SICKLE CELL TRAIT AND HEART TRANSPLANTATION

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UK
DISCLOSURES

• Ad Boards: Novartis, Agios, Werfen, Cosmopharma
• Research Grants: Haemosonic, Cosmopharma
• Educational Support: Novartis
CASE PRESENTATION
PATIENT HISTORY

• 49 year old female of Jamaican descent

• Referred to Papworth with severe heart failure thought to be related to peripartum cardiomyopathy

• PMH
  • Rheumatic heart disease – Mechanical mitral valve replacement 2013
  • Atrial fibrillation
  • Anaemia – menorrhagia (uterine fibroids)
  • Hypertension
  • Sickle cell trait – last recorded HbS – 38%
TRANSPLANT ASSESSMENT

- Assessment for transplantation
  - Severely impaired cardiac function
  - CKD III – Creatinine 99
  - Haemoglobin 133g/l

- Haemoglobin electrophoresis was not performed during assessment
A SERIES OF UNFORTUNATE EVENTS

- Transplant team sent sample which was booked into CUH system confirming sickle trait due to a processing error became unsolicited and was not accessible to requesters.
- Advice re the sickle trait was sought from haematology but due to the use of paper records not recorded to be easily visible when she was called for a transplant.
- Transplant surgeon at the time of operation unaware of the patient’s sickle trait status.
- Repeat sample sent from lab but booked as antenatal and rejected due to missing FOQ form.
TRANSPLANT PROCEDURE

• Uneventful implantation

• Cooled to 34.0°
• Retrograde COLD cardioplegia infused continuously
• Haemoglobin was between 75.2 – 96.1 g/l
• Cell saver used as redo sternotomy and preoperative warfarin
• Warm ischaemic time = 46 minutes
TRANSPLANT PROCEDURE

• Off CPB after 77 minutes of reperfusion with minimal inotropic support

• Global cardiac dysfunction developed

• Failure to stabilize with maximal inotropic support → Back onto CPB

• Further failed wean → VA-ECMO instituted
ECMO
• VA-ECMO suddenly stopped requiring cardiac massage back onto CPB

• TOE performed:
TRANSPLANT PROCEDURE
TRANSPLANT PROCEDURE

- Large thrombus within LA and LV
  - → Left atrium opened and thrombus evacuated from LA and LV
- ECMO circuit examined:
TRANSPANT PROCEDURE

- VA-ECMO circuit re-established

- Patient transferred to ITU
  - Chest packed due to coagulopathy
  - Inotrop support
  - Central VA-ECMO

- Implanted heart was asystolic
<table>
<thead>
<tr>
<th></th>
<th>Surgery start</th>
<th>Reperfusion of donor heart</th>
<th>Wean off CPB</th>
<th>On CPB and start ECMO</th>
<th>On CPB and second ECMO</th>
<th>ECMO clotted</th>
<th>On CPB and third ECMO</th>
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<tbody>
<tr>
<td>Red blood cells</td>
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<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<td>Fresh frozen plasma</td>
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</table>
ITU MANAGEMENT

- Haemofiltration for acidosis and lactaemia
- Ongoing coagulopathy

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<tr>
<th>Parameter</th>
<th>Preoperatively</th>
<th>ICU admission</th>
<th>12 hours post ICU admission</th>
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<tbody>
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<td>PT (10.1 – 15.3s)</td>
<td>22.3</td>
<td>Out of range</td>
<td>54.3</td>
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<td>APTT (27 – 35s)</td>
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<td>96.3</td>
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<td>TT (12 – 18s)</td>
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<td>Out of range</td>
<td>31.1</td>
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<td>Fibrinogen (1.46 – 3.33)</td>
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<td>0.7</td>
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<td>Platelets (150 – 400)</td>
<td>203</td>
<td>11</td>
<td>36</td>
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### ITU Management

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<thead>
<tr>
<th>Procedure</th>
<th>0-6 hours</th>
<th>7-12 hours</th>
<th>13-18 hours</th>
<th>19-24 hours</th>
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ITU MANAGEMENT

- No recovery of cardiac function
- Multiorgan failure
- Treatment withdrawn following discussion with family
POST MORTEM

- Extensive myocardial infarction
- Infarction of the liver and kidneys
- Evidence of intravascular red cell sickling

➤ Cause of death: catastrophic sickling crisis
SICKLE CELL AND CARDIAC TRANSPLANTATION
CARDIAC SURGERY AND SICKLE CELL

- Cardiopulmonary bypass presents many precipitating factors for a sickling crisis:
  - Inflammatory response, Cooling, Cardioplegia, Hypotension, Hypoxia, Cell saver

- Some advocate pre/peri-operative exchange transfusion
  - Increase haemoglobin – aiming for >100
  - Reduce proportion of HbS – aiming <30%

- However several series of cases without any modification of management
  - Even in SCT patients with HbS >30% and Sickle cell anaemia

- There is no consensus / guidelines on the perioperative management of these patients
HEART TRANSPLANTATION AND SICKLE CELL

- 3 cases of SCT and 7 with SCD, undergoing heart transplantation reported

- Only 2 cases describing intraoperative management

  - 46 year old male in Saudi Arabia SCT HbS 38%
    - Preoperative and intraoperative exchange transfusion aiming for HbS <10%. Cooled to 32°C

  - 33 year old male in Paris SCA
    - Was receiving regular transfusion so HbS 6%. No perioperative exchange transfusion. Cooled to 35°C
Figure 3 | HbS polymerization and erythrocyte deformation. Long polymers of sickle haemoglobin (HbS) align into fibres, which then align into parallel rods. The polymer has a helical structure with 14 HbS molecules in each section. 

The polymerization of HbS depends on many factors, including the HbS concentration, partial pressure of oxygen (pO₂), temperature, pH, 2,3-diphosphoglycerate (2,3-DPG) concentration and the presence of different Hb molecules. 

The basic concept of HbS polymerization kinetics is the double nucleation mechanism. Before any polymer is detected, there is a latency period (delay time) in which deoxygenated HbS molecules form a small nucleus, which is followed by rapid polymer growth and formation. Free cytoplasmic haem can increase the attraction of the HbS molecules and the speed of nucleation and polymer formation.

Cation homeostasis is abnormal in sickle erythrocytes, leading to the dehydration of cells. Potassium loss occurs via the intermediate conductance calcium-activated potassium channel protein 4 (also known as the putative Gardos channel) and K⁺-Cl⁻ cotransporter 1 (KCC1), KCC3 and/or KCC4 (REFS 269,270). Plasma adenosine can also reprogramme the metabolism of the erythrocyte, altering sphingosine-1-phosphate (S1P), ADORA2B, adenosine receptor A2b; AE1, band 3 anion transport protein; HbA, haemoglobin A; HbF, fetal haemoglobin.
Initial nucleation is followed by a delay time comparable to a timer—the cell may escape the microvascular bed where the nucleation has been triggered.

**Rigidity = m_{\text{poly}}^2**

Formation of Hybrids occurs.

Cell volume affects saturation and can increase delay time (10% -> 16x delay).
Figure 4: Mechanisms in sickle cell disease. Damage and dysfunction of the erythrocyte membrane caused by sickle hemoglobin (HbS) polymerization lead to hemolysis. Oxidized membrane protein self-aggregates that bind to existing antibodies, and membranes expose phosphatidylserine; both mechanisms promote phagocytosis of erythrocytes by macrophages, a path of extracellular hemolysis. Intravascular hemolysis releases the contents of erythrocytes into the plasma. Hb S scavenges nitric oxide (NO), arginase 1 depletes the L-arginine substrate of NO synthase (NOS), and asparagine diaphorase (NDA) inhibits NO synthases. Reactive oxygen species (ROS) further deplete NO, leading to vasoconstriction and vascular remodelling, especially in the lung. Adenine nucleotides and NO deficiency promote platelet activation and aggregation of blood clotting proteins. TNF-α and other danger-associated molecular pattern (DAMP) molecules activate the innate immune system. Lipid-bound Toll-like receptor 4 (TLR4) and TLR2 activate monocytes/macrophages to release inflammatory cytokines, which promote an inflammatory state and activation of endothelial cells. TLR4 activation on platelets promotes their adhesion to neutrophils, which internalize DNA to form neutrophil extracellular traps (NETs). Circulating blood cells adhere to each other and to the activated endothelium, contributing and potentially exacerbating vaso-occlusion. In postcapillary venules, activated endothelial cells that express P-selectin and E-selectin can bind rolling neutrophils. Activated platelets and adhesion molecules on endothelial cells adhere to circulating or endothelium-bound neutrophils and form aggregates. Sickled erythrocytes might also bind directly to the activated endothelium. This figure shows only some examples of the complex and redundant receptor-ligand interactions involved in the adhesion of circulating neutrophils to the damaged endothelium and exposed subendothelium. As in the case of other inflammatory processes, vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), leukocyte function-associated antigen 1 (LFA-1), and arterial endothelial growth factor (VEGF) promote the activation of endothelial cells and platelets, which in turn release NO, reactive oxygen species, and inflammatory cytokines. These factors act in concert to promote the formation of NETs, which are released from neutrophils and contribute to the formation of aggregates. The increased synthesis of ROS and NO further contributes to the vasoconstriction and vascular remodelling, leading to increased blood flow resistance and decreased oxygen delivery to tissue. The accumulation of sickled erythrocytes and the formation of aggregates further impede blood flow, leading to tissue ischemia and inflammation. This cycle of events perpetuates the inflammatory response, contributing to the development and progression of sickle cell disease. The figure highlights the complex interplay between various cellular and molecular components in the pathogenesis of sickle cell disease.
Figure 1.
In vitro disease model to study sickle trait blood flow using a microfluidic platform. (A) Schematic of the experimental platform built around the microfluidic device including an oxygen gas source, PBS hydration flow regulator, pressure regulation of whole blood, oxygen sensor, and high-speed camera. Inset (B) shows a cross-sectional view of the microfluidic device, which comprises of the gas, hydration, and blood layers as described in methods (C). Illustration of the blood microchannels in the device. A single blood channel starts at the inlet and loops around allowing for the simultaneous imaging of 4 sections of the channel as shown by the inset. Arrows along the channels depict the directionality of the blood as it traverses through the microchannels. (D) Photographs of blood as it traverses the microfluidic channels.

Figure 2.
Rheological behavior of SCT blood becomes oxygen-dependent near venous oxygen tension. (A) Normalized, steady-state flow velocity of a non-sickle (genotype AA) individual's blood sample does not depend on oxygen tension. Oxygen tension was varied in a stepwise manner as described in methods. The red to blue shaded gradient above the plot corresponds to oxygen tensions typically found in arterial circulation (red) and venous circulation (blue). Supra-physiological oxygen tension (white) is also displayed towards the right side of the box. (B) Normalized steady-state flow velocity of an individual with sickle...
Red: 70-85% SCD
Orange: 46-48%
Blue: 16-18%
Purple: 5-6%
Grey: SCT behaviour with confidence intervals

Graphs C/D position of graph shows transition I/II flow.
PRACTICE CHANGE

• Measure HbS in all patients prior to listing

• Pre-operative exchange transfusion for HbS >30%

• Aim for normothermic bypass
CONCLUSION

• This case highlights the danger of complacency in patients with sickle cell trait undergoing cardiac surgery with cardiopulmonary bypass
I want nothing.
I want nothing.
I want no quid pro quo.
I'll tell you to do the right thing.
This is the final word from the boss of the day.