospective study found higher complication rates in nontransfused patients than in transfused patients undergoing minor procedures. Recent nonrandomized or retrospective studies comparing transfused and nontransfused patients undergoing moderate-risk procedures such as abdominal or orthopedic procedures have had varied results. Interpretation is confounded by small group sizes and uncontrolled additional risk factors. The effectiveness of prophylactic transfusion is therefore not clearly established at present.

If blood is transfused, extensive crossmatching for minor blood groups should be performed. Sickle cell patients have a high incidence of alloimmunization, which may lead to life-threatening or fatal hemolytic transfusion reactions.

**Oxygenation**

Although hypoxia and an increase in sickling are traditionally considered to be a trigger of perioperative sickle exacerbations, there are no definitive clinical accounts in the anesthetic or surgical literature to demonstrate this. Avoidance of acute hypoxia is a basic standard of anesthetic care in any patient population, as in sickle cell patients. However, there is no direct evidence to support hyperoxygenation or prolonged oxygen supplementation beyond the levels needed to support the patient’s baseline oxygen saturation. Pulse oximetry tends to underestimate true hemoglobin oxygen saturation by about 2% because of the high concentration of coexisting methemoglobin.

**Thermoregulation**

Hypothermia causes a left shift in the oxygen dissociation curve, and thus in isolation would tend to retard sickling. Patients have suggested that skin cooling may be a precipitant of acute complications occurring in community settings, but the
relevance of this to anesthetic-induced hypothermia is unclear. Maintenance of normothermia is a basic anesthetic aim in the general population, and therefore presumably should be the goal in sickle patients. Uneventful hypothermia during cardiopulmonary bypass has been reported.

**Acid-Base Regulation**

Acidosis has been suggested as precipitant of complications, but it is difficult to separate the effects of acidemia from an underlying pathologic condition. It seems unlikely that minor fluctuations in acid-base status are a potent trigger of acute problems.

**Regional Anesthesia**

A retrospective study of 1079 anesthetics noted a higher incidence of postoperative complications associated with regional anesthesia compared with general anesthesia, but this finding was confounded by obstetric anesthetics. Later studies did not detect an association of increased complications with neuroaxial anesthesia. Neuroaxial anesthesia is commonly used for orthopedic and obstetric indications, as well as the treatment of pain crises. Sickle cell children report more pain and use more morphine postoperatively than nonsickle children, so regional anesthesia may be an effective alternative for postoperative pain management.

**Specific Procedures**

Outpatient surgery may be appropriate for selected patients and procedures. The baseline health of the patient, the type of procedure, and the rapid access to health care should problems arise are factors to be considered.

Since cholelithiasis associated with high erythocyte turnover is common, cholecystectomy is a frequent surgical procedure. The incidence of perioperative sickle complications is approximately 10% to 20%. Laparoscopic techniques are now typically used in preference to open cholecystectomy.

There is an increased incidence of spontaneous abortion, intrauterine growth retardation, antepartum hospitalization, premature labor, and postpartum infection in parturients with sickle cell disease. Complications of sickle cell disease increase during pregnancy. The incidence of pregnancy complications is higher in homozygous hemoglobin S parturients than in those with hemoglobin SC. Pregnancy, outcome is unaffected by sickle cell trait. The reported incidence of postoperative complications is 14% to 19% following dilation and curettage, and 11% to 17% after cesarean section and hysterecomy. Rates of adverse birth outcomes and neonatal complications in infants with sickle cell disease are similar to rates for normal infants. The predominant neonatal hemoglobin is fetal hemoglobin F, which contains chains rather than the mutant chain.

Orthopedic procedures to treat sickle cell complications, such as drainage of bone infection, joint replacement, or correction of musculoskeletal deformities, are frequent indications for anesthesia. In a study comparing sickle cell and control patients undergoing hip surgery, the onset time of atracurium was delayed, although total duration of action was unchanged; the investigators suggested this was due to the increased intravascular volume of sickle cell disease. The reported incidence of sickle complications after hip surgery ranges from 0% to 19%. Arterial cerebrovascular disease is a common and often devastating complication of sickle cell disease, leading to multiple thrombosis or hemorrhagic strokes, neurologic impairment, and death. Anesthesia is often needed for neurovascular imaging, and for radiological or surgical ablation of intracranial aneurysms. Moyamoya disease,
an unstable neovascularization, is another complication that can be treated surgically. Modern nonionic contrast dyes seem to be safe for use with sickle cell disease. Although historically aggressive transfusion has been used for these procedures, more recent management involves the avoidance or conservative use of blood transfusion.

