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Study Title

Pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension in Cape Town, South Africa

Lead/Co-investigator
Dr Sophie Davies-van Es
DVSSOP001

Supervisor/Principal investigator
Prof Gregory Calligaro

Co-supervisor/Co-investigator
Dr Gregory Symons

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Declaration

I, Sophie Angharad Davies-van Es, declare that the research reported within this dissertation has been undertaken by myself, with assistance from my supervisor and co-supervisor. It is being submitted for the degree of Master of Medicine (MMed) in Medicine at the University of Cape Town, and neither the whole nor any part of this work is being or is to be submitted for another degree to any other university. No part of this work has been reported or published prior to registration of the above degree. Full ethics approval has been granted by the local ethics committee.

This dissertation has been submitted to the Turnitin module and I confirm that my supervisor has seen my report and any concerns revealed by such have been resolved with my supervisor.

Name: Sophie Angharad Davies-van Es

Student number: DVSSOP001

Signature: Signed by candidate

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Format, author contributions and acknowledgements

Format

This dissertation is being submitted in the form of a publication ready manuscript, according to style guidelines set out for submission to the African Journal of Thoracic and Critical Care Medicine (AJTCCM).

The manuscript will be submitted to the AJTCCM for consideration for publication.

Author contributions

SDvE, TP, JB, GS and GC were involved in conceptualising and designing the study. JB and TP assisted with access to the database, data collection and review of the surgical aspects of the paper. SDvE did all other data collection. SDvE, GC and GS interpreted the data and wrote the first draft. All authors read and commented on the final manuscript.

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I would like to acknowledge the contributions of all my co-authors, who had the idea for this study and helped me greatly at multiple stages of its development. A special thank you must go to Greg Calligaro for his invaluable help and guidance in the statistical analysis and writeup of this manuscript.

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Pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension in Cape Town, South Africa

Sophie A. Davies-van Es, MBChB, FCP (SA)[1]; Timothy C. Pennel, MBChB, MMed, FCS (SA), PhD[2]; Johan Brink, MBChB, FCS (SA)[2]; Gregory J. Symons, MBChB, FCP (SA), Cert Pulm (SA)[1,3]; Gregory L. Calligaro, BSc (Hons), MBBCh, FCP (SA), MMed, Cert Pulm (SA)[3,4]

[1] Department of Acute General Medicine, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa.

[2] Chris Barnard Division of Cardiothoracic Surgery, Department of Surgery, University of Cape Town, Cape Town, South Africa.

[3] Division of Pulmonology, Department of Medicine, Groote Schuur Hospital.

[4] Centre for Lung Infection and Immunity, Division of Pulmonology, Department of Medicine and UCT Lung Institute and South African MRC/UCT Centre for the Study of Antimicrobial Resistance, University of Cape Town, Cape Town, South Africa.

Corresponding author:
Sophie Davies-van Es, MBChB, FCP (SA)
Department of Medicine, J floor, Old Main Building, Groote Schuur Hospital *and*
University of Cape Town, Observatory 7925, SOUTH AFRICA.
Email: sophiedve@gmail.com
Tel: +27 84 879 9142

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ABSTRACT

Introduction: Pulmonary endarterectomy (PEA) is the only definitive and potentially curative therapy for chronic thromboembolic pulmonary hypertension (CTEPH), associated with impressive improvements in symptoms and haemodynamics. However, it is only offered at a few centres in South Africa. The characteristics and outcomes of patients undergoing PEA in Cape Town have not been previously reported.

Methods and objectives: We interrogated the Adult Cardiothoracic Surgery database at the University of Cape Town (UCT) between December 2005 and April 2021 for patients undergoing PEA at Groote Schuur Hospital and Netcare UCT Private Academic Hospital. The primary outcome was the difference in World Health Organisation (WHO) functional class (WHO-FC) before and at least 6 weeks after surgery.

Results: A total of 32 patients underwent PEA: 8 patients were excluded from the final analysis due to incomplete data or a histological diagnosis other than CTEPH. The workup of these patients for surgery was variable: all had CT pulmonary angiograms, 7 (29%) had ventilation: perfusion scans, 5 (21%) underwent right heart catheterisation, and none had pulmonary angiograms. The perioperative mortality was 4/24 (17%): 1 patient (4%) had a cardiac arrest on induction of anaesthesia, 2 patients (8%) died of postoperative pulmonary haemorrhage, and 1 patient (4%) died of septic complications in the intensive care unit. In survivors, the median (IQR) improvement in WHO-FC was 2 classes (1-3, p=0.0004); 10/16 patients (63%) returned to a normal baseline (WHO-FC I).

