Royal Papworth Hospital
NHS Foundation Trust

SICKLE CELL TRAIT AND HEART TRANSPLANTATION

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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

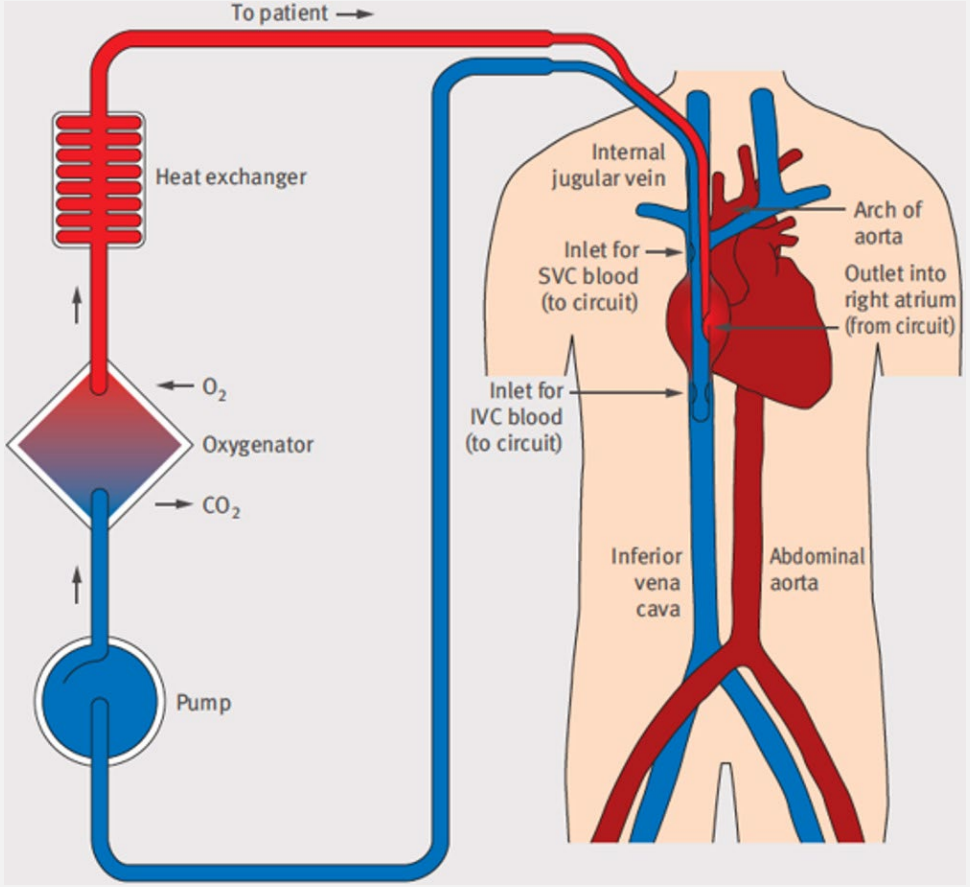
TRANSPLANT PROCEDURE

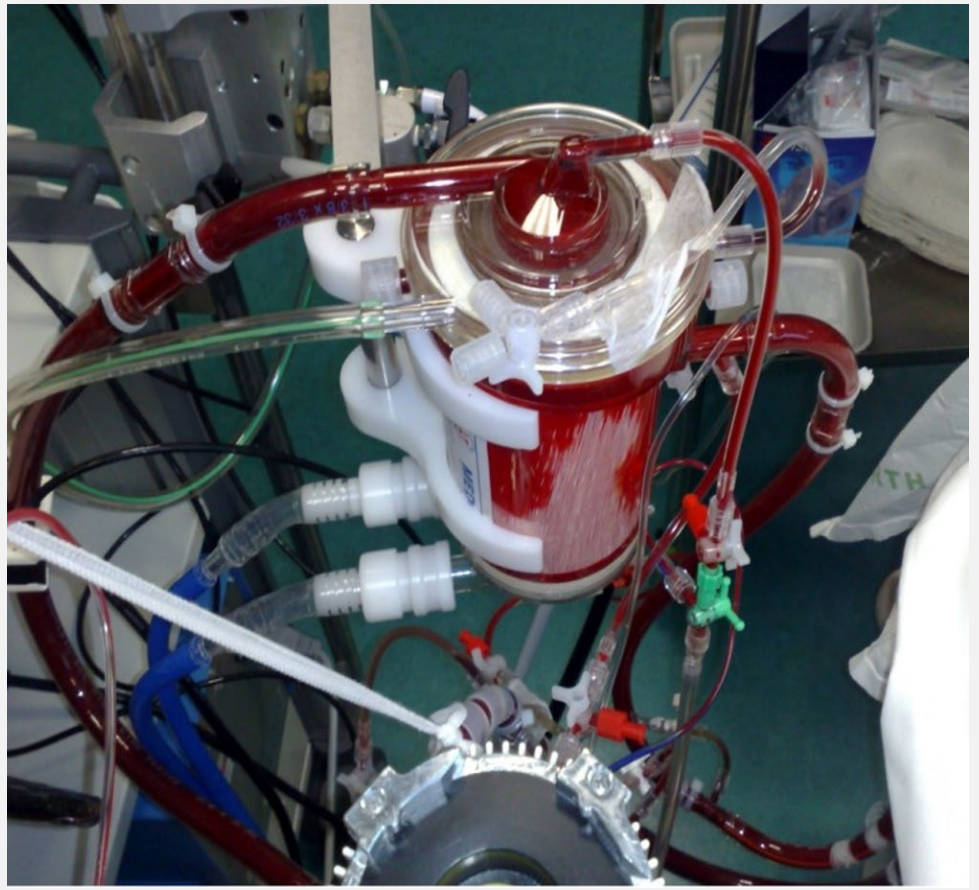
- Uneventful implantation
  - Cooled to 34.0°
  - Retrograde COLD cardioplegia infused continuously
  - Haemoglobin was between 75.2 – 96.1g/l
  - Cell saver used as redo sternotomy and preoperative warfarin
  - Warm ischaemic time = 46 minutes

