INTRODUCTION

Pulmonary endarterectomy (PEA) is now well-established as the best treatment for patients with chronic thromboembolic pulmonary hypertension (CTEPH) [1–5]. However, patients with abnormalities of haemoglobin and red cell membrane constitute a unique population who are both more predisposed to developing CTEPH, and have other potential reasons for pulmonary hypertension (PH). These patients have more distal thromboembolic disease, making surgery more technically demanding. They are at risk of greater morbidity during PEA, as procedures involving cardiopulmonary bypass hypothermic circulatory arrest, we used exchange blood transfusion. Immediately postoperatively, there was a significant improvement in pulmonary vascular resistance (938 ± 462 to 260 ± 167 dyne s cm⁻⁵; P < 0.0001). One patient died 81 days following surgery; 18 patients had abnormal haemoglobin or congenital haemolytic anaemia. We reviewed diagnosis, exchange transfusions on cardiopulmonary bypass, preoperative and postoperative pulmonary haemodynamic and functional data and outcomes for this group. Paired data analysis was performed by Student’s t-test; P < 0.05 was statistically significant.

RESULTS: Between the start of our PEA programme in 1997 and April 2015, we performed PEA in 19 patients with haemoglobinopathy or congenital haemolytic anaemia. The mean age was 52 ± 15 years. There were 9 patients with sickle cell trait, 2 with coexisting alpha+ thalassaemia trait, 2 patients with HbSC disease, 2 patients with beta-thalassaemia major, 3 patients with hereditary spherocytosis, 2 patients with stomatocytosis (one with the cryohydrocytosis subtype) and 1 patient with HbC trait. In the 9 HbAS patients, the mean HbS% was 31.9 ± 6%; in the HbSC patients, the mean HbS% was 46.5 ± 13% preoperatively. To reduce this HbS to ≤20%, for safe PEA with deep hypothermic circulatory arrest, we used exchange blood transfusion. Immediately postoperatively, there was a significant improvement in pulmonary vascular resistance (938 ± 462 to 260 ± 167 dyne s cm⁻⁵; P < 0.0001). One patient died 81 days following surgery; 18 patients are alive at a median follow-up of 3.4 ± 3 years. Six months postoperatively, the patients showed significant improvement in New York Heart Association status (P < 0.0001), and in 6-min walk distance from 251 ± 111 to 399 ± 69 m (P < 0.05 was statistically significant).

CONCLUSIONS: Results of PEA in this complex patient group were satisfactory. Expert haematological advice is important and exchange blood transfusions may be necessary. The presence of abnormal haemoglobin does not contra-indicate PEA surgery.

Keywords: Pulmonary endarterectomy • Chronic thromboembolic pulmonary hypertension • Haemoglobinopathy • Haemolytic anaemia • Sickle cell • Sickle cell trait • Exchange transfusions
(CPB) may be more challenging due to predisposition of the abnormal haemoglobin-laden erythrocytes to undergo sickling in hypothermia in patients with haemoglobin S, and thereby sludging in the microcirculation, leading to microinfarcts, the conduct of CPB may therefore need to be adapted. Abnormally rigid erythrocytes as seen in spherocytosis and stomatocytosis encounter a similar problem as they struggle to pass through the sluggish microcirculation under hypothermic conditions.

In beta-thalassaemia, major abnormal red cells have been shown to promote coagulation and to exert platelet-like actions in supporting coagulation activity. In cryohydrocytosis, the red cells release potassium at low temperatures and reabsorb potassium on rewarming. In hereditary spherocytosis (HS), red cells show increased volume and increased osmotic fragility, which is not known to affect the bypass circuit, but has not been studied in detail in deep hypothermic cardiac arrest (DHCA).

Haemoglobin C paradoxically will show improved solubility at the above conditions provided it is not compound heterozygote with HbS and has again not been studied in detail in DHCA. These unique pathologies may require considerable alteration in conventional management protocols [6-8].

Therefore, the results of PEA may not be as good as previously reported in patients with CTEPH and normal haemoglobin [1-5] and there may also be less benefit from surgery as well as higher risks for these patients. Apart from a few isolated case reports [6, 8], the results of PEA in this patient population have not been previously reported. We present our experience in managing these complex patients to share our knowledge.

