Features and Management of Pulmonary Embolism at Chris Hani Baragwanath Academic Hospital

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A research report submitted to the University of the Witwatersrand, Johannesburg in fulfilment for the requirements of the degree of Master of Medicine 2016.

DECLARATION

I, Swati Meel, declare that this research report is my own work which is being submitted for the degree Master of Medicine (in the submissible format with my protocol and an extended literature review) in the branch of Internal Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

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...12.....Day of....JUNE.....2017

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ABSTRACT

Background:

Pulmonary embolism (PE) is the most common cause of preventable deaths in hospitalized patients.

Objectives:

To determine the incidence and associated features of PE at Chris Hani Baragwanath Academic Hospital (CHBAH) over one year.

Methods:

A retrospective study was performed of patients with confirmed PE on computed tomography of the pulmonary arteries (CTPA) during 2013 and by means of a formatted data collection sheet, demographical and other relevant data was collected.

Results:

There were 498 CTPAs requested at CHBAH in 2013 and 147 (30%) of these confirmed the presence of PE. The mean age of the patients with PE was 47 ± 15.49 years. At least 41 % of the patients with PE were HIV positive. The Wells and revised Geneva score were comparable in predicting clinical probability of PE. Only 15% of the patients with high risk PE were thrombolysed, with no documented complications.

Conclusion:

PE is a common and serious medical condition in CHBAH and its management needs further optimization to improve clinical outcomes.

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LIST OF ABBREVIATIONS

ACCP	American College of Chest Physicians
CHBAH	Chris Hani Baragwanath Academic Hospital
CMV	Cytomegalovirus
CT	Computer Tomography
CTPA	Computer tomography of the pulmonary arteries
ELISA	Enzyme-linked immune-sorbent assay
ESC	European Society of Cardiology
HIV	Human immunodeficiency virus
MAI	Mycobacterial avium intracellulare
MOPETT	Moderate Pulmonary Embolism Treated With Thrombolysis
MTB	Mycobacterium tuberculosis
PASP	Pulmonary arteriolar systolic pressure
PE	Pulmonary embolism
PI	Protease inhibitor
PIOPED	Prospective investigation of pulmonary embolism diagnosis
PJP	Pneumocystis jiroveci pneumonia
RV	Right ventricle
SBP	Systolic blood pressure
USA	United States of America
VTE	Venous Thromboembolism

Chapter 1: PROTOCOL WITH EXTENDED LITERATURE REVIEW

1.1 Introduction

Pulmonary embolism (PE) occurs when there is an occlusion to the blood supply to a portion of the lung caused by a blood clot which embolises to lungs from peripheral veins. This prevents oxygenated blood from reaching the brain and other vital organs.[1]

The European Society of Cardiology (ESC) guidelines have proposed classifying PE according to the estimated risk of early death (inpatient or 30 day mortality) directly related to the PE. With this classification a high risk PE is characterized by haemodynamic instability, which according to the ESC guidelines is defined as a systolic blood pressure (SBP) of less than 90 or a drop in blood pressure of ≥ 40mmHg for more than 15 minutes that cannot be explained by another cause such as new onset arrhythmia, hypovolaemia or sepsis.[2,3] High risk PE may or may not be accompanied by right ventricular (RV) dysfunction and myocardial injury, it carries a short term mortality of 15%.[2]

Non-high risk PE is divided into moderate risk and low risk PE. Moderate risk PE is diagnosed when there is RV dysfunction and/or myocardial injury in a haemodynamically stable patient and low risk PE is when there is neither RV dysfunction nor myocardial injury.[2] In the more recent ESC guidelines from 2014 the subdivision of non-high risk PE into moderate and low risk PE is not mentioned, most likely to not complicate the clinically relevant distinction between high and non-high risk PE.[3]

1.2 Epidemiology

The annual incidence of PE in South Africa is unknown but in the United States of America (USA) it is estimated at 600 000 cases.[2,4] The prevalence amongst hospitalized patients over a 21 year period (1979 -1999) in the USA was 0.4%.[2,5] Mortality figures for acute PE

range from 7 – 11% .[2] In Sweden, an analysis of 2356 autopsies performed in 1987, showed venous thromboembolism (VTE) in 595 (25%) and PE in 431 (18.3%). In 308 of the autopsies, PE was considered to have caused or contributed to the deaths.[2,6] PE is regarded as the most common cause of preventable deaths in hospitalized patients and in its chronic phase is also a cause of great morbidity.[3] The annual healthcare cost attributable to treatment of VTE is estimated to be more than 1.5 billion US dollars.[7] These studies leave no doubt that PE is a prevalent condition, and is associated with a high mortality rate.