Conclusion: PEA – even in a low volume centre – is associated with significant improvements in WHO-FC and a return to normal baseline in survivors.

Abstract word count: 255

KEYWORDS Chronic thromboembolic pulmonary hypertension (CTEPH), pulmonary endarterectomy (PEA), pulmonary emboli (PE), pulmonary hypertension (PH).

INTRODUCTION

The natural history of acute pulmonary embolism (PE) in most patients is complete fibrinolysis with a near-total resolution of vascular obstruction, a reduction in pulmonary vascular resistance (PVR) and restoration of normal haemodynamics. However, a small minority of patients will have persistent elevations in mean pulmonary arterial pressure (mPAP) and PVR several months after a precipitating event despite effective anticoagulation, termed chronic thromboembolic pulmonary hypertension (CTEPH)[1,2]. The diagnosis of CTEPH should be considered in all patients with unexplained pulmonary hypertension since a quarter of patients with CTEPH do not have any preceding history of PE or deep vein thrombosis[3]. Staphylococcal infection, endothelial dysfunction, defective fibrinolysis, and dysfunctional angiogenesis have been proposed as pathophysiological mechanisms for the failure of thrombus resolution[4]. Clinical risk factors for CTEPH include permanent intravascular devices, inflammatory bowel disease, polycythaemia vera, splenectomy, antiphospholipid syndrome, high dose thyroid replacement therapy and malignancy[5,6].

The pathological basis for the elevation in mPAP and PVR is unresolved thrombus which has not undergone fibrinolysis but instead has been transformed into hard, hyalinised material. This organised thrombus becomes incorporated into the pulmonary arterial wall and causes chronic obstruction of the major pulmonary arteries, either completely via total occlusion of blood flow or incompletely by the formation of bands and webs (irregular areas of adherent thromboembolic material)[7]. The increase in PVR leads to chronic right ventricular strain, and ultimately, over a period of months to years, right heart failure[2,7]. CTEPH has been assigned its own grouping (Group IV) in the World Health Organisation classification of pulmonary hypertension due to unique considerations around its diagnosis and treatment[8].

Pulmonary endarterectomy (PEA) is the treatment of choice for patients with CTEPH[1,4], provided there are no contraindications, and is potentially curative[9]. The procedure involves bilateral complete endarterectomies down to the subsegmental branches of the pulmonary vasculature, performed during periods of deep hypothermic circulatory arrest (DHCA), via a median sternotomy, and on cardiopulmonary bypass[10,11]. PEA has been shown in multiple previous studies to significantly improve pulmonary vascular resistance and pulmonary artery pressure to normal or near normal as well as improving 6-minute walk test (6MWT) distance and World Health Organisation functional class (WHO-FC)[11-16].

Cardiothoracic expertise in performing PEA for CTEPH is not widely available in South Africa (SA) in both the public and private sectors. Little is known about outcomes in South African

patients who have undergone this potentially life-saving procedure. We aimed to describe the pre-operative characteristics of patients who have undergone PEA in Cape Town, SA, as well as report the in-hospital mortality and functional and haemodynamic outcomes of these patients after surgery.

METHODS

Study design and oversight

We conducted a retrospective study of patients undergoing PEA at Groote Schuur Hospital (GSH) and at a second private hospital in Cape Town, South Africa. Informed consent was waived as only routine clinical data was used. Ethical approval was granted by the University of Cape Town's Human Research Ethics Committee (HREC; ref: 568/2019). The study is reported in accordance with the STROBE statement for observational trials[17].

Study population

Patients undergoing surgery between December 2005 and April 2021 were enrolled. Determination of candidacy was based on conventional physiological and radiological assessments of operability as determined by a multidisciplinary team (pulmonologists, cardiac surgeons and radiologists). Selection criteria and preoperative workup were not protocolised, but factors considered were the surgical accessibility of the disease, co-existing comorbidities and adherence to anticoagulation. Patients who were referred for consideration for surgery but not deemed eligible had no data captured.