METHODS
We performed a retrospective analysis, from our dedicated prospectively captured PH database, to identify all patients who underwent PEA surgery and had abnormal haemoglobin, between the commencement of the programme in 1997 and April 2015. We have previously described our surgical techniques which are now well-established [2, 5]. We reviewed the haemoglobin diagnosis, measured the fraction of HbS in patients with sickle cell trait/disease, reviewed the management of CPB, ischaemic and deep hypothermic circulatory arrest times and preoperative and postoperative pulmonary haemodynamic and functional data and outcome for this group. The latter included New York Heart Association (NYHA) status for dyspnoea scoring, and 6-min walk test. Right heart catheter studies were performed preoperatively and 6-month postoperatively to document right atrial (RAP) and pulmonary arterial pressures (PAP), pulmonary vascular resistance (PVR), cardiac output and indices. Data were cross-checked with the individual patient record, perfusion data records and the intensive care information system. Paired data analysis was performed by Student's t-test for paired data, with \( P < 0.05 \) used for statistical significance.

RESULTS
Patient characteristics
Between the start of our PEA programme in 1997 and April 2015, we have performed PEA in 19 patients (1.4% of our total experience) with haemoglobinopathy or congenital haemolytic anaemia. The mean age was 52 ± 15 years. Eleven patients (58%) were male. The diagnosis of CTEPH was confirmed in all patients at surgery, with Jamieson disease type of 2 or 3.

Haemoglobinopathies and diagnosis
There were 9 patients with sickle cell trait, 2 of which were also alpha+ thalassaemia trait, 2 patients with HbSC disease, 2 patients with beta-thalassaemia major, 3 patients with HS, 2 patients with stomatocytosis, 1 of whom had the cryohydrocytosis subtype and 1 patient with HbC trait.

In the 9 HbAS patients, the mean HbS fraction was 31.9 ± 6%, and in the HbSC patients, the mean HbS fraction was 46.5 ± 1.3% prior to surgery. For safe PEA with deep hypothermic circulatory arrest, we decided that we had to reduce this HbS to ≤20% based on the experience of Yung et al. [8]. To achieve this, we used exchange blood transfusion.

There were 7 patients (4 males) with abnormal red cell membranes leading to haemolysis (age 47 ± 14 years)—2 beta-thalassaemia major, 3 HS, 2 stomatocytosis (1 with the cryohydrocytosis subtype (Patients 12–18) and 1 female patient with Hbc trait (Patient 19). With the exception of the patient with Hbc trait, all had haemolysis or impaired red cell production, and the requirement for multiple blood transfusions throughout their life. Five patients in this group had undergone splenectomy—2 with beta-thalassaemia major, 1 with HS and 2 with stomatocytosis. Clearance was good in all patients. One cryohydrocytosis patient underwent automated red cell exchange prior with 14 units of blood to the procedure, and the patient with stomatocytosis not further classified did not receive additional precautions [9].

HbAS patients. There were 7 patients with sickle trait (HbAS), and 2 with combined HbAS disease and alpha+ thalassaemia trait (Patients 3–11). Their mean age was 58 ± 16 years. There were 6 males and 3 females. The mean HbS fraction was 31.9 ± 6% prior to surgery.

Four patients with HbAS had a mean of 10.8 ± 3 units of blood exchanged preoperatively by automated transfusions prior to surgery at their referring hospital, and 4 patients had a mean of 4.5 ± 1.3 units of blood exchange transfused immediately pre-CPB.

One patient, early in our series, had no additional preparation and underwent PEA without exchange transfusion but had two units transfused postoperatively. The variation in approach was caused by subjective advice given by haematologists over time, accumulated institutional experience and the scarcity of published guidance.

HbSC disease. There were 2 patients with HbSC disease, Patient 1: 36-year old male, and Patient 2: 61-year old female, both NYHA III with Type-3 disease. These constitute a unique population homozygous for sickle cell gene and rest of Hb being Hbc, no Hba [10]. Both had high levels of Hbs preoperatively: 45.5 and 47.4%, respectively, and required eight to nine units of exchange transfusion in their referring hospital and four units pre-CPB to reduce Hbs to <20%.