In a study from the USA conducted in 2009, reviewing the trends of PE it was found that the majority of the patients with PE were nonsurgical (71.2%), this may be attributable to various studies finding discrepancies in the use of VTE prophylaxis between surgical and non-surgical patients.[7]

1.3 Thrombolysis

According to the ESC and American College of Chest Physicians (ACCP) guidelines, thrombolytic therapy is indicated in high risk PE, even up to 14 days after the onset of symptoms, unless there are contra-indications present (Table 1).

In cases where there are contra-indications present to thrombolysis or where thrombolysis has failed, surgical or percutaneous catheter embolectomy should be performed where feasible.[2,3]

The first report of thrombolysis (streptokinase) being used in PE was published in 1964[8], and the first randomized controlled trial, the urokinase PE trial showed better acute response with thrombolytic therapy than with anti-coagulants alone.[9] In the urokinase PE

trial published in 1970 urokinase was proven to be superior when compared to heparin in achieving resolution of pulmonary emboli at 24hrs, as assessed by angiography and perfusion scans.[9] Another study by Sharma et al looked at pulmonary capillary perfusion and diffusion as endpoints after treatment for PE and found a significantly greater improvement in both these parameters when thrombolytics were used.[10] Follow – up of these patients at an average of seven years after therapy, showed lower pulmonary arterial pressures and pulmonary vascular resistance in the thrombolytic group compared to the group that received anticoagulation alone, demonstrating a long term benefit of thrombolysis.[11] In a randomized controlled trial by Goldhaber et al in 1993 which included 101 patients treated with either a thrombolytic or heparin assessed the echocardiographic changes in right ventricular function and the change in pulmonary perfusion in these two groups. Patients who received a thrombolytic showed increased improvement in right ventricular function and pulmonary perfusion than those who only received heparin. [12] All these studies demonstrate an improvement in haemodynamics with the use of thrombolytics than with heparin alone and therefore haemodynamically unstable patients as specified in the ESC guidelines should be treated with thrombolysis.

Use of thrombolysis for non-high risk PE with haemodynamic stability and features of right ventricular (RV) enlargement or hypokinesia or the elevation of biomarkers of RV injury was explored in the Moderate Pulmonary Embolism Treated with Thrombolysis (MOPETT trial) where low dose thrombolysis for "moderate" PE was used and the pulmonary arterial systolic pressures (PASP) assessed at 28 months after thrombolysis.[13] The investigators found a significant decrease in the PASP at approximately 28 months in patients with non-high risk PE with features of RV strain treated with a low dose thrombolytic agent. [13]

A large observational study of unstable patients with acute PE (n = 72,230) found that thrombolytic therapy was associated with lower all-cause mortality (15 versus 47 percent), as well as lower mortality attributable to PE (8.4 versus 42 percent).[14] The same study highlighted that thrombolysis was underutilized (only used in 30% of unstable patients) and less likely to be administered in older patients (> 60yr) and in patients with co-morbid conditions.[14] Only 16% of the unstable patients diagnosed with PE died on the day of admission and did not receive thrombolytic therapy, despite having enough time to do so.[14] This brings to light an area of clinician uncertainty and lack of confidence in the indication for thrombolysis. In a follow up study performed by the same group, it was found that unstable patients who received thrombolytic therapy regardless of age and co-morbidities, had a lower in hospital mortality rate.[15]

According to the ESC guidelines percutaneous catheter embolectomy is indicated when there are absolute contraindications to thrombolysis or in cases where thrombolysis has failed. It may also be considered as an alternative to surgery in high risk PE patients in centers where cardiopulmonary bypass facilities are not available.[2,3]