The PEA procedure was performed as outlined above. The initial strategy used for DHCA was to cool patients to 25 degrees Celsius with ten-minute arrest intervals. As experience developed to operate on more distal disease, the DHCA strategy was adjusted to cool patients to 20 degrees Celsius for twenty-minute arrest intervals. All patients were treated by the same team of pulmonologists, anaesthetists and cardiac surgeons at both institutions, received standard intensive care unit (ICU) care and had the same access to extracorporeal membrane oxygenation (ECMO) once it became available. Post-operative follow-up and investigations were driven by clinician request and patient preference.

Study procedures

Socio-demographic and clinical data on our patients was extracted from the Chris Barnard Division of Cardiothoracic Surgery database (HREC ref: R045/2016). Where possible, missing data was obtained by folder review. Demographic and clinical data, data from special

investigations and information regarding the pre-, intra-, and post-operative course were captured into a data collection sheet and from there into a password protected Excel database, accessible only to the specified investigators. The full list of variables can be found in the 'Data collection sheet' in the appendix.

Outcomes

The primary outcome was the difference in the WHO-FC before and at least 6 weeks after PEA (when the patient was deemed to have recovered from the effects of surgery). Anticipated secondary outcomes were changes in 6MWT distance, right ventricular end-systolic pressure (RVSP, measured by echocardiography) and post-operative haemodynamics (mPAP, PVR and average cardiac output, measured by right heart catheterisation (RHC)).

Statistical analysis

Continuous variables were presented as means with standard deviation (for normally distributed data) and medians with interquartile range (for non-normally distributed data), and categorical data as frequencies and percentages. Assumption of normality was determined by the Shapiro-Wilk test; normally and non-normally distributed data were compared for pre- and post-surgical values (when available) using students t-test or Wilcoxon rank sum test, respectively. Statistical analyses were performed using Stata (V.12.1, Stata Corp, College Station, Texas, USA).

RESULTS

Study population

Between December 2005 and April 2021, 32 patients underwent PEA and were enrolled in the registry. For this total number of surgeries, the median (IQR) number of cases per year was 2 (1-3). Eight patients were subsequently excluded from the final analysis: three patients were found to have pulmonary artery sarcoma (and not CTEPH) on histology, one patient was incorrectly captured as a PEA but underwent acute thrombectomy for fresh PE, and patient notes could not be found for the final four patients (see Figure 1). 16/24 patients (67%) underwent surgery at the state facility, while 8/24 (33%) underwent surgery at the private facility.

Twenty-four patients with confirmed CTEPH and with available data were included in the final analysis; their demographic and clinical details are shown in Table 1. Almost 80% were in

WHO-FC III or IV, and 11/24 (46%) were in clinical right heart failure. All were anticoagulated. Only two thirds of patients (16/24, 67%) had a history of previous documented venous thromboembolism (VTE). The median (IQR) time from diagnosis of CTEPH to surgery was 123 (21-287) days.

Pre-operative workup and PEA procedure

The pre-operative workup (Table 2) was highly variable. All patients had a pre-operative computed tomography pulmonary angiogram (CTPA) showing proximal obstructive burden, while only 7/24 (29%) had a ventilation/perfusion (V/Q) scan. Only 5/24 patients (21%) had pre-operative RHC, and none had pulmonary angiograms. Relevant haemodynamics from these five RHCs are presented in Table 3. All patients had a pre-operative echocardiogram: in two patients, there was no tricuspid regurgitation, and the RVSP could not be measured; in the remainder, the median (IQR) RVSP was 82 (64-89) mmHg. Only 13/24 patients managed a pre-operative 6MWT, for which the mean (SD) distance was 322 (140) metres. Details of the median cardio-pulmonary bypass time, aortic cross-clamp time and circulatory arrest time during deep hypothermia are given in Table 4. Three patients (13%) had concomitant procedures performed during the operation; 2 patients had tricuspid valve annuloplasties, and 1 patient had a mitral valve annuloplasty.