There is a large case literature of cardiopulmonary bypass in sickle cell patients. Most involve reports of the correction of congenital anomalies in young children. Although earlier reports described the use of exchange transfusion, more recently there are reports of bypass being performed without transfusion. Children can survive with right-to-left shunts so the rationale of interventions to minimize sickling in an artificial circuit designed to repair a natural circuit that allows circulation of sickled cells is unclear. Whereas cardiopulmonary bypass can be performed without specific alterations to standard practice, the optimal management of this patient group is not established. Sickle cell trait does not seem to affect outcome after cardiopulmonary bypass and specific alterations to management are not indicated.

**Management of Complications**

Painful crises are a common complication, and often present difficult management problems. The relative roles of psychological vulnerability, exacerbation of the pain experience by recurrent exposure to opioids, acquired tolerance to analgesics, and the variability of each attack are not clearly defined. There are few controlled trials of pain management, perhaps due to the wide variability in the presentation of pain and the difficulty of objective assessment.

Pain crises may be mild, and treatable with oral analgesics in an outpatient setting. Conversely, pain may be severe enough to require admission and prolonged treatment with high doses of multiple analgesics. Pain should be closely assessed and measured using a pain scale. A randomized comparison of intravenous infusion and oral sustained-release morphine showed no benefit from intravenous administration. However, intravenous administration of opioids is commonly used, as a continuous infusion or with patient-controlled analgesia. This is a more effective regime than scheduled dosing with optional supplementation. Additional analgesics such as acetaminophen and nonsteroidal anti-inflammatory drugs are often used. Ketamine in low doses may be a useful accessory drug, and is currently undergoing investigation. Regional anesthesia for localized sites of pain is an effective analgesic technique.

Other factors are important. Reassurance, empathy, and support are essential. A search should be made for occult infection, a potential precipitant of complications. As the acute chest syndrome may complicate painful crises, the lungs should be examined regularly. Incentive spirometry decreases atelectasis and may prevent further pulmonary problems. Supplemental oxygen does not affect pain duration or analgesic use. Erythrocyte transfusion is not indicated during uncomplicated pain crises. Aggressive hydration is often used, although the benefits of this are not clearly established.

The acute chest syndrome is a frequent postoperative problem. In a study of 604 surgical patients, symptoms typically presented 3 days after surgery and lasted for 8 days. Early incentive spirometry, bronchodilator therapy, supplemental oxygen, adequate analgesia, and broad-spectrum antibiotics are recommended treatment. Correction of anemia with transfusion can improve oxygenation, although the effect on outcome has not been clearly established. The outcome following mechanical ventilation for respiratory failure is usually good.
Thalassemias

The thalassemias are a broad group of hemoglobinopathies characterized by a disruption of the normal 1:1 ratio of the \(\alpha\)- and \(\beta\)-polypeptide chains. The disease was initially described in children of Mediterranean ethnic origin; the word thalassemia derives from the Greek word for sea, thalassa. The thalassemias are commonest in people of Mediterranean, African, and South-east Asian descent. As with sickle cell disease, carrier states give some protection against severe forms of malaria.

Thalassemias are classified by whether the \(\alpha\)- or \(\beta\)-chain production is affected. The \(\alpha\)-thalassemias result from a deficiency or deletion of one or more of the quartet of \(\alpha\)-1 and \(\alpha\)-2 genes. The clinical severity varies with the differing genotypes that produce the disease. When all genes are abnormal, hemoglobin Bart hydrops fetalis syndrome results with demise in utero or shortly after birth. Hemoglobin Bart is a \(\gamma\)-chain tetramer produced in the absence of \(\alpha\) chains. When three of the four genes are dysfunctional, hemoglobin H disease results. This condition is characterized by severe anemia, hepatosplenomegaly, jaundice, and vascular damage. Hemoglobin H is an abnormal hemoglobin made of four \(\beta\) chains, in the setting of severe underproduction of \(\alpha\) chains. Thalassemia caused by two missing or damaged copies of the \(\alpha\) gene has a mild anemia, whereas a single aberrant copy of the gene may result in a clinically silent carrier state. The \(\beta\)-thalassemias arise from the absence (\(\beta\)-0 thal) or reduction (\(\beta\)+ thal) of the synthesis of \(\beta\)-globin chains. Homozygous or coinheritance of two mutant alleles results in thalassemia intermedia or thalassemia major, a clinical classification based on the severity of the symptoms. The inheritance of a single mutant gene results in the carrier state, characterized by a mild microcytic, hypochromic anemia and a slightly elevated concentration of hemoglobin A2. Coinheritance of thalassemia mutations with hemoglobin S will produce sickle cell disease, whereas coinheritance of hemoglobin E leads to symptoms of thalassemia.

The disruption of the normal balance of \(\alpha\)- and \(\beta\)-chain production produces unstable hemoglobin, rapid breakdown, release of iron complexes, and damage to the erythrocyte membrane. As in sickle cell disease, the chronic hemolysis and disturbed nitric oxide physiology are associated with progressive vascular damage, pulmonary hypertension, and activation of coagulation. Ineffective erythropoiesis results in accelerated apoptosis, disruption of erythroid maturation, and marked erythroid marrow expansion. Extramedullary erythropoietic tissue expansion in the thorax, head, and paraspinal regions can lead to deformation of the face and skull, demineralization/osteopenia, and fractures. Anemia, splenomegaly, and increased plasma volume due to shunting through expanded marrow are other sequelae. Iatrogenic iron overload and hemochromatosis are complications of chronic transfusion therapy.

Common indications for anesthesia include cholecystectomy, splenectomy, vascular access needed for frequent transfusions, osteotomies of bony deformities, or repair of fractured demineralized bone. The anesthetic literature is scant; reported issues include airway access and hemodynamic control of a vasculopathic population. Bony abnormalities of the maxillofacial area may occasionally complicate airway access, making intubation difficult.\(^74,75\) Laparoscopic techniques have been successfully used for cholecystectomy and splenectomy,\(^76\) although perioperative hypertension may be a problem.\(^77\) Blood loss can be managed with cell salvage, avoiding the chronic complications of repeated transfusion.\(^78,79\) Successful cardiopulmonary bypass with cautious use of sodium nitroprusside in two patients with hemoglobin H disease has been reported.\(^80\)
Hemoglobin C and E

Hemoglobin C, a β-chain variant, is commonest in people of West African descent whereas another β-hemoglobinopathy, hemoglobin E, is commonest in South-east Asia. Homozygous inheritance of either mutant allele causes a mild hemolytic anemia and mild to moderate splenomegaly.81 The combination with another mutation, for example hemoglobin SC disease or hemoglobin E β-thalassemia, produces disease symptoms of sickle cell disease or thalassemia, respectively.

Other Congenital Hemoglobinopathies

A small number of other hemoglobinopathies have been reported to affect anesthetic management. The central issue is the accuracy and interpretation of pulse oximetry in the presence of an abnormal hemoglobin.82–88 Pulse oximeters rely on the principle of spectrophotometry, based on the Beer–Lambert law.1 Using two absorption spectra, the degree of oxygen binding is calculated from the differences in absorption spectra of oxygenated and deoxygenated hemoglobin. Dyshemoglobins, such as methemoglobin, carboxyhemoglobin, or sulfhemoglobin, have different absorption spectra or oxygen affinities. The presence of large quantities of these hemoglobins can make oximetry calculations and assumptions about oxygen delivery inaccurate. Some hemoglobinopathies similarly have differing absorption spectra, and the usefulness of pulse oximetry may be limited. Co-oximetry uses multiple waveforms, allowing analysis of multiple hemoglobins, and may provide a more accurate picture than pulse oximetry.88 As an alternative, measurement of arterial blood gas can be used as an estimate of arterial oxygenation and delivery.

Several hemoglobinopathies, designated hemoglobin M variants, closely resemble methemoglobin but have slightly different absorption spectra.1 This group of hemoglobinopathies has an altered oxygen affinity that results in a cyanosis that is usually asymptomatic. Methemoglobin is produced by the oxidation of ferrous iron (Fe^{2+}) to ferric iron (Fe^{3+}). Typical levels of less than 1% are abnormally raised when the enzyme responsible for reducing methemoglobin, reduced nicotinamide adenine dinucleotide (NADH)-cytochrome b5 reductase, is congenitally deficient or disabled by a drug. By contrast, the oxygen affinity of the iron in hemoglobin M variants is abnormal due to amino acid substitutions in the α and β chains close to the heme groups. These may variously produce increased auto-oxidation to methemoglobin, or altered absorption spectra to pulse oximetry.

Hemoglobin MIwate is an unstable hemoglobin with an accelerated auto-oxidation into the ferric methemoglobin form.88 The oxygenated form has a similar absorption spectrum to methemoglobin. The high levels of methemoglobin and altered absorption spectrum of the oxygenated form make pulse oximetry ineffectual. HemoglobinCheverley (B45 Phe→Ser) and HemoglobinHammersmith (B42 Phe→Ser) similarly produce low readings that preclude use of the oximetry to monitor arterial oxygenation.85 By contrast, HbKohn, a hemoglobin with an abnormal α chain, has an increased oxygen affinity. Despite the left-shifted oxygen dissociation curve, however, pulse oximetry readings are paradoxically low.82,83 In these settings, knowledge of the limitations of conventional oximetry, attention to detail, increased vigilance, and alternative monitoring such as arterial blood gas analysis, co-oximetry, and end-tidal oxygen concentration may assist the delivery of a safe and uncomplicated anesthetic.85,87

SUMMARY

Hemoglobinopathies are a large and diverse group of disorders that present many interesting and challenging situations. Common problems relating to the instability...
of the hemoglobin molecule are often present in these diseases. Close communication and collaboration between the surgeon, anesthesiologist, and hematologist are essential to ensure the safe and optimum management of people with these disorders.

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