Table 1: Adopted from the ESC guidelines 2014

Contraindications to fibrinolytic therapy
Absolute contraindications
Haemorrhagic stroke or stroke of unknown origin at any time
Ischaemic stroke in preceding 6 months
Central nervous system damage or neoplasms
Recent major trauma/surgery/head injury (within preceding 3 weeks)
Gastrointestinal bleeding within the last month
Known bleeding risk
Relative contraindications
Transient ischaemic attack in preceding 6 months
Oral anticoagulant therapy
Pregnancy or within 1 week post-partum
Non-compressible puncture site
Traumatic resuscitation
Refractory hypertension (systolic blood pressure > 180mmHg)
Advanced liver disease
Infective Endocarditis
Active peptic ulcer

1.4 Serum D-dimer

D-dimer is a degradation product of cross linked fibrin and can be detected in serum through various assays, and its sensitivity and specificity for the diagnosis of pulmonary embolism has been studied extensively.[16] The Enzyme-Linked ImmunoSorbant Assay (ELISA) and quantitative rapid ELISA carry a sensitivity of 95% to 100% but the specificity is better with the rapid whole-blood test (73.3% versus 67.9%). The positive predictive value was poor for both tests. Various conditions, (recent surgery, infection, malignancy, pregnancy and puerperium, renal dysfunction, cigarette smoking, and old age) cause raised D-dimer levels.[16]

A negative D-dimer test reasonably excludes acute VTE , especially in patients with a low or intermediate clinical probability and is comparable to a lung scan in low clinical probability patients.[16] The sensitivity of D-dimer also decreases from the onset of symptoms with a drop of 25 % from the initial value after 1-2 weeks.[16] One study concluded that acute VTE could not be excluded if the D-dimer was done 1 week after

onset of symptoms.[16] D-dimer levels are also affected by anti-coagulation and levels decreased by 25% over 24 hours with a resultant decrease in sensitivity.[16] Elaboration on the usefulness of D-dimer levels in special circumstances is mentioned below.

1.4.1 Malignancy

D-dimer testing has the highest sensitivity and negative predictive value in oncology patients to exclude a VTE , although the validity of the test is not too reliable due to high levels even in the absence of thrombosis.[16] D-dimer levels > 8mg/l are more associated with the presence of a malignancy. The following risk factors increase the likelihood of VTE in oncology, location of the primary tumour, stage and initial period after diagnosis of tumour and associated comorbidities.[16]

1.4.2 Pregnancy

Pregnancy is a prothrombotic state and the risk of VTE is raised in the postpartum period with an incidence of 1 in 1000 pregnancies.[2,3,16] Normal D-dimer levels vary in pregnant patients depending on the gestation.[16] At cut off values for the first, second and third trimester of 0.286mg/l, 0.457mg/l and 0.644mg/l respectively, serum D-dimer testing has a 100% sensitivity.[16]

1.4.3 Renal failure

In renal failure patients the serum D-dimer test is of limited value as it represents increased fibrin turnover as well as decreased elimination.[16] The risk of VTE in patients with renal dysfunction increases as the glomerular filtration rate reaches 75ml/min/1.73m^2 with the relative risk of 2.1 as this stage approaches.[16]

1.4.4 The elderly population

The role of D-dimer testing after the age of 80 years is limited.[2,16] The specificity of D-dimer levels is dramatically reduced to 10% in patients above 80 years of age.[3] In one meta-analysis where age adjusted cut offs were used (age x 10µg/l above 50 years) , the specificity of D-dimer levels increased by 34-36% while the sensitivity stayed >97%.[3,17] This would also allow a reduction in the number of false positive results.

The level of D-dimer has been shown to correlate with the likelihood of VTE, with the specificity being 93% with levels > 4mg/l.[16] Thus, a higher D-dimer level should instigate a more aggressive diagnostic approach.