Treatment outcomes

In-hospital mortality was 4/24 (17%) with 2/4 (50%) of these mortalities being female patients: one patient (4%) had a cardiac arrest on induction of anaesthesia, was placed on bypass and the surgery performed as a salvage procedure but could not be weaned off bypass; two patients (8%) died of post-operative pulmonary haemorrhage; and 1 patient (4%) died in ICU of septic complications 9 days after surgery. The median (IQR) length of stay in survivors in the ICU was 4 (2-5) days, with a median (IQR) length of mechanical ventilation of 1 (1-1) day. The median (IQR) length of hospital stay was 9 (8-20) days. 17/24 cases (71%) were performed after the ECMO programme was established, with one patient (4%) requiring ECMO in the post-operative period. Sixteen patients (67%) experienced one or more intra-/post-operative complications: bleeding requiring transfusion (5/24, 21%), arrhythmias (3/24, 13%), sternal wound sepsis (3/24, 13%), anaesthetic complications (2/24, 8%), need for re-look surgery (2/24, 8%), acute renal failure (3/24, 13%), pericardial effusion/cardiac tamponade (2/24, 8%), pleural effusion requiring repeat draining (1/24, 4%), haemothorax (1/24, 1%) and pneumonia with septic shock and multiorgan failure (1/24, 1%).

Post-operative outcomes

Of the 20 patients (83%) who survived to hospital discharge, 16 were seen for clinical follow up between 6 weeks and 11 months post-surgery (median (IQR) follow up period 4 (2-5) months); their post-operative outcomes are shown in Table 5. Of the 4 patients lost to follow up, 3 were still alive at 4 months post-surgery (based on National Health Laboratory data), making the 4-month mortality 4/23 (17%). The median (IQR) improvement in WHO-FC was 2 (1-3) classes (p=0.0004); 10/16 patients (63%) returned to a normal baseline (WHO-FC I). A 6MWT was performed for 9 patients, with a mean (SD) distance of 445 (108) metres attained. No patients underwent a post-operative RHC; those who had a post-operative echocardiogram with measurable RVSP (6 patients) had a median (IQR) RVSP of 33 (30-52) mmHg. A comparison of pre- and post-operative WHO-FC, 6MWT distance and RVSP can be found in Table 6.

DISCUSSION

This study, which is to our knowledge the only report of outcomes of CTEPH surgery in South Africa, has four main findings. First, that PEA results in significant improvement in functional class for patients with CTEPH. Second, that PEA is underutilised in our setting for the treatment of CTEPH. Third, that our in-hospital mortality is worse than that reported in other large international cohorts and lastly, that diagnostic approaches, pre-operative workup, and post-operative follow-up of CTEPH at our institution are not standardised and require strengthening.

CTEPH is a potentially surgically curative form of pulmonary hypertension, with PEA resulting in significant overall improvements in exercise capacity (median decrease in severity of 2 functional classes) and a return to a normal baseline (WHO-FC I) for almost two-thirds of survivors in this study. Median time at assessment in our study was 4 months; improvement in functional class and exercise capacity may take 3 to 12 months while the right heart undergoes remodelling[4], so this improvement may have been even greater if assessed at a later time point.

The small number of patients operated on over a 15-year period shows that PEA is severely underutilised in our setting, in both public and private sectors. A recent prospective observational study (the FOCUS study) which followed up patients after acute PE showed a

cumulative incidence of 2.3% for CTEPH at two years[18]; estimates from other smaller studies range between 0.1% and 9.1%[4]. There is no data available on the overall annual incidence of PE in our drainage area (which includes 3 secondary-level state hospitals, a tertiary referral centre and multiple private facilities) to estimate the expected number of referrals for PEA. Studies from 2 of these secondary level hospitals showed the number of patients with confirmed PE at each institution over a two-year period to be 41[19] and 43[20]. If this is extrapolated across the four institutions, using the expected incidence from the FOCUS study, the estimated number of CTEPH cases per year would be 2. If all these patients were deemed to be surgical candidates, this should have resulted in approximately 30 PEA surgeries at the state facility over the 15-year study period, almost double that which actually took place. Additionally, of the 16 patients operated on at this facility during that period, some were referred in from facilities in other provinces. Therefore, even using conservative estimates for CTEPH after PE in this population (which would already underestimate the true incidence, as there is not always a history of prior VTE), a diagnostic and treatment gap is apparent. Potential factors accounting for the low number of CTEPH diagnoses and PEAs performed affect every part of the referral and treatment pathway. Under-recognition and underdiagnosis (including access to diagnostic imaging) and the paucity of specialist pulmonary hypertension services are important obstacles in resource limited countries[21]. In addition, a lack of awareness of the surgical options for management, resource constraints on cardiothoracic and ICU capacity (which limit centre volume), competing priorities, and a conservative institutional approach to addressing pulmonary arterial obstruction beyond level 1(involving one of the main pulmonary arteries) and 2 (starting at the level of the lobar branches or past the origin of the upper lobe artery)[9] disease may play a role.