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


To patient
Heat exchanger
O_2
Oxygenator
CO_2
Pump
Internal jugular vein
Arch of aorta
Inlet for SVC blood (to circuit)
Outlet into right atrium (from circuit)
Inlet for IVC blood (to circuit)
Inferior vena cava
Abdominal aorta



TRANSPLANT PROCEDURE

- VA-ECMO suddenly stopped requiring cardiac massage back onto CPB
- TOE performed:

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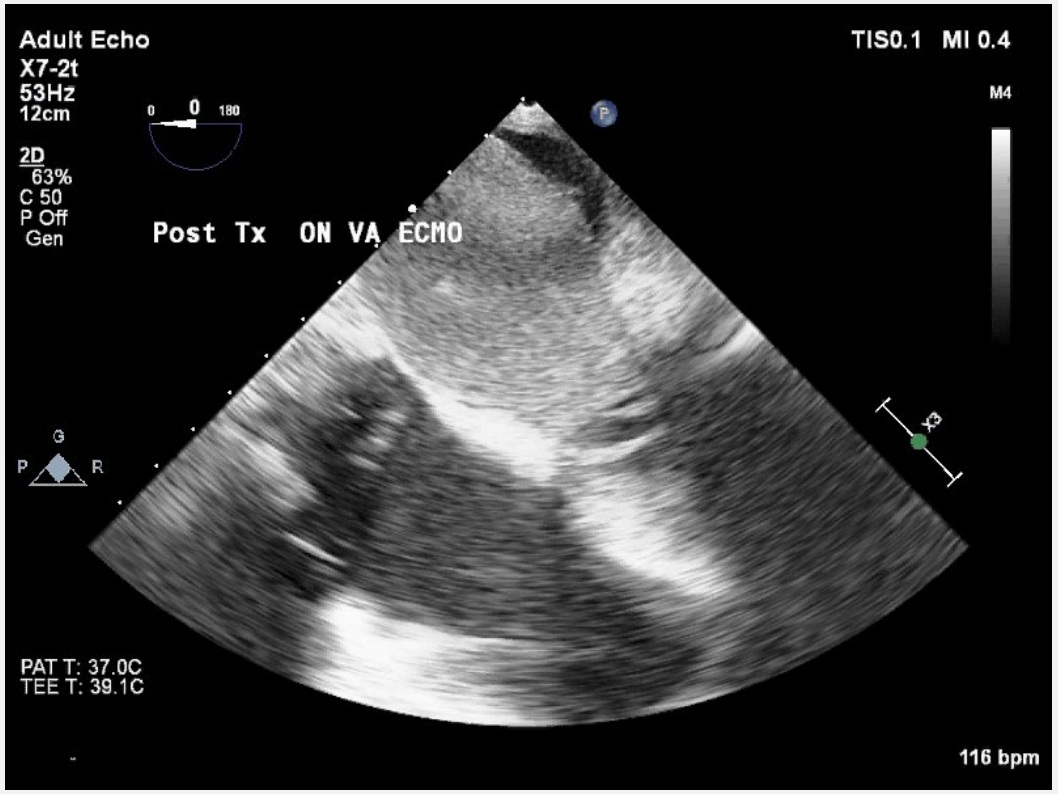
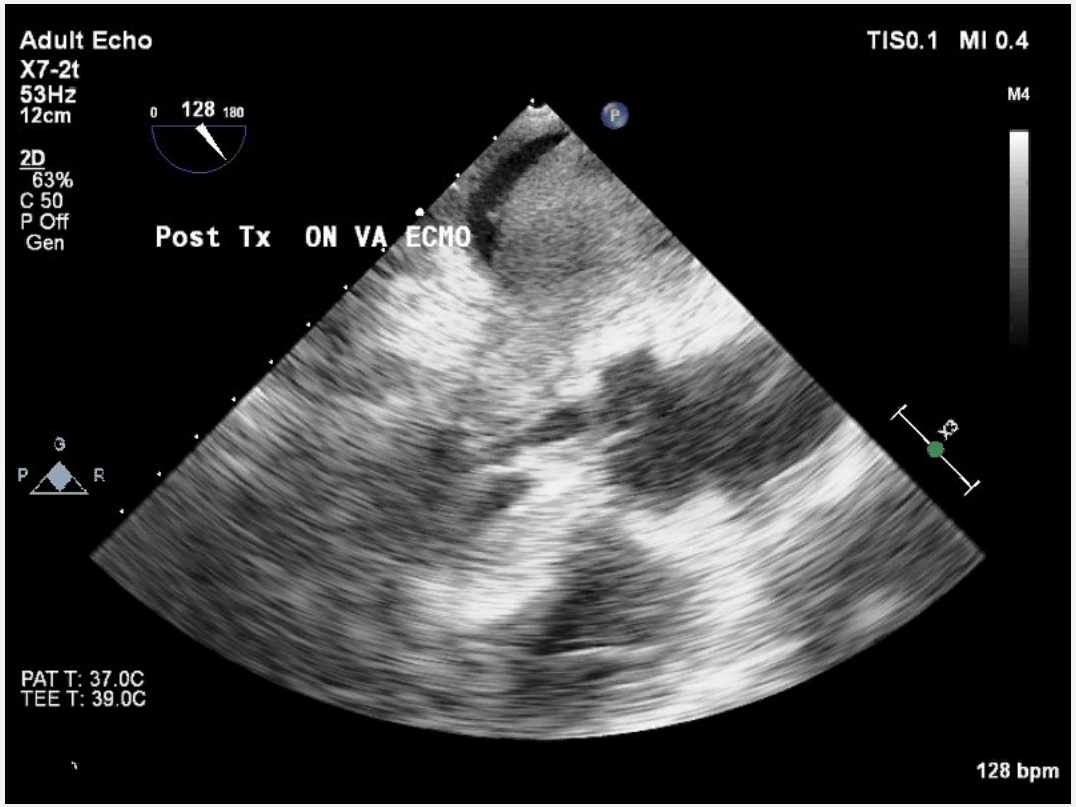
TRANSPLANT PROCEDURE