1.5 The Wells and revised Geneva scores

The Wells score is a predictor of probability of PE and is based on six objective and one subjective clinical judgment.[2,18] It has been validated in 2 schemes, the 3 category scheme and the 2 category scheme (Table 2).[2,18] The three category scheme divides the score in low, intermediate and high probability categories and the two category scheme is divided into PE likely and PE unlikely categories.[2,18] A more simplified version of the original Wells score which assign only one point per variable was derived in 2008 by Gibson NS et al and validated as being comparable and just as clinically useful as the original Wells score.[3,19]

The revised Geneva score although less commonly used is based on all objective criteria (Table 2).[2,20] Both scores have however yielded similar results.[2] As with the Wells score a simpler version of the revised Geneva score has been validated which also only assigns one point per variable to lead to easier calculation of the score and improve clinical utilization.[3,21]

Table 2: Clinical predictor rules for PE adapted from ESC guidelines 2014

Items	**Clinical decisions rule points**	
Wells rule	**Original Version**	**Simplified version**
Previous PE or DVT	1.5	1
Heart rate ≥ 100 b.p.m	1.5	1
Surgery or immobilization within the past four weeks	1.5	1
Haemoptysis	1	1
Active cancer	1	1
Clinical signs of DVT	3	1
Alternative diagnosis less likely than PE	3	1
Clinical probability		
Three-level score		
Low	0-1	N/A
Intermediate	2-6	N/A
High	≥7	N/A
Two-level score		
PE unlikely	0-4	0-1
PE likely	≥5	≥2
Revised Geneva score	**Original Version**	**Simplified version**
Previous PE or DVT	3	1
Heart rate		
75-94 b.p.m	3	1
≥95b.p.m	5	2
Surgery or fracture within the past month	2	1
Haemoptysis	2	1
Active cancer	2	1
Unilateral lower limb pain	3	1
Pain on lower limb deep venous palpation and unilateral oedema	4	1
Age > 65 years	1	1
Clinical probability		
Three-level score		
Low	0-3	0-1
Intermediate	4-10	2-4
High	≥11	≥5
Two-level score		
PE unlikely	0-5	0-2
PE likely	≥6	≥3

N/A – not applicable; b.p.m beats per minute

1.6 Human immunodeficiency virus and venous thrombo-embolism

Evidence shows that patients with human immunodeficiency virus (HIV) have multiple risk factors and a 2-10 fold increased risk of venous thrombo-embolism (VTE) compared to the general population.[22,23,24] In patients with HIV infection, the rate of VTE is increased in patients < 50 years of age as compared to controls and also those who have a CD4 count < 200 cells/mm^3.[22,23,24] The increased incidence of VTE at a younger age is partially explained by the so called "premature aging" which occurs in HIV positive individuals through defects in the immune system which are more commonly seen at CD4 counts < 200 cells/mm^3. These defects include a low CD4:CD8 ratio, low naïve : memory cell ratio and abnormal T cell function.[25]

HIV infection is a prothrombotic state through various risk factors related to the host, the virus itself and anti-retrovirals.[25] Host factors include age, intravenous drug use (15 times increased risk of VTE compared to HIV infected patients who did not use intravenous drugs) and hypercoagulability.[25] The hypercoagulability is attributable to various haematological abnormalities such as protein S deficiency and protein C deficiency, presence of anticardiolipin and lupus anticoagulant antibodies, increased tissue factor expression, increased level of microparticles and homocysteine and lastly abnormal endothelial function secondary to HIV itself.[25]

The viral factors include CD4 counts < 200 cells/mm^3, presence of active opportunistic infections, (especially cytomegalovirus (CMV) infection, *pneumocystis jiroveci* pneumonia (PJP), *mycobacterium tuberculosis* and *mycobacterium avium intracellulare* (MAI) infections) and HIV associated malignancies especially Kaposi sarcoma.[25] CMV infection, particularly with gastrointestinal involvement is associated with VTE and its prevalent with comorbid HIV infection is reported at 9.8%. [25] There is an increased occurrence of

antiphospholipid syndrome in PJP patients with HIV and may explain the increased incidence of VTE in these patients.[25] MTB induces cytokines through activation of macrophages. These cytokines (TNF-α, IL-1 and IL-6) promote coagulopathy by various means, such as blocking the protein C pathway and altering new platelet function.[25] Anticardiolipin antibodies are induced by MAI and MTB but a causal relationship with VTE in these patients is lacking.[25]