The in-hospital mortality reported in this study from a low-volume centre is considerably worse than that reported in large international cohorts. The latest in-hospital mortality rate reported by the centre with the greatest experience globally with PEA (University of California San Diego) is 2.2%[11], with mortality in the international CTEPH registry (which includes centres in Canada and Europe) reported as 4.7%[13]. PEA outcomes in high-volume centres approach that of routine cardiac surgery due to improved management of the cardiac and pulmonary complications of PEA and the well-established use of ECMO[4,8]. The inverse association between centre volume and outcome, which has been described for multiple other complex cardiothoracic procedures [22-25], undoubtedly also applies here. In addition, we have evolving

institutional experience with extracorporeal support during the study period, having only established a nascent programme towards the end of 2015. However, despite most of the cases being performed after the service was established, the use of rescue ECMO in our study was rare, similar to the ~5% incidence reported in other large surgical series[4]. This high mortality rate is likely a function of small patient numbers which include many high-risk cases at a low-volume centre with evolving expertise.

Finally, our study demonstrates that diagnostic approaches, pre-operative workup and post-operative follow-up of CTEPH at our institution is not standardised and probably suboptimal. Preoperative RHC was performed sparingly despite being mandated in all pulmonary hypertension guidelines to confirm the diagnosis as well as establish the severity of the haemodynamic impairment. Pulmonary angiography, the gold standard for depicting the pulmonary vasculature to diagnose CTEPH[4], which can be performed at the same time as the RHC, was not done on any patient, likely because there has been a lack of institutional expertise in both the performance and interpretation of this modality. The finding on histology of pulmonary artery sarcomas (a rare and aggressive malignant tumour, often mistaken for pulmonary embolism based on similar clinical and radiological features[26]) in almost 10% of patients reinforces the importance of thorough pre-operative imaging and evaluation. Postoperative non-invasive follow-up was also inconsistent, with even echocardiographic assessments generally lacking. Guidelines for diagnosis of CTEPH and for follow-up post-PEA have been outlined in a recent consensus statement from the International Society for Heart and Lung Transplantation[4] and should be a reference document for centres going forward. At our institution, we have subsequently taken measures to aim towards a standardised practice falling in line with these recommendations, including mandating VQ scans and pulmonary angiograms.

Several limitations of this study deserve emphasis. First, while the number of patients undergoing PEA was already small, a quarter had to be excluded from the initial analysis and there was ultimately only outcome data for half of the operated patients. These exclusions and incomplete data for the remaining patients may affect the conclusions that can be drawn from this study, particularly comparisons of the pre- and postoperative 6MWT and RVSP where there are significant gaps. Small numbers also prevented analysis of risk factors for mortality. Second, we only included patients who actually underwent PEA; the number of patients

referred with CTEPH but not considered operable could not be established due to the retrospective nature of the study. This is important as up to a quarter of patients deemed inoperable are in fact candidates after additional imaging like pulmonary angiography, which as mentioned was not performed in this study. Up to 90% of the patients are surgical candidates in expert centres[27,28] and it would have been interesting if we could have reported our denominator of referrals for PEA. Lastly, the pre-operative assessment and postoperative follow-up was not standardised, and there was a dearth of data on haemodynamics as measured by RHC, precluding analysis of this anticipated outcome. However, functional class (although subjective) remains an easy-to-record and patient-centred outcome measure for this group.

In summary, this study gives insight into current practices and outcomes at our institution regarding PEA for CTEPH. Although the mortality rate was high, surviving patients experienced significant functional improvement (assessed subjectively); haemodynamic outcomes could not be assessed. Prolonged ICU stay was not required and the need for ECMO was minimal. Pre-operative workup was variable, and this may have influenced patient selection for surgery. In addition, consideration should be given to longer term specialist follow-up for those presenting with acute pulmonary embolism, as the diagnosis of CTEPH in our setting is almost certainly missed or significantly delayed.

STUDY SYNOPSIS

What this study adds

Surviving patients who have undergone PEA for CTEPH at our institution have a marked improvement in their functional status with many returning to a normal functional baseline; however, in-hospital mortality was high (17%). The small number of patients included in this study indicates that PEA is likely underutilised. Pre- and post-operative assessment is inconsistent, despite availability of established guidelines.