Intraoperative data
All patients had PEA with DHCA; the mean CPB, ischaemic and DHCA times were 310 ± 48, 64 ± 18 and 35 ± 12 min, respectively. Immediately following surgery, after chest closure, in the operating room, the patients showed a significant improvement in PVR (938 ± 462 to 260 ± 167 dyne s cm⁻²; \( P < 0.0001 \)).
Table 1: Showing improvement in functional status 6 months after pulmonary endarterectomy in the entire cohort

<table>
<thead>
<tr>
<th>Respiratory function</th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>n = 19</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MW distance</td>
<td>251 ± 111</td>
<td>399 ± 69</td>
<td>&lt;0.0001</td>
<td></td>
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<tr>
<td>Post 6MWT sats</td>
<td>85.6 ± 5.6</td>
<td>94.5 ± 2.4</td>
<td>&lt;0.0001</td>
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<tr>
<td>NYHA</td>
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<td>NYHA 1</td>
<td>15</td>
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<td></td>
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<tr>
<td>NYHA 2</td>
<td>6</td>
<td>3</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>NYHA 3</td>
<td>11</td>
<td>2</td>
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SD: standard deviation; 6MW: 6-min walk test; NYHA: New York Heart Association; P-value: level of significance for paired T-test.

Postoperative complications and long-term follow-up

Three patients required resternotomy for bleeding to secure haemostasis. One patient died 81 days following surgery. The patient was transferred to another local hospital ICU and died of sepsis and multiorgan failure. A post-mortem examination was unfortunately not performed in the other hospital. For the remaining 18 patients, the median ICU stay was 4 ± 5 days and the median hospital stay was 18.6 ± 7 days; they are alive at a median follow-up of 3.4 ± 3 years. Six months following surgery, the patients showed a significant improvement in NYHA status (P < 0.0001), and in 6-min walk distance from 251 ± 111 to 399 ± 69 m (P < 0.0001) (Table 1). Commensurate with this, there was a significant improvement in the pulmonary haemodynamic parameters, which showed a decrease in mean RAP, mean PAP and PVR (Table 2). All patients in the early part of this series had inferior vena caval filters inserted preoperatively, but since March 2014 this is no longer our standard protocol for PEA surgery. All patients were anticoagulated with Coumadin (warfarin) postoperatively.

DISCUSSION

In our cohort of 19 patients with CTEPH and haemoglobinopathies or haemolytic anaemias, we have demonstrated that PEA is safe and the early outcome is not different from that previously reported in patients with normal haemoglobin and erythrocytes [1–5]. In particular, with the precautions we employed, no problems were observed during hypothermic CPB and the early recovery phase. Despite the association of haemoglobinopathies as an independent risk factor for PH, and the known potential of patients with splenectomy to develop more distal CTEPH, the improvement in haemodynamics and functional status was substantial.

Sickle cell patients

A point mutation in Position 6 of the beta chain causes production of HbC or HbS depending on whether the Glutamate has been changed to Lysin or Valine, respectively.

This predisposes to polymerization of Hb molecules (HbS) with distortion of the erythrocyte architecture, or if combined with HbC to red cell dehydration and deformity due to HbSC by affecting the K+/Cl− membrane transport. HbC in isolation paradoxically shows improved solubility under low oxygen conditions [7]. The HbS% is highest in HbSS (nearly 100%), followed by HbSC (~50%) and lowest in HbAS (30–40%). The total Hb is lowest in HbSS (50–110 g/l), but may be normal in HbSC and will be normal in HbAS. Coexistent alpha+ thalassaemia trait reduces the HbS or HbC fraction more than the HbA fraction and may be apparent only by microcytosis in HbSS. Bone marrow infarction leading to fat embolization may contribute to vascular occlusion, particularly in the pulmonary circulation [6–8]. The distorted erythrocytes are cleared by the spleen and the reticulo-endothelial system, leading to haemolytic anaemia [7, 11]. HbSC has a milder clinical phenotype than HbSS but shows an increased frequency of thromboembolic complications [10].