The third risk factor relates to anti-retrovirals and in particular to protease inhibitors (PI).[22,25] These drugs are associated with promoting thrombosis through various mechanisms. PIs have an effect on metabolism in the liver, especially on the cytochrome P450 system and promote a thrombotic state by interfering with regulation of thrombotic proteins. They are also associated platelet and endothelial dysfunction and undermining the anticoagulant pathways.[25]

1.7 Complications of thrombolysis

Bleeding is a much feared risk of thrombolytic therapy and has led to reluctance in its use despite there being clear indications to thrombolyse patients. In a retrospective study that included 312 patients from five previous studies of thrombolysis for PE, intracranial haemorrhage occurred in 6 patients (1.9%) and 2 of these were patients where thrombolysis was contraindicated due to the presence of pre-existing intracranial disease. the frequency of intracranial haemorrhage was 1.9% [26] In the prospective International Cooperative Pulmonary Embolism Registry which consisted of 2454 patients, there was 3% incidence of intracranial haemorrhage in patients who received thrombolysis[26]

According to the ESC guidelines, thrombolysis is the first line of treatment in patients with high risk PE presenting with cardiogenic shock and/or persistent arterial hypotension, with

very few absolute contra-indications (table 1).[2,3] This recommendation is shared by the ACCP guidelines who advise the use of thrombolytic therapy in patients with acute PE associated with hypotension, SBP < 90 mm Hg and who do not have a high bleeding risk.[26]

1.8 Computed tomography of the pulmonary arteries (CTPA)

CTPA is the investigation of choice for imaging of the pulmonary vasculature up to the segmental level. [2] The Prospective Investigation On Pulmonary Embolism Diagnosis study II series (PIOPED) showed that (multi detector) CTPA carries a sensitivity of 83% and a specificity of 96%.[2,28] This study also emphasized the importance of clinical evaluation in patient's suspected of having PE and categorizing them according to high, intermediate and low risk based on the Wells criteria, as this influences the interpretation of the CTPA report. The correlation between a positive CTPA and a high, intermediate or low clinical probability of pulmonary embolism based on the Well's criteria was 96%, 92% and 58% respectively .The likelihood that a patient did not have a PE based on a negative CTPA in the low, intermediate and high risk groups was 96, 89 and 60 % respectively.[2,28] Therefore the PIOPED series which included 824 patients and is the largest study of its kind, emphasizes the importance of concomitant clinical risk evaluation for accurate interpretation of CTPA reports.[2]

1.9 Study aim and objectives

1.9.1 Aim

No similar studies focusing on the features and management of PE have been conducted in South Africa (SA). This study will assess the number of high risk and non-high risk PE confirmed on CTPA at CHBAH over the period of one year.

The clinical significance of the various characteristics in patients with confirmed PE will be reviewed and the management of PE at CHBAH will be evaluated.

1.9.1 Objectives

1. To determine the incidence of PE (high risk and non-high risk) over the period of 2013 in CHBAH in cases where a CTPA was ordered.
2. To determine the HIV status and CD4 counts (whether above or below 200) of patients with confirmed PE on CTPA.
3. To determine the level of D-dimers in patients with a positive CTPA for PE.
4. To compare the accuracy of the Wells and revised Geneva score in determining the probability of PE in patients with positive CTPAs.
5. To determine whether thrombolytic therapy was administered for high risk PE, as confirmed on CTPA and to assess the occurrence of complications related to thrombolytic therapy.
6. To determine whether surgical or percutaneous catheter embolectomy was used in patients with high risk PE where thrombolytic therapy was contraindicated or had failed.

1.10 Methods

1.10.1 Study design

This will be a retrospective, descriptive and analytical study where the files of patients with confirmed PE on CTPA within the period of 1 January 2013 to 31 December 2013.

1.10.2 Study population

All patients that had CTPAs requested at the Department of Radiology at CHBAH and had a PE confirmed between 1 January 2013 – 31 December 2013 will be included – 498 patients have been identified.