Implications of the findings

More patients should be referred to specialist centres for assessment for this potentially curative procedure. Use of guidelines to standardise investigations and monitoring of patients with CTEPH may improve patient selection for surgery. Future studies should focus on prospectively gathering both clinical and haemodynamic data to strengthen these conclusions.

Declarations

This study was performed as part of an MMed (Internal Medicine) by SDvE. GC is a member of the AJTCCM editorial board; another editor will be given responsibility for overseeing the peer review of this submission.

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Author contributions

SDvE, TP, JB, GS and GC were involved in conceptualising and designing the study. JB and TP assisted with access to the database, data collection and review of the surgical aspects of the paper. SDvE did all other data collection. SDvE, GC and GS interpreted the data and wrote the first draft. All authors read and commented on the final manuscript.

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Conflicts of interest

None of the authors have any conflicts of interest related to this study.

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TABLES AND DIAGRAMS

Figure 1: CONSORT flow diagram

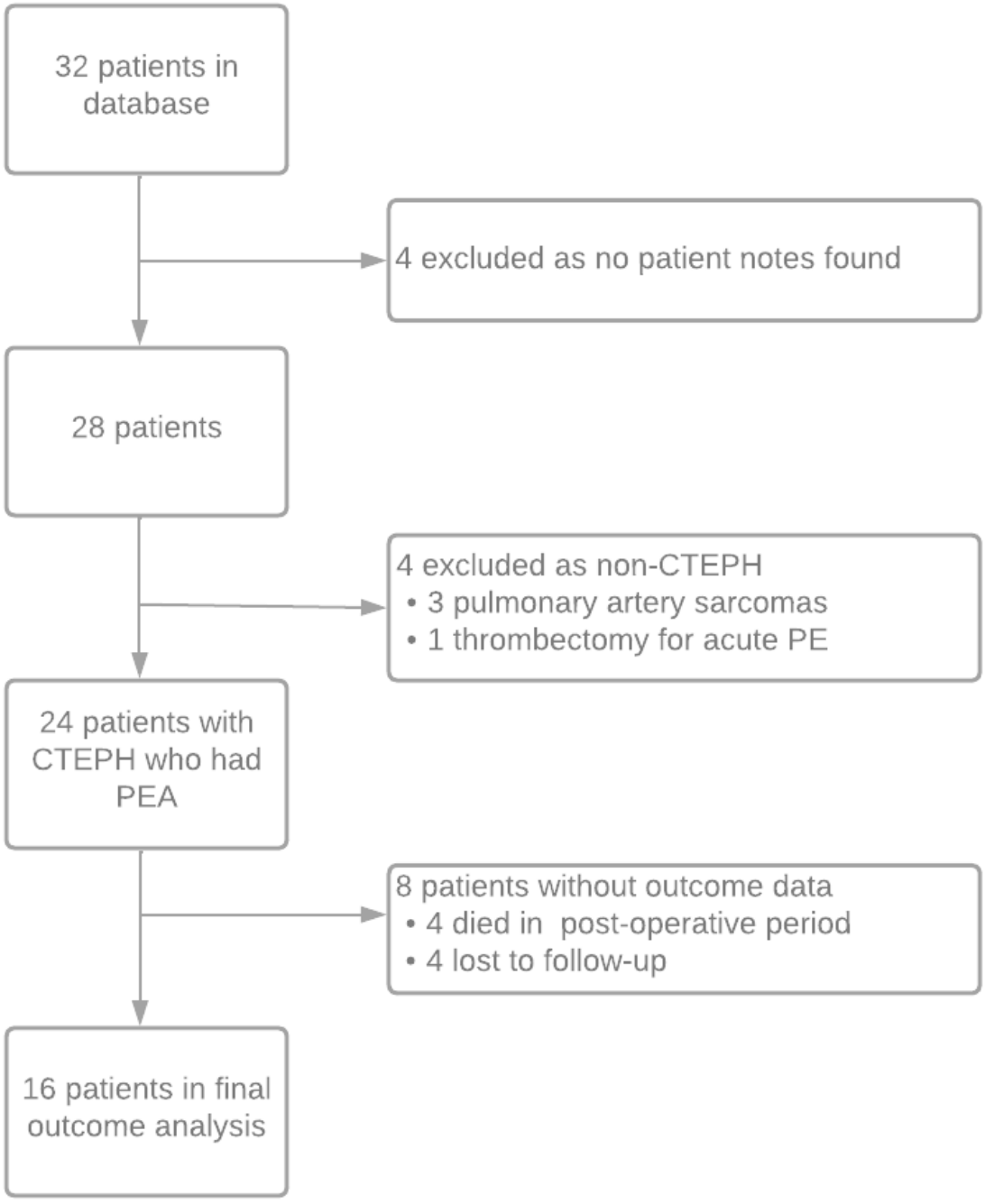

Table 1: Patient characteristics

(n=24)