TRANSPLANT PROCEDURE

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

TRANSPLANT PROCEDURE

- VA-ECMO circuit re-established
- Patient transferred to ITU
  - Chest packed due to coagulopathy
  - Inotropic support
  - Central VA-ECMO
- Implanted heart was asystolic

BLOOD PRODUCT TRANSFUSION

	Reperfusion of donor heart	Wean off CPB	On CPB and start ECMO	On CPB and second ECMO	ECMO clotted	On CPB and third ECMO
Surgery start						
Red blood cells	**1**	**1**	**1**	**2**	**3**	-
Platelets	-	-	-	-	-	-
Fresh frozen plasma	-	-	-	-	-	-
Cryoprecipitate	-	-	-	-	-	-
Beriplex	-	-	**3**	-	-	-

ITU MANAGEMENT

- Haemofiltration for acidosis and lactaemia
- Ongoing coagulopathy

Parameter	Preoperatively	ICU admission	12 hours post ICU admission
PT (10.1 – 15.3s)	22.3	Out of range	54.3
APTT (27 – 35s)	33.3	Out of range	96.3
TT (12 – 18s)	-	Out of range	31.1
Fibrinogen (1.46 – 3.33)	-	Out of range	0.7
Platelets (150 – 400)	203	11	36

ITU MANAGEMENT

	Reperfusion of donor heart	Wean off CPB	On CPB and start ECMO	On CPB and second ECMO	ECMO clotted	On CPB and third ECMO
Surgery start						
Red blood cells	1	1	1	2	3	-
Platelets	-	-	-	-	-	-
Fresh frozen plasma	-	-	-	-	-	-
Cryoprecipitate	-	-	-	-	-	-
Beriplex	-	-	3	-	-	-

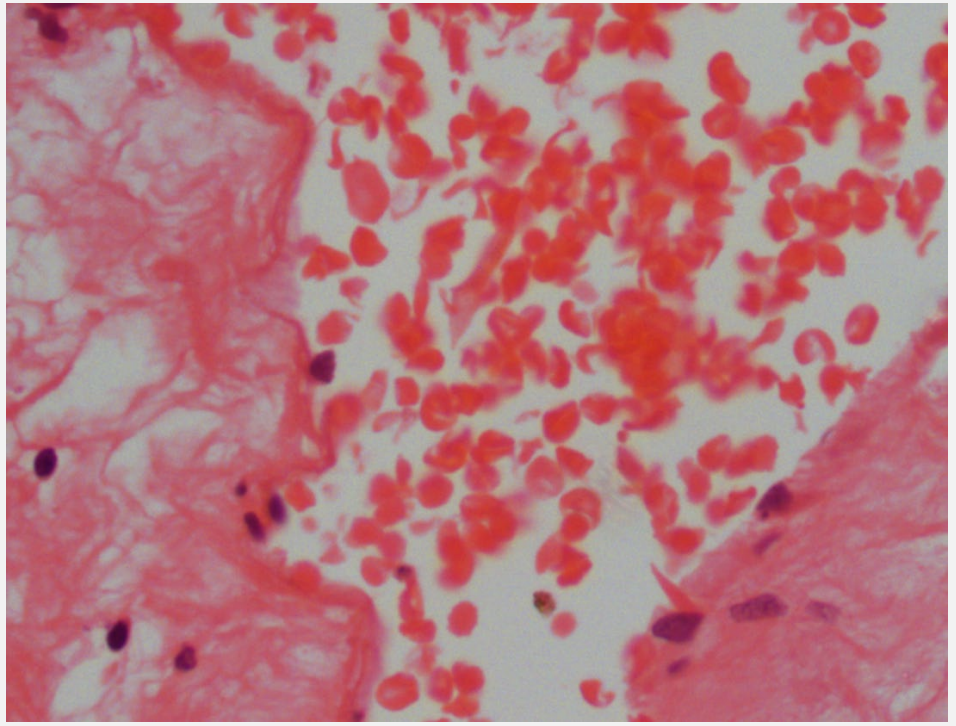
	0-6 hours	7-12 hours	13– 18 hours	19– 24 hours
Transfer to ITU				
Drain blood loss	2539	1225	840	555
	6	2	4	1
	3	1	0	2
	5	4	0	5
	2	2	0	2
	-	-	-	-

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°
  - 33 year old male in Paris SCA
    - Was receiving regular transfusion so HbS 6%. No perioperative exchange transfusion. Cooled to 35

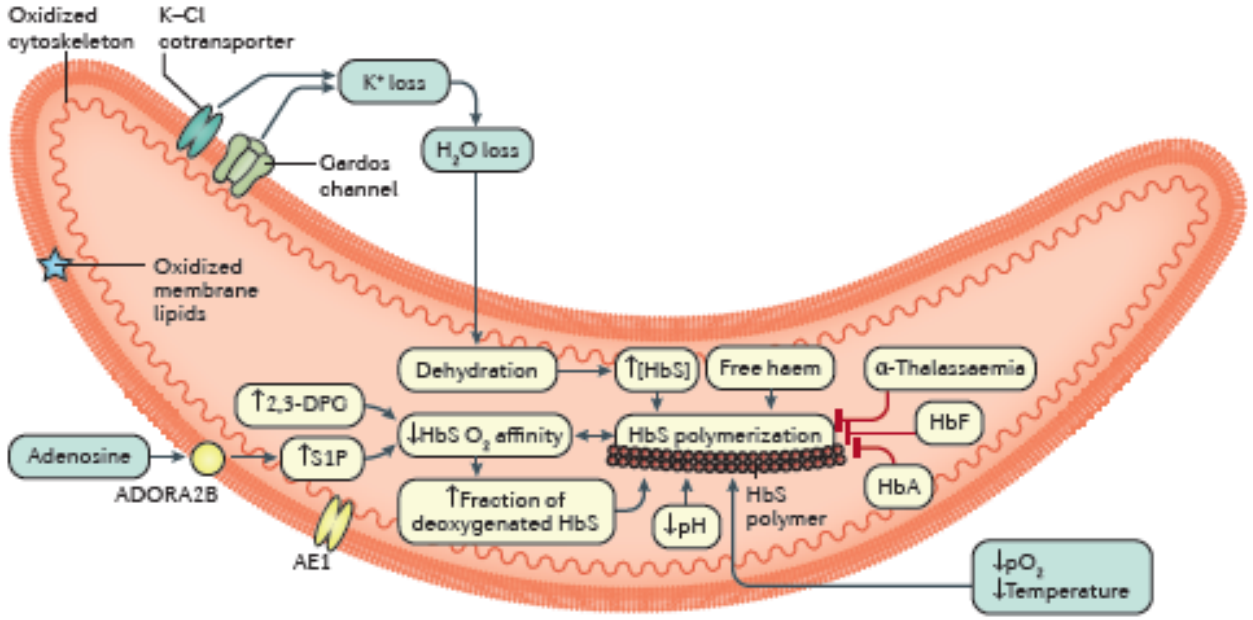


Figure 3 | **HbS polymerization and erythrocyte deformation.** Long polymers of sickle haemoglobin (HbS) align into fibres, which then align into parallel rods. The polymer has a helical structure with 14 HbS molecules in each section[42,55,262]. The polymerization of HbS depends on many factors, including the HbS concentration, partial pressure of oxygen (pO_2), temperature, pH, 2,3-diphosphoglycerate (2,3-DPG) concentration and the presence of different Hb molecules[263–265]. 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[266,267]. Free cytoplasmic haem can increase the attraction of the HbS molecules and the speed of nucleation and polymer formation[268]. 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.

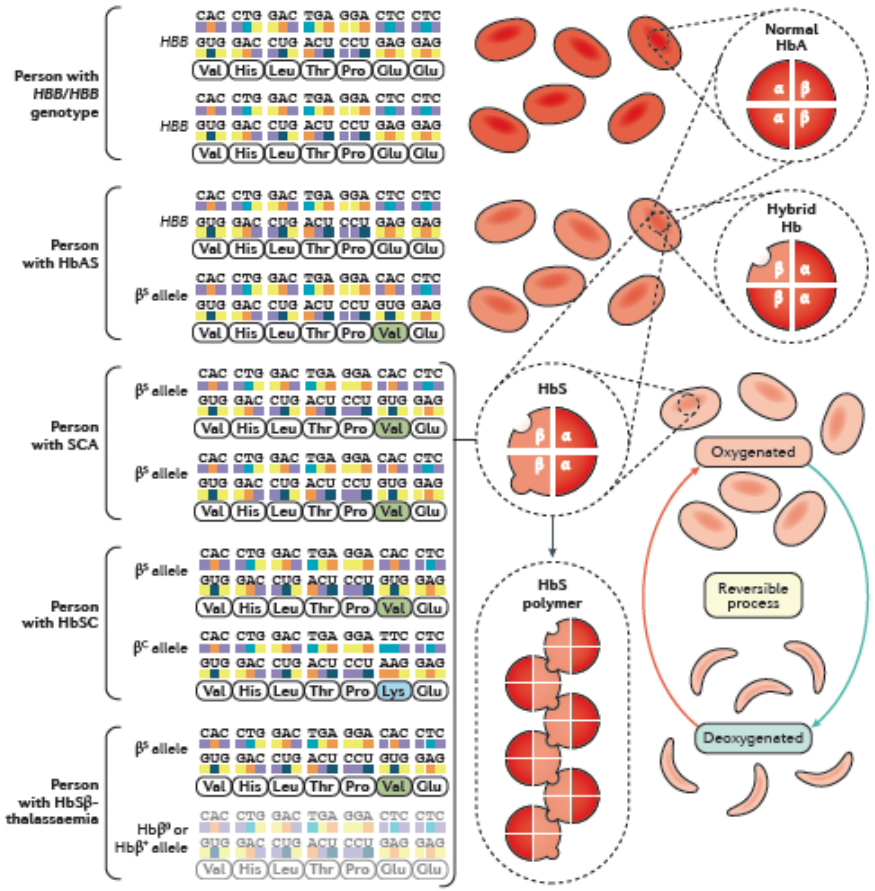


Figure 1 | **Genetic alterations in *HBB*.** Normal haemoglobin A (HbA) is formed by two α-globin subunits and two β-globin subunits, the latter of which are encoded by *HBB*. The sickle Hb (HbS) allele, β^S, is an *HBB* allele in which an adenine-to-thymine substitution results in the replacement of glutamic acid with valine at position 6 in the mature β-globin chain. Sickle cell disease (SCD) occurs when both *HBB* alleles are mutated and at least one of them is the β^S allele. Deoxygenated (not bound to oxygen) HbS can polymerize, and HbS polymers can stiffen the erythrocyte. Individuals with one β^S allele have the sickle cell trait (HbAS) but not SCD; individuals with sickle cell anaemia (SCA), the most common SCD genotype, have two β^S alleles (β^S/β^S). Other relatively common SCD genotypes are possible. Individuals with the HbSC genotype have one β^S allele and one *HBB* allele with a different nucleotide substitution (*HBB* Glu6Lys, or β^C allele) that generates another structural variant of Hb, HbC. The β^C allele is mostly prevalent in West Africa or in individuals with ancestry from this region[16]. HbSC disease is a condition with generally milder haemolytic anaemia and less frequent acute and chronic complications than SCA, although retinopathy and osteonecrosis (also known as bone infarction, in which bone tissue is lost owing to interruption of the blood flow) are common occurrences[239]. The β^S allele combined with a null *HBB* allele ($Hb\beta^0$) that results in no protein translation causes $HbS\beta^0$-thalassaemia, a clinical syndrome indistinguishable from SCA except for the presence of microcytosis (a condition in which erythrocytes are abnormally small)[240]. The β^S allele combined with a hypomorphic *HBB* allele ($Hb\beta^+$; with a decreased amount of normal β-globin protein) results in $HbS\beta^+$-thalassaemia, a clinical syndrome generally milder than SCA owing to low-level expression of normal HbA. Severe and moderate forms of HbSβ-thalassaemia are most prevalent in the eastern Mediterranean region and parts of India, whereas mild forms are common in populations of African ancestry. Rarely seen compound heterozygous SCD genotypes include HbS combined with HbD, HbE, HbO^{Arab} or Hb Lepore (not shown)[241].

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_{poly}^2

Formation of Hybrids occurs

Cell volume affects saturation and can increase delay time (10% ->16x delay)

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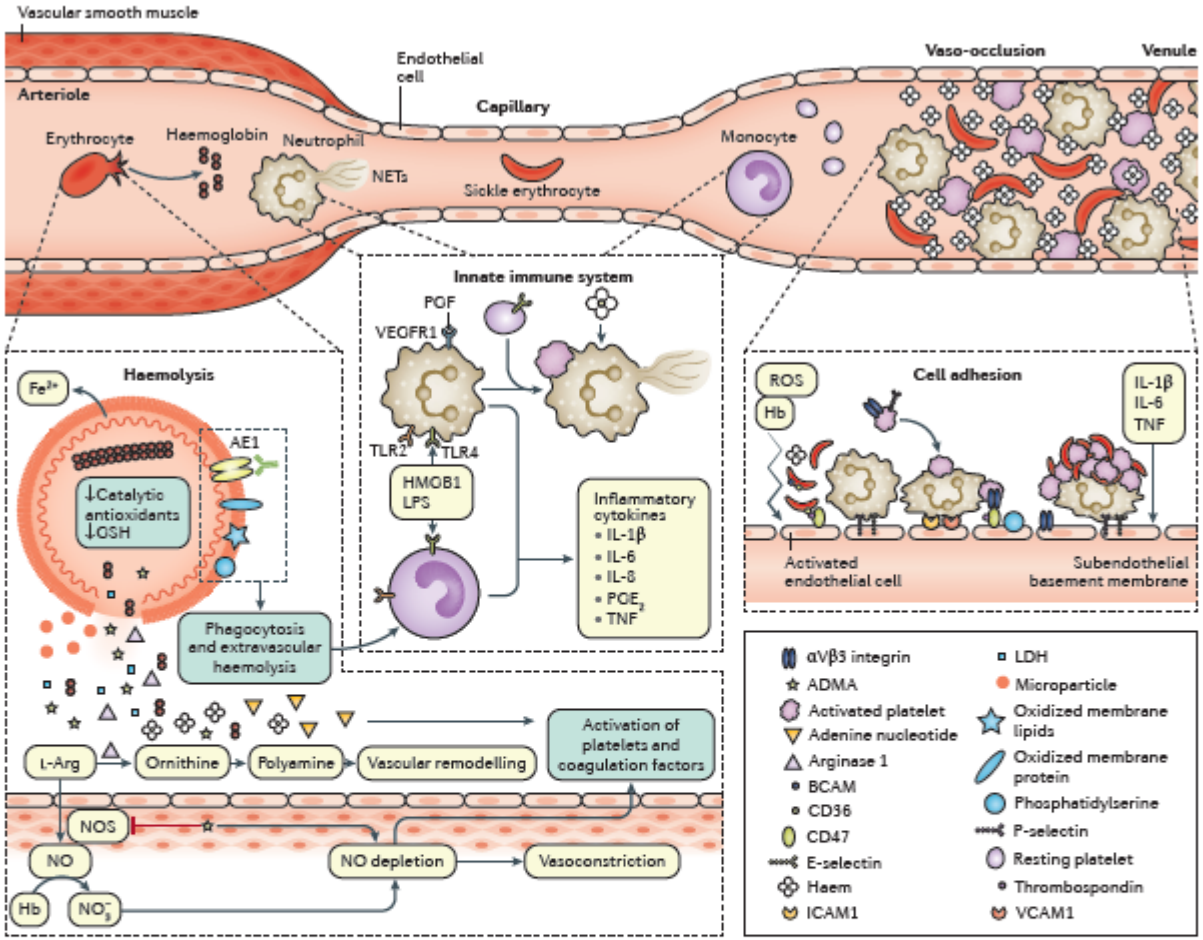