The level of HbS < 20% was based on our estimation of the results of Yung et al. [8] even though they did not quote the absolute HbS level at the time of DHCA. Most clinicians advise extreme caution in the above abnormal physiological states in both HbAS and sickle disease. There are no published case reports of intraoperative sickling on CPB and sickling occurs post-mortem in sickle patients, the presence of sickle cells alone in the tissues does not provide the pathological link between the haemoglobinopathy and a particular adverse outcome alone.
Mechanism of pulmonary hypertension in patients with sickle cell disease. Haemolysis is hypothesized to cause endothelial dysfunction, reduction in nitric oxide bio-availability and subsequent proliferative changes in the intima and smooth muscle of blood vessels, leading to systemic and PH [6, 7, 11]. Vaso-occlusive episodes resulting from erythrocyte sickling and thrombosis may contribute to the development of CTEPH [6, 11]. Bone necrosis and fat embolism may play a contributory role [8]. Moderate to severe PH affects about 30% of patients with sickle cell anaemia; its incidence in sickle cell disease is increasing as these patients live longer and is a major risk factor for increased mortality [7, 8, 12, 13]. PH and pulmonary thrombosis promote the development of vasculopathy and may be worsened by splenectomy [6, 13, 14].

Problems during pulmonary endarterectomy in HbAS and HbSC disease patients and how to counter them. Patients with HbAS and HbSC disease are at the risk of sickling crisis during deep hypothermic circulatory arrest because of hypothermia, hypoxaemia, acidosis and low-flow states. Preoperative large volume automated exchange transfusions followed by intraoperative partial exchange transfusion to reduce the level of HbS/HbSC combined to ≤20% remain the mainstay of our protocol for PEA in these patients, along with correction of anaemia to raise the level of Hb to baseline; this approach has been adopted by some centres [6-8]. Over the time frame of our experience, different techniques were employed to reduce the fraction of abnormal HbS to ≤20% with patients with HbAS receiving a partial exchange transfusion several days before PEA, and more recently patients having partial exchange transfusion prior to CPB [6-8].

The approach adopted currently is that of immediate preoperative red cell exchange transfusion with four to five units of HbS negative blood during induction and prior to venesection as the ideal compromise to achieve an HbS% of nearly 20% with much reduced blood use.

Rh- and Kell-matched products should also be used in all patients with haemoglobinopathy although there is no specific guidance for patients who only carry a trait (HbAC or HbAS) as they have no increased lifetime risk of transfusion.

During CPB, particular attention should be paid to maintain good flows to limit end-organ ischaemia, and maintain normal acid–base status. The use of a cell saver is controversial; filtered and washed blood from the cell saver system may be more prone to sickling and therefore may not be recommended [6].

Thalassaemia patients

Chronic haemolysis associated with thalassaemia and abnormal red cell membranes contributes to a hypercoagulable state [13, 15, 16]. Singer et al. [15] examined 25 thalassaemia patients and identified moderate PH in 17 (68%) patients; this was significantly associated with prior splenectomy, and high platelet counts and P-selectin levels, all pointing to platelet activation in the pathogenesis of PH. Chronic hypoxia was postulated as a mechanism for pulmonary vascular remodelling, contributing to significant PH in up to 75% of their patients with thalassaemia [15]. Blood should be Rh- and Kell-matched as above. Patients who have been transfused throughout their life pose additional challenges in that there could significant cardiac and hepatic iron overload complicating their management. Long-term chelation therapy may predispose patients to infection.

Erythrocyte membrane disorders: hereditary spherocytosis and stomatocytosis patients

Other varieties of haemolytic anaemia causing pulmonary hypertension are pyruvate kinase deficiency, HS and hereditary stomatocytosis (HSC) [13]. HS is characterized by the presence of spherical erythrocytes on the peripheral blood smear, thus with decreased deformability and increased membrane fragility [17] and is typically autosomal dominant, but caused by a number of different mutations (e.g. spectrin or ankyrin) in the red cytoskeleton. Entrapment and destruction of these erythrocytes in the spleen leads to haemolysis [18]. Splenectomy is advocated in the presence of splenomegaly and moderate to severe haemolysis in HS [19]. However, splenectomy is associated with a hypercoagulable state leading to thrombosis in the pulmonary, coronary, cerebral and mesenteric vascular beds [19]. Schilling et al. described a large series of >500 patients with HS. They reported up to 32% incidence of arterial or venous thromboembolic events following splenectomy in this population, compared with 3% in those that did not, an almost 10-fold risk. They attributed this hypercoagulable state post-splenectomy to thrombocytosis, and release of platelet-derived prothrombotic factors, leading to PH [19]. A similar association with splenectomy, and a prothrombotic, hypercoagulable state leading to CTEPH has been reported by others [20]. Ongoing haemolysis in these cases appears to be a contributing factor [19, 20].

HSC is a heterogeneous disorder inherited as an autosomal dominant trait characterized by abnormally stomatocyte-shaped red cells with a variable phenotype. Four subtypes are recognized: overhydrated, dehydrated, cryohydrocytosis and familial pseudohyperkalaemia. The red cells are enlarged with high mean corpuscular volume and low mean cell haemoglobin concentration (MCHC) in the overhydrated form and enlarged with high MCHC in the dehydrated form. The mechanism for haemolysis is incompletely understood but non-immune.

Splenectomy is recommended in cases of moderate to severe haemolysis and splenomegaly in HS, but should be undertaken only with extreme caution in patients with HSC or cryohydrocytosis. Post-splenectomy, these abnormal erythrocytes and the ensuing thrombocytosis contribute to a hypercoagulable state characterized by major thrombotic episodes and CTEPH, very similar to HS. In HSC vaso-occlusive crises similar to sickle cell disease have been described post-splenectomy [18, 21, 22]. Treatment by PEA [9] or in extreme cases, heart lung transplantation [23] is successful.

Cryohydrocytosis

This disorder is characterized by increased red cell permeability, change of shape with low temperatures and a brisk haemolysis at 4°C. This may cause hyperkalaemia and hypokalaemia in turn as the patient is cooled and then rewarmed during CPB, respectively [24]. The abnormal red cells have increased oxygen affinity, increased adenosine diphosphate, reduced 2,3 diphosphoglyceric acid with increased adenosine triphosphate production. The patient with cryohydrocytosis was discussed with a national expert in this disease and it was decided that on balance of risk the patient should undergo preoperative red cell exchange in order to minimize the fraction of unstable red cells present during the extremely low core temperature. The patient underwent exchange transfusion with the help of a blood warmer with 14 units of blood.
HbC trait

HbC trait is not of known pathological significance in the CTEPH process and the patient with this trait likely carried it only by coincidence. Its only importance is in the antenatal setting where partner screening is advised as a significant sickle cell disease in combination with other traits may result. There are however no publications on patients with HbC trait undergoing DHCA for PEA therefore we included this trait in our series.

Limitations

There are a few limitations; this is a retrospective analysis of a prospectively collected data examining the outcomes of PEA in patients with haemoglobinopathies and red cell membrane disorders; however, owing to the nature of this pathology, prospective studies are difficult to perform. The management of these patients changed over the era according to the best advice at the time and increasing experience and this is described. The dataset does not directly compare patients undergoing PEA in the absence of haemoglobinopathies, i.e. there is no control group, as the latter group is more than 50 times larger.

CONCLUSIONS

The results of PEA in this complex patient group are satisfactory and comparable with those reported in a large cohort from the European CTEPH registry [4]. Expert haematological advice should be sought. Careful preoperative preparation is important and we have utilized exchange transfusions to reduce HbS to ≤20% to enable the safe performance of PEA in patients with sickle cell trait.

Automated preoperative red cell exchange may be unnecessary in HbAS patients in the preparation of DHCA given the comparable results with intraoperative pre-CPB exchange transfusion. The presence of abnormal haemoglobin or red cells should not be a contra-indication to PEA surgery, and in the short and mid-term, these patients derive symptomatic and prognostic benefit.

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REFERENCES