Age (years), mean (SD)	41 (10)
Females	18 (75%)
Medical comorbidities	
Hypertension	7 (29%)
HIV	6 (25%)
Asthma/COPD	3 (13%)
CKD	3 (13%)
Obesity	2 (8%)
Valvular heart disease	2 (8%)
Thrombophilia	2 (8%)
Diabetes	1 (4%)
History of previous VTE (all)	16 (67%)
Pulmonary embolism	13 (54%)
Deep vein thrombosis	3 (13%)
Days from diagnosis to surgery, median (IQR)	123 (21-302)
WHO functional class	
I	0 (0%)
II	5 (21%)
III	14 (58%)
IV	5 (21%)
Signs of right heart failure	11 (46%)
Type of anticoagulation	
Warfarin	19 (79%)
DOAC	4 (17%)
LMWH	1 (4%)
Diuretic therapy	17 (71%)
PH-specific therapy (sildenafil)	2 (8%)
Preoperative IVC filter	9 (38%)
Mechanical ventilation pre-op	0 (0%)
Inotropes pre-op	0 (0%)

HIV, Human Immunodeficiency Virus; COPD, Chronic Obstructive Pulmonary Disease; CKD, Chronic Kidney Disease; VTE, venous thromboembolism; WHO, World Health Organisation; DOAC, direct oral anticoagulant; LMWH, low molecular weight heparin; PH, pulmonary hypertension; IVC, inferior vena cava.

Table 2: Pre-operative investigations

(n=24 unless otherwise shown)

CTPA performed	24 (100%)
V/Q scan performed	7 (29%)
Echocardiogram performed	24 (100%)
RVSP (mmHg), med (IQR)	82 (64-89) (n=22*)
6MWT performed	13 (54%)
6MWT distance (m), mean (SD)	322 (140) (n=13)
RHC performed	5 (21%)
mPAP (mmHg,) mean (SD)	49 (3.5) (n=5)
PVR (Wood units), med (IQR)	7.9 (6.3-13.7) (n=5)
Cardiac output (L/min), mean (SD)	4.0 (0.7) (n=5)

CTPA, computed tomography pulmonary angiogram; V/Q, ventilation perfusion; RVSP, right ventricular systolic pressure; 6MWT, six-minute walk test; RHC, right heart catheterisation; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance

*Unable to assess RVSP for 2 patients as no tricuspid regurgitation.

Table 3: Right heart catheterisation

(n=5)

Patient	Age (years)	Mean PAP (mmHg)	PVR (Wood units)	Average CO (L/min)
1	33	52	13.5	3.4
2	59	53	13.7	3.7
3	42	45	6.3	5.1
4	48	49	7.9	3.5
5	64	46	6	4.4

PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; CO, cardiac output

Table 4: PEA procedure

(n=24 unless otherwise shown)

Cardiopulmonary bypass time (minutes), med (IQR)	155 (137-174) (n=23)
Cross-clamp time (minutes), med (IQR)	80 (46-91) (n=23)
Circulatory arrest time (minutes), med (IQR)	25 (14-35)
Lowest core temperature (degrees celsius), med (IQR)	24 (22-25)
Concomitant procedures performed (all)	3 (13%)
Tricuspid valve annuloplasty	2 (8%)
Mitral valve annuloplasty	1 (4%)
ECMO	1 (4%)
Days in ICU, median (IQR)	4 (2-5)
Days in hospital, median (IQR)	9 (8-20)
Days ventilated, median (IQR)	1 (1-1)
Patients with complications (all)	16 (67%)
Bleeding (requiring transfusion)	5 (21%)
Sternal wound sepsis	3 (13%)
Acute renal failure	3 (13%)
Arrhythmia	3 (13%)
Need for re-look surgery	2 (8%)
Anesthetic complication	2 (8%)
Pleural effusion	2 (8%)
Haemothorax	1 (4%)
Pericardial effusion/cardiac tamponade	2 (8%)
Pneumonia	1 (4%)
In hospital mortality	4 (17%)

PEA, pulmonary endarterectomy; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.

Table 5. Post-operative outcomes

(n=16 unless otherwise shown)

4-month mortality	4 (17%) (n=23)
Time to follow up post-surgery (months), median (IQR)	4 (2-5)
WHO functional class at follow up	
I	10 (63%)
II	5 (31%)
III	1 (6%)
IV	0 (0%)
Signs of right heart failure	2 (13%)
Post-op echocardiogram performed	8 (50%)
RVSP (mmHg), med (IQR)	33 (30-58) (n=6*)
Post-op 6MWT performed	9 (56%)
Post-op 6MWT distance (m), mean (SD)	445 (108) (n=9)
Post-op RHC performed	0

WHO, World Health Organisation; RVSP, right ventricular systolic pressure; 6MWT, six-minute walk test; RHC, right heart catheterization

*Unable to assess RVSP for 2 patients as no tricuspid regurgitation.

Table 6. Comparison of pre- and post-operative outcome variables

Outcome	Pre-operative (n=24)	Post-operative (n=16)
WHO-FC I	0 (0%)	10 (63%)
WHO-FC II	5 (21%)	5 (31%)
WHO-FC III	14 (58%)	1 (6%)
WHO-FC IV	5 (21%)	0 (0%)
6MWT distance (m), mean (SD)	322 (140) (n=13)	445 (108) (n=9)
RVSP (mmHg), med (IQR)	82 (64-89) (n=22)	33 (30-58) (n=6)

WHO-FC, World Health Organisation functional class; 6MWT, six-minute walk test; RVSP, right ventricular systolic pressure

APPENDICES

Appendix 1: Data collection sheet

Pre-op characteristics	
Age (years)	
Sex	
Date of surgery	
Mechanical ventilation pre-operatively	
On inotropes pre-operatively	
Imaging studies	
- CTPA	
- VQ	
- Both CTPA and VQ	
Treatment prior to surgery	
- Anticoagulation	
- Diuretics/digoxin	
- PH specific therapy	
Inferior vena cava filter	
Comorbidities	
Time from diagnosis to PEA (days)	
History of previous VTE	

Pre- and post-op haemodynamics on RHC	Pre-op	Post-op
Systolic PAP (mmHg)		
Diastolic PAP (mmHg)		
Mean PAP (mmHg)		
PVR (WU)		
Average CO (L/min)		
PCWP (mmHg)		

Pre- and post-op haemodynamics on echo	Pre-op	Post-op
Ejection fraction (%)		
Systolic PAP (mmHg)		
Diastolic PAP (mmHg)		
Mean PAP (mmHg)		
RVSP		

Pre- and post-op functional class and 6MWD	Pre-op	Post-op
WHO functional class		
6-minute walk distance (m)		
Signs of right heart failure i.e. oedema		

Intra-operative course	
Cardiopulmonary bypass time (minutes)	
Aortic cross-clamp time (minutes)	
Circulatory arrest time (minutes)	
Lowest core temperature (Celsius)	
Concomitant procedures	

Post-operative course	
Days in ICU	
Days in hospital	
Days ventilated	
ECMO	
Mortality in-hospital (survival to hospital discharge)	

Post-operative complications	
Residual PH	
Reperfusion oedema	
Pneumonia	
Bleeding	
Acute renal failure	
Arrhythmias	
Sternal wound infection	
Haemothorax	
Pneumothorax	
Chylothorax	
Pericardial effusion	
Pleural effusion	
CVA	
Seizure	
GIT bleed	

Appendix 2: UCT HREC approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

23 August 2019

HREC REF: 568/2019

Dr G Calligaro
Division of Pulmonology
E-16 Respiratory Clinic
NGSH

Dear Dr Calligaro

PROJECT TITLE: PULMONARY ENDARTERECTOMY FOR CHRONIC THROMBOEMBOLIC HYPERTENSION IN CAPE TOWN, SOUTH AFRICA (MMed candidate - DR S DAVIES-VAN ES)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 August 2020.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Dr Sophie Davies-Van Es will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

Appendix 3: AJTCCM instructions to authors

Available at the following link:

http://www.ajtccm.org.za/index.php/sarj/about/submissions