Figure 4 | **Mechanisms in sickle cell disease.** Damage and dysfunction of the erythrocyte membrane caused by sickle haemoglobin (HbS) polymerization lead to haemolysis. Oxidized membrane proteins reveal antigens that bind to existing antibodies, and membranes expose phosphatidylserine; both mechanisms promote phagocytosis of erythrocytes by macrophages, a pathway of extravascular haemolysis. Intravascular haemolysis releases the contents of erythrocytes into the plasma. Hb scavenges nitric oxide (NO), arginase 1 depletes the L-arginine substrate of NO synthase (NOS), and asymmetric dimethylarginine (ADMA) inhibits NOS. 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 activation of blood clotting proteins. Haem and other danger-associated molecular pattern (DAMP) molecules activate the innate immune system. Ligand-bound Toll-like receptor 4 (TLR4) and TLR2 activate monocytes and 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 in turn release DNA to form neutrophil extracellular traps (NETs). Circulating blood cells adhere to each other and to the activated endothelium, contributing and potentially even initiating vaso-occlusion. In postcapillary venules, activated endothelial cells that express P-selectin and E-selectin can bind rolling neutrophils. Activated platelets and adhesive sickle erythrocytes can adhere to circulating or endothelium-bound neutrophils and form aggregates. Sickle erythrocytes might also bind directly to the activated endothelium. The figure shows only some examples of the complex and redundant receptor–ligand interactions involved in the adhesion of circulating cells to the damaged endothelium and exposed subendothelium. AE1, band 3 anion transport protein; BCAM, basal cell adhesion molecule; GSH, glutathione; HMGB1, high mobility group protein B1; ICAM1, intercellular adhesion molecule 1; LDH, lactate dehydrogenase; LPS, lipopolysaccharide; PGE_2, prostaglandin E2; PGF, placenta growth factor; TNF, tumour necrosis factor; VCAM1, vascular cell adhesion protein 1; VEGFR1, vascular endothelial growth factor receptor 1.

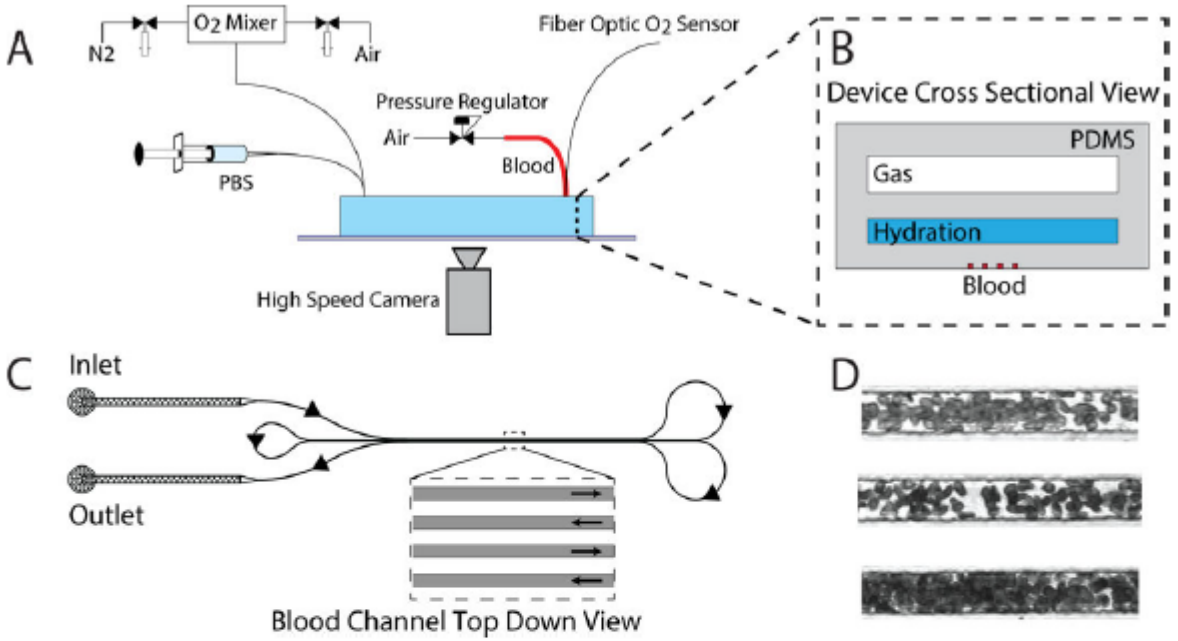


Figure 1.
In vitro disease model to study sickle trait blood flow using a microfluidic platform. (A) Schematic of the experimental platform built around the microfluidic device including an oxygen gas mixer, PBS hydration flow regulator, pressure regulation of whole blood, oxygen sensor, and high speed camera. Insert (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.

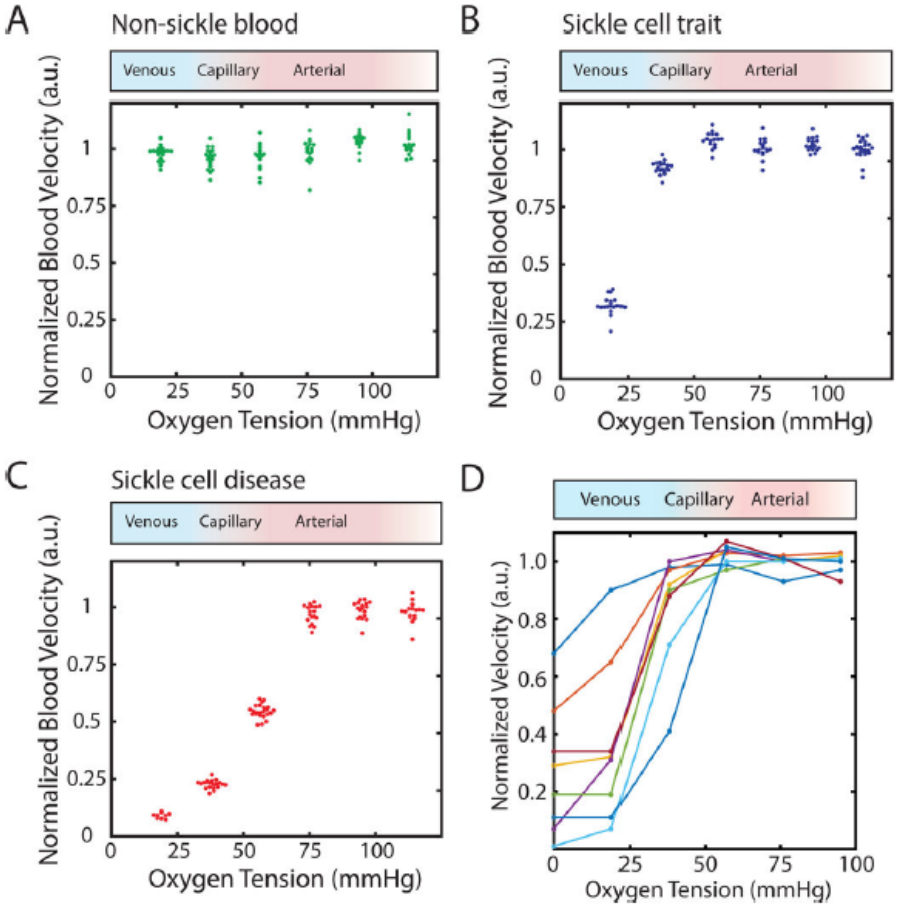


Figure 2.
Rheological behavior of SCT blood becomes oxygen-dependent near venous oxygen tension. (A) Normalized, steady state flow velocity of a non-sickle (genotype AA) individual's blood sample does not depend on oxygen tension. Oxygen tension was varied in a stepwise manner as described in methods. 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

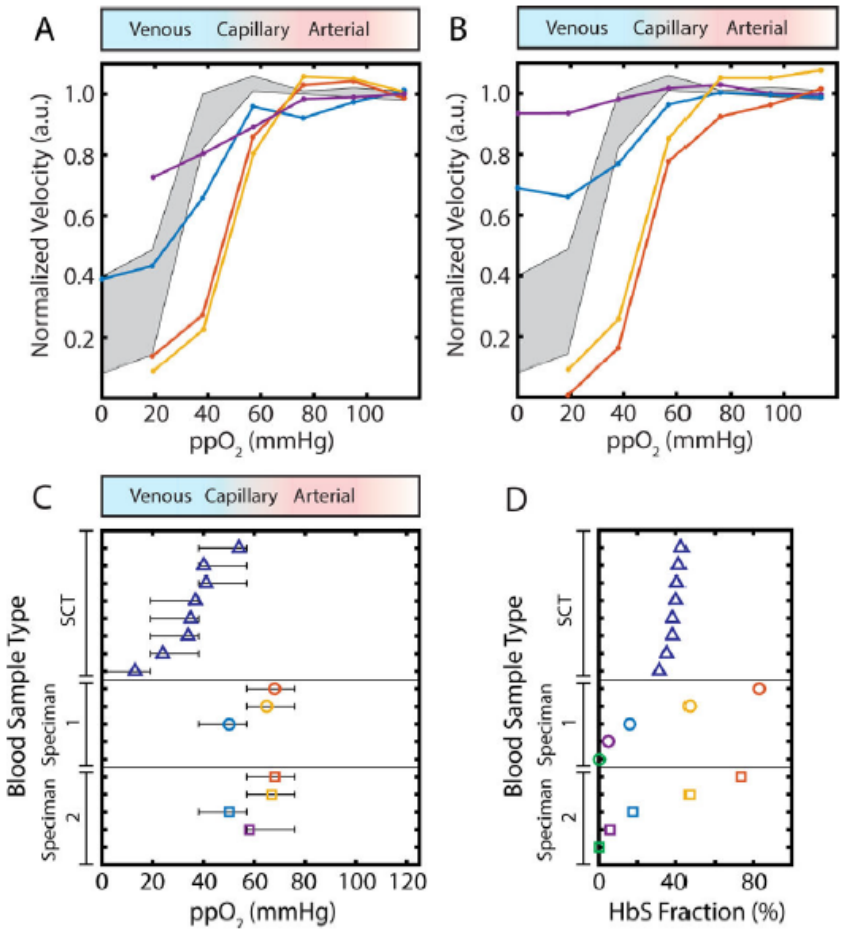


Figure 4.

Oxygen-dependence of rheology for transfused SCD compared to SCT. (A,B) Normalized, median velocity under steady state conditions for the two transfusion blood samples we measured. Simulated transfusion specimens shown are ~5–6% (purple), ~16–18% (blue), ~45–48% (orange), and ~70–85% (red) genotype SS blood by volume. Grey, shaded region shows the interquartile range of normalized blood velocity in response to oxygen tension for all SCT blood samples. Blue to red to white color gradient bar above plot represents typical oxygen tension found in venous, arterial, and supraphysiologic circulation respectively. (C) cell trait is dependent on oxygen tension. At high oxygen tension (>38 mmHg), velocities are oxygen- independent and exhibit regime I flow behavior. Between 19 and 38 mmHg, flow behavior transitions to regime II where steady state velocities become impaired and are sensitive to oxygen tension. (C) Normalized steady state flow velocity for an individual with homozygous sickle cell disease is dependent on oxygen tension. High oxygen tension (>76 mmHg) results in oxygen-independent regime I flow behavior. Intermediate oxygen tension (>19 mmHg and <76 mmHg or 19<ppO2<76 mmHg) displays impaired, oxygen-dependent regime II flow behavior, and low oxygen tension (<19 mmHg) exhibit severely impaired/ nearly occluded regime III behavior. (D) Normalized, median, steady state velocities for 8 different SCT blood samples. Each colored line corresponds to a unique SCT blood sample.

LU ET AL AM J HEMATOL 2018; 93(10):1227-35

Red: 70-85% SCD
Orange : 46-48%
Blue: 16-18%
Purple 5-6%
Grey: SCT behaviour with confidence intervals

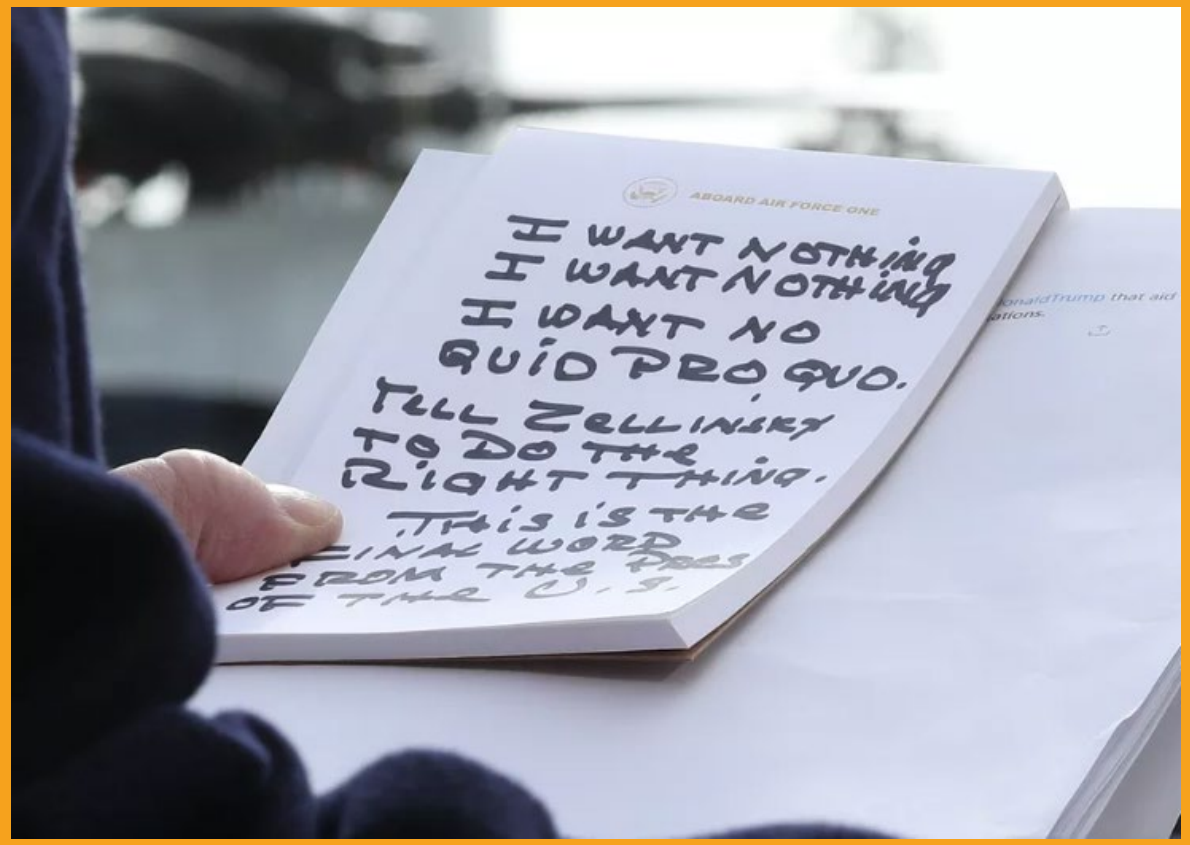
Graphs C/D position of graph shows transition I/II flow

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



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