1.11 Data analysis

After collection of files of patients with confirmed PE within the period of one year, the PE will be classified into high risk and non-high risk PE and their management noted in terms of whether thrombolysis or anti-coagulation was used. If thrombolysis was not used in patients with high risk PE due to the presence of contraindications, these will also be noted (figure 1). The other features being analysed will be the HIV status, the level of d-dimers, the Wells score and revised Geneva score, any complications of thrombolysis in the setting of high risk PE and the type of complication, whether surgical or percutaneous embolectomy was used in patients where thrombolysis was contra-indicated in the setting of high risk PE. Categorical variables were compared using the chi square test. The students t test was used to compare continuous and normally distributed variables and the McNemar's test was used where variables were not variably distributed. An additional analysis was also included which was not part of the initial objectives and this analysed the various predictors of mortality in patients with confirmed PE by means of univariate and multiple logistic regression analysis(Figure 1and Table 4,5).

1.12 Ethics

Ethical approval will be sought from the Human Research Ethics Committee of the University of the Witwatersrand and the Department of Internal Medicine Protocol Assessment Committee. No identifiable patient information will be used in this research project and their anonymity and confidentiality will be maintained. Only the primary researcher will have access to the data set and permission to conduct the research will be sought from the CEO of CHBAH.

1.13 Timing

	2014				2015		2016
	Jan – March	Apr-May	June	July-Dec	Jan - Aug	Sept-Dec	Jan-Dec
literature Review							
Preparing Protocol							
Protocol Assessment							
Ethics Application							
Data Collection							
Data Analysis							
Writing up Thesis							
Writing up Paper							

1.14 Funding

Photocopying and printing are the only expenses that will be incurred to carry out this research project and these will be covered by myself.

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Chapter 2: SUBMISSIBLE ARTICLE

Title:

Features and Management of Pulmonary Embolism at Chris Hani Baragwanath Academic Hospital.

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Conflict of Interest: nil

Keywords: Pulmonary embolism

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Background:

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Objectives:

To determine the incidence and associated features of PE at Chris Hani Baragwanath Academic Hospital (CHBAH) over one year.

Methods:

A retrospective study was performed of patients with confirmed PE on computed tomography of the pulmonary arteries (CTPA) during 2013 and by means of a formatted data collection sheet, demographical and other relevant data was collected.

Results: There were 498 CTPAs requested at CHBAH in 2013 and 147 (30%) of these confirmed the presence of PE. The mean age of the patients with PE was 47 ± 15.49 years. At least 41 % of the patients with PE were HIV positive. The Wells and revised Geneva score were comparable in predicting clinical probability of PE. Only 15% of the patients with high risk PE were thrombolysed, with no documented complications.

Conclusion:

PE is a common and serious medical condition in CHBAH and its management needs further optimization to improve clinical outcomes.

Introduction

Pulmonary embolism (PE) occurs when there is an occlusion to the blood supply to a portion of the lung caused by a blood clot which embolises to lungs from peripheral veins. This prevents oxygenated blood from reaching the brain and other vital organs.[1]

The European Society of Cardiology (ESC) guidelines have proposed classifying PE according to the estimated risk of early death (inpatient or 30-day mortality) directly related to the PE. With this classification a high risk PE is characterized by haemodynamic instability, which according to the ESC guidelines is defined as a systolic blood pressure (SBP) of less than 90 or a drop in blood pressure of ≥ 40mmHg for more than 15 minutes that cannot be explained by another cause such as new onset arrhythmia, hypovolaemia or sepsis.[2,3] High risk PE may or may not be accompanied by right ventricular (RV) dysfunction and myocardial injury, it carries a short term mortality of 15%.[2]

Non-high risk PE is divided into moderate risk and low risk PE. Moderate risk PE is diagnosed when there is RV dysfunction and/or myocardial injury in a haemodynamically stable patient and low risk PE is when there is neither RV dysfunction nor myocardial injury.[2] In the more recent ESC guidelines from 2014 the subdivision of non-high risk PE into moderate and low risk PE is not mentioned, most likely to not complicate the clinically relevