**Abstract**: A review of the available literature on genetics and pathophysiology of Sickle Cell Anaemia was performed with special emphasis on the intra-operative management during cardiac surgery. Hypoxia, acidosis and hypothermia have been identified as independent sickling provoking factors. Although no official guidelines on transfusion for Sickle Cell patients have been published, useful directives on preoperative transfusion could be derived from available data. Additionally, we bundled and reviewed the published expertise in the management of cardiopulmonary bypass and the necessity of hypothermia during cardiac surgery in Sickle Cell patients. Our conclusion is that the available data in case reports and case series on cardiac surgery in case of Sickle Cell Anaemia suggest a necessary preoperative or on bypass blood transfusion to guarantee an uncomplicated course of cardiopulmonary bypass and hypothermia.

**Key words**: Sickle cell anaemia; sickle cell trait; sickle cell disease; genetics; pathophysiology; transfusion guidelines; cardiopulmonary bypass; hypothermia; cell saver.

In 1904 Dresbach published a case report on an American medical student who had found elliptical red blood cells instead of circular red blood cells in his own blood sample (1). Only one year later Dresbach reported that this young student had died abruptly from ‘cardiac failure subsequent to an attack of acute inflammatory rheumatism preceded by tonsilitis’ (2). More than 100 years later, we now know that this young man was suffering from Sickle Cell Disease (SCD).

This review focuses on the most recent literature on SCD. First, the genetic background, the pathophysiology and the perioperative management in case of SCD will be reviewed. In a second part, we tried to bundle all available publications on cardiac surgery in patients suffering from SCD. Special attention has been paid to the consequences of SCD on the use of cardiopulmonary bypass and hypothermia. To our knowledge, the only available data on the experience of cardiac surgery in case of SCD are case reports and case series.

**GENETICS**

Sickle Cell Anaemia was found to be a hereditary haemoglobinopathy with an autosomal recessive mode of transmission. The responsible gene is located on chromosome 11 and codes for the assembly of the β-globin chain of haemoglobin A.

Normal adult haemoglobin is built up by two α and two β chains and is referred to as haemoglobin A (HbA). Foetal haemoglobin is called haemoglobin F and contains two α and two γ chains.

In the mutant gene there is only one point mutation: on the 17th nucleotide, adenine is replaced by thymine resulting in the change of the 6th amino acid in the β-globin chain: valine instead of the negatively charged glutamic acid. The β-chain hereby loses part of its negative charge causing a reduction in the stability and the solubility of the structure of the β-chain. The haemoglobin that is built up by the mutated β-globin chains is called haemoglobin S (HbS) (3).

**PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS**

As Sickle Cell Anaemia is transmitted in an autosomal recessive way, two different patterns are distinguished: homozygotes produce only haemoglobin S, while the heterozygotes generate a
mixture of the normal adult haemoglobin A and the mutated haemoglobin S.

As the presence of haemoglobin A diminishes the clinical impact of haemoglobin S, the heterozygote form has a less serious phenotype, referred to as Sickle Cell Trait (SCT). The homozygote form has more serious clinical consequences and is called Sickle Cell Disease (SCD) (3-5).

**Pathophysiology**

When the intracellular oxygen level decreases, the haemoglobin chains undergo conformational changes: polymers of haemoglobin chains will be formed, causing destabilisation of the erythrocytes: the red blood cells change from their stable and flexible donut-like shape into a vulnerable sickle-shaped cell. This phenomenon is referred to as “sickling of erythrocytes” (3, 4, 6-8).

Normal erythrocytes are flexible and migrate easily through the arterial and venous microcirculation, while the sickled cells are less flexible than the normal erythrocytes. This will result in arterial and venous microcirculatory obstruction. Consequently to the obstruction of blood flow through small arteries and veins, repetitive vaso-occlusive crises and multi-organ failure will occur.

Two factors contribute to the degree of polymerisation of the haemoglobin S.

First, the duration of deoxygenation of the haemoglobin: the erythrocytes start sickling if the arterial or venous oxygen tension is dropping below 40 mmHg during at least two to four minutes. In conditions of low blood flow or extreme low levels of oxygen tension, the red blood cells will start sickling and cause obstruction of the microcirculation. Although sickling can be reversed if the oxygen tension is re-established, the conformational switch between sickling and “unsickling” generates damage to the cell membrane. Finally, irreversible sickled conformation and premature cell death will occur (3-8).

The second predictive factor for the extent of sickling of the erythrocytes is the proportion of haemoglobin S, haemoglobin A and haemoglobin F in red blood cells. As haemoglobin A and haemoglobin F do not undergo polymerisation in case of cell deoxygenation, these types of haemoglobin play a protective role for the deoxygenated erythrocytes. The higher the percentage of haemoglobin S in a red blood cell, the more the erythrocyte will tend to sickle and cause vaso-occlusion (3-8).

The influence of hypothermia on sickling crises seems to be dubious. Peripheral vasoconstriction as a result of hypothermia leads to a state of low blood flow and might induce sickling of the erythrocytes. On the other hand, it has been found that hypothermia can slow down the *in vitro* polymerisation of the β-chains, avoiding sickling events (6).

Recent research suggests other factors than sickling of red blood cells to be involved in the pathophysiology of vaso-occlusion.

It has been found that in case of SCD, the vascular endothelium is in a state of chronic inflammation. This state of inflammation is supposed to be the result of cycles of ischemia and reperfusion caused by vaso-occlusion. Reperfusion of ischemic tissue leads to the expression of endothelial cell-adhesion molecules known as Vascular Cell Adhesion Molecule 1 (VCAM 1), Intercellular Cell Adhesion Molecule 1 (ICAM 1), P-selectin and E-selectin. Reperfusion events cause also an increase in the production of inflammatory cytokines like Interleukin-1 (IL-1), Interleukin 6 (IL-6) and Tumor Necrosis Factor (TNF).

This up-regulation of cytokines and endothelial cell-adhesion molecules leads to a destroyed equilibrium between vasodilatation and vasoconstriction. This imbalance in vascular tone promotes the stasis of blood flow and creates the ideal circumstances for the erythrocytes to sickle (6, 7).

Also nitric oxide (NO) is found to play a key role in the pathophysiology of SCD (3-7, 9-11).

In physiologic conditions, NO is produced by the endothelium of the pulmonary vascular bed. After binding of NO with intracellular haemoglobin, it is transported as S-nitroso-haemoglobin to the peripheral microvasculature to regulate the vasodilator tone and to inhibit the production of the VCAM-1, ICAM-1, P-selectin and E-selectin.

In case of SCD the protective role of NO is impaired in three ways:

1. Since the total amount of haemoglobin is low in SCD because of continuous haemolysis, the total carrier capacity for NO is strongly reduced.
2. The high level of haemolysis will result in a high level of free haemoglobin circulating in the plasma. The free haemoglobin strongly binds the released NO to form heme-nitrosyl-haemoglobin. The bio-available NO is hereby inactivated.
3. Arginine is a required substrate for the synthesis of NO. Arginase-1 is the enzyme that catalyses the chemic reaction to break arginine down into ornithine and urea. Since arginase-1 is
released in the plasma by haemolysis, arginine will be less available in case of SCD resulting in a lower level of NO-production. 

Figure 1 shows a schematic overview of all the factors involved in the pathophysiology of SCD.

Clinical manifestations of Sickle Cell Disease

The clinical manifestations of SCD are very heterogeneous: some phenotypes have mild symptoms with good survival while others suffer severe organ damage and die young (12).

Table 1 gives an overview of the complications of SCD with their prevalence and their clinical consequences.

Pain as a consequence of vaso-occlusion

Episodes of heavy ischemic pain are a key element in SCD, mostly as a consequence of vaso-occlusive crises. In early childhood the vaso-occlusion in the small bones of hands and feet is often the first manifestation of SCD, known as dactylitis (6, 12, 13).

Infection

Because the spleen is affected by the vaso-occlusive crises, a state of functional asplenism often arises. This makes a patient extremely vulnerable for infections with encapsulated bacteria. Infection with Streptococcus Pneumoniae, Neisseria Meningitides and Hemophilus influenzae can cause a fulminant sepsis with a high mortality rate. Vaccination prevents this life-threatening condition and is advised in every child diagnosed with SCD (6, 12, 13).

Acute Chest Syndrome (ACS)

The definition of ACS is a new pulmonary infiltrate on chest radiography, plus one or more of the following symptoms: fever, cough, sputum production, tachypnoea, dyspnoea or new onset of hypoxia.

ACS is treated with broad-spectrum antibiotics, oxygen therapy, adequate analgesia and bronchodilation. Mechanical ventilation is often required. Blood transfusion can be necessary. The use of dexamethasone in case of an ACS remains controversial, as it might improve the clinical evolution in an acute event but might evoke an earlier recurrence of ACS (14, 15).

The first trials on the role of inhaled NO reveal beneficial pain-relieving effects in children suffering from vaso-occlusive crises (11).

<table>
<thead>
<tr>
<th>Complication</th>
<th>Prevalence (%)</th>
<th>Clinical consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaso-occlusive crises</td>
<td>58</td>
<td>Pain</td>
</tr>
<tr>
<td>Acute aplastic anaemia</td>
<td>46</td>
<td>Anaemia</td>
</tr>
<tr>
<td>Acute chest syndrome</td>
<td>44.8</td>
<td>Pain, fever, cough, dyspnea</td>
</tr>
<tr>
<td>Acute splenic sequestration</td>
<td>26</td>
<td>Pain, bacterial infections, anaemia</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>12</td>
<td>Pain, fever</td>
</tr>
<tr>
<td>Meningitis-septicaemia</td>
<td>11.4</td>
<td>Pain, fever, shock</td>
</tr>
<tr>
<td>Stroke</td>
<td>6.7</td>
<td>Motor and mental retardation</td>
</tr>
</tbody>
</table>
ACS is the most common cause of hospitalisation and death in case of SCD (6, 12, 13).

Anaemia

Splenic sequestration crises and aplastic crises with suppression of the normal erythropoiesis lead to acute drops in haemoglobin levels in patients with SCD (6, 12, 13).

Neurologic complications

Ischemic cerebrovascular accidents with clinical relevant implications are found in 5% of the children suffering from SCD (6, 12, 13).

Adams et al proved that children at risk for a stroke could be identified by transcranial Doppler ultrasonography (16). Prophylactic transfusion to keep the haemoglobin S proportion lower than 30 percent reduced the incidence of ischemic cerebrovascular accidents in these children (17).

Urogenital complications

Progressive glomerular fibrosis leading to chronic renal failure is the consequence of repeated renal vaso-occlusive crises and the chronic vascular endotheliopathy seen in SCD. In men suffering from SCD, episodes of priapism and reduced fertility can occur (6, 12, 13).

Cardiovascular changes

Pulmonary hypertension is found in 30% of adults with SCD. The presence of severe pulmonary hypertension is a strong predictor of near-term death.

Remarkably, intravascular occlusion of the coronary arteries is an uncommon finding in SCD (6, 12, 13).

No official guidelines for SCD are available, but based on the published data, transfusion in patients with SCD should be targeted at (19, 20):

(1) Hematocrit value of less than 30%
(2) Proportion of haemoglobin S less than 30%

Indications for transfusion

(1) Acute symptomatic anaemia
(2) Aplastic crises
(3) Acute sequestration crises by the spleen or liver
(4) Stroke
(5) Acute Chest Syndrome

SicklE cell anaemia and cardiac surgery: What is the expertise?

The provoking factors for sickling of red blood cells are hypoxia, states of low blood flow, acidosis and hypothermia. Cardiac surgery with the use of cardiopulmonary bypass and hypothermia is therefore a great challenge for both the anaesthetist and the surgeon. Especially when circulatory arrest is unavoidable, sickling of erythrocytes is thought to become unavoidable as well.

We reviewed the recent literature on cardiac surgery in patients with Sickle Cell Anaemia. Except for 2 retrospective analyses (22, 23), the only available literature are case reports. A schematic overview of these publications is given in Table 2.

Transfusion and cardiopulmonary bypass

The upper part of Table 2 gives an overview of publications on cardiac surgery on patients suffering from Sickle Cell Disease.

In the majority of these cases (14 out of 20 cases), patients received red blood cell transfusion in preparation for surgery. Different options for the timing of transfusion have been reported:

(1) Preoperative transfusion: therapeutic phlebotomy followed by exchange transfusion prior to surgery (24-28).
(2) Preoperative transfusion: erythrocytes transfusion not proceeded by phlebotomy prior to transfusion (29).
(3) Intraoperative transfusion after induction of anaesthesia and before surgical incision under continuous monitoring of the haemodynamics (30).
(4) Complete exchange transfusion by priming the cardiopulmonary bypass with HbSS-free red blood cells and plasma. At initiation of the cardiopulmonary bypass, the initial amount of venous drainage corresponding to the total body circulation was collected in a cardiotomy reservoir and replaced by HbSS-free blood through the arterial cannula (24, 31-36).

No transfusion before the initiation of cardiopulmonary bypass was performed in 6 out of 20 cases because of the following reasons:

1) **High hemoglobin F fraction:**

Harban et al. reported a series of three children undergoing cardiac surgery. Because of their young ages (3 weeks, 3 months and 18 months old) their fraction of circulating Haemoglobin S was lower than the adult value. The lower the age, the higher the proportion of circulating protective Haemoglobin F will be (34).

2) **Priming of the bypass circuit with normal blood:**

In both publications where no preoperative exchange transfusion was performed, the cardiopulmonary bypass was primed with normal red blood cells to reduce the circulating Haemoglobin S and the first volume of venous drainage was discarded (37, 38). In the publication of Frimpong-Boateng et al., the children were even given two units of normal red blood cells postoperatively.

Based on the available literature we can conclude that no experience has been published on
transfusion-free cardiac surgery in case of SCD. This means that, at this time, there is lack of evidence that cardiac surgery without perioperative transfusion can be performed safely. The classical perioperative guidelines for the management of patients suffering from SCD (target hematocrit value of less than 30% and target proportion of haemoglobin S less than 30%) are thus not valid for cardiac surgery.

The lower part of Table 2 contains the publications on cardiac surgery in patients suffering from SCT.

Maddali et al. retrospectively report 43 patients undergoing cardiac surgery. No transfusion was administered before the initiation of cardiopulmonary bypass. Whole blood was administered in 82% of the cases during bypass or postoperatively because of a low value of hematocrit (≤ 18%). They concluded that the risk of transfusion-related complications outweighs the risk of vaso-occlusive crises in case of Sickle Cell Trait (22).

The publication of Youssafzai et al. retrospectively studied 47 patients suffering from SCD or SCT, but it was unclear from their data what the exact proportion of each was in their cohort. The patients underwent both preoperative as well as intraoperative transfusion to decrease the proportion of haemoglobin S in the circulation and none of the patients had symptoms of vaso-occlusive events (23).

As in the case of SCD, there is lack of evidence to state that transfusion-free cardiac surgery with cardiopulmonary bypass is safe in patients suffering from SCT. The classical guidelines for transfusion as mentioned above are also limited for non-cardiac surgery in case of SCT.

There is no clear evidence on how to calculate the amount of red blood units that should be transfused in any case of indication for transfusion. In our opinion, the practice of transfusion will be based on the clinical signs and the laboratory results to reach the target hematocrit and proportion of hemoglobin S.

As mentioned in the available case reports on cardiac surgery, clinical practice mostly consists of performing a complete exchange transfusion in preparation to the start of cardiopulmonary bypass.

Hypothermia and cardiopulmonary bypass

In 10 out of the 20 published cases of SCD, hypothermia was used during cardiopulmonary bypass without adverse sickling events. However, in 50% of these cases reporting hypothermia, the body temperatures were kept at 34°C or even 34.9°C which is not really hypothermia. All patients that were cooled had undergone transfusion before or during cardiopulmonary bypass.

To avoid sickling of erythrocytes in the coronary arteries during cardiopulmonary bypass, cardioplegia was mostly initiated with a warm cardioplegic solution to wash out the erythrocytes. When cardioplegia had to be repeated, a cold solution could be used since the erythrocytes had already been washed out (25, 31, 34, 38, 39).

Even though the general opinion is that hypothermia promotes the sickling of erythrocytes, in vitro studies have demonstrated that hypothermia might slow the polymerization of hemoglobin S and delay the onset of sickling of the erythrocytes (6). However, this benefit of hypothermia must be weighed against its potential adverse effects on increasing capillary transit time in vivo, resulting from vasoconstriction and slugging of red blood cells (24).

Since there is no consensus on the safety of the use of hypothermia, we checked the available literature on cardiac surgery without hypothermia during cardiopulmonary bypass. One case of an aortic valve replacement on a warm, beating heart in a patient suffering from SCD has been reported by Usman et al. (27). The patient underwent a preoperative exchange transfusion, was kept normothermic throughout the procedure and no cardioplegia was used. As all the sickling-evoking factors were avoided, this case might represent the ideal conditions for cardiac surgery in case of SCD. But again, insufficient experience exists to draw general conclusions.

Hypothermia without adverse sickling events has been applied in both retrospective studies about patients suffering from SCT (22, 23). Although no sickling crises have been reported in the cooled patients, the paucity of data does not guarantee the safety of hypothermia on cardiopulmonary bypass in case of Sickle Cell Anaemia.

The use of Cell Saver in case of Sickle Cell Anaemia

Only one publication was found on the expertise of using a Cell Saver in case of Sickle Cell Anaemia (40). In the presented case, the Cell Saver was used in a patient suffering from SCT undergoing an orthotopic liver transplantation. They experienced that the cell saving process of the collected blood resulted in sickling of 50% of the
present erythrocytes impeding the reinfusion of this cell saving fluid. Although the available evidence is little, the efficacy of using the Cell Saver in case of Sickle Cell Anaemia might be questioned.

The role of Calcium Channel Blockers in the prevention of sickling of erythrocytes

Two publications report the role of Calcium Channel blockers (41, 42) and they both suggest a positive role as they might inhibit (in vitro) the formation of irreversibly sickled cells. Since these publications report only in vitro results and no further research has been done in vivo, the clinical impact of these results is debatable.

The use of Tranexamic Acid and Sickle Cell Anaemia

To our knowledge, the only publication where the use of tranexamic acid has been described in a patient with Sickle Cell Anaemia, tranexamic acid was used to treat persistent haematuria (43). To our knowledge, there is no available evidence on the use of tranexamic acid in patients with SCD undergoing cardiac surgery.

The intra-operative management of cardiopulmonary bypass in patients with SCD

Unfortunately, no official guidelines exist for the settings of the cardiopulmonary bypass in case of SCD.

In the few available case reports that describe the material used for cardiopulmonary bypass, the classical centrifugal pumps and oxygenators were used and no adverse sickling events were reported.

Although no official guidelines for the settings of the cardiopulmonary bypass in case of SCD have been published, it is generally agreed that avoidance of acidosis, maintenance of adequate blood flow and high oxygen tension during cardiopulmonary bypass are essential in the management of sickle cell patients. This implies that continuous monitoring of arterial oxygen tension, acid-base balance and temperature control are essential (35).

One study explicitly describes some clinical parameters during the course of cardiopulmonary bypass: venous oxygen saturation was kept higher than 80% and the pH of the serum was maintained between 7.34 and 7.44. Flow rates during cardiopulmonary bypass were kept around 5 L/min for adults and 0.9 L/min for infants and mean perfusion pressures were around 77 mmHg for adults and 54 mmHg for children (23).

Preoperative and postoperative management in case of Sickle Cell Anaemia

The guidelines of the American College of Cardiology and the American Heart Association (ACC/AHA) are the basics for a valuable preoperative assessment of a patient’s physical status (44). These guidelines are still applicable but are not sufficient for a complete preoperative check-up in case of Sickle Cell Anaemia.

As a consequence of the repetitive vaso-occlusive crises, chronic organ failure will arise at a younger age. Preoperative screening should therefore include at least an ECG, chest radiography and extensive blood analyses (hematocrit value, proportion of haemoglobin S, coagulation parameters, function of the kidney, liver enzymes). Following the ACC/AHA-guidelines the preoperative assessment might be extended with echocardiography if the patient’s functional status is low.

We need to emphasize the importance of the present proportion of haemoglobin S in a patient’s circulation. Referring to the guidelines on transfusion, the patient might need to be transfused in preparation for surgery. If no preoperative transfusion is necessary, it is advised to order cross-matched blood units in time because the presence of irregular antibodies might delay the availability of matching blood units.

The challenge of postoperative care is to avoid the sickling provoking factors. Adequate analgesia and the avoidance of hypoxia, acidosis, hypothermia and dehydration are the key elements of an uneventful postoperative process.

Conclusion

More than a hundred years of research and expertise on the treatment of Sickle Cell Anaemia have led to the conclusion that avoiding of sickling of the erythrocytes is still the protagonist in the management of SCD. Management of the cardiopulmonary bypass is no exception to this rule.

Having reviewed the available literature on cardiac surgery in case of SCD, we advise anaesthesiologists and surgeons to keep the head cool, while keeping the circulation of the patient warm and well oxygenated. The available expertise on cardiac surgery in case of SCD suggests that perioperative transfusion is unavoidable to guarantee an uncomplicated course of cardiopulmonary bypass and hypothermia. However, since the available expertise is very limited, these are only preterm conclusions.
and future research and publications should bring more clarity. To increase the available evidence, every experience with cardiac surgery in SCD patients should be reported.

**Competing Interests**

No external funding and no competing interests declared.

**References**

1. Dresbach M., Elliptical human red cells coruscates, SCIENCE, 19, 469-70, 1904.


40. Braitbord D., Johnson D., Ramsay M., Paulsen W., Swygert T., Ramon V., Hargis D., Use of the cell saver in patients with sickle cell trait, Anesthesiology, 70, 878-879, 1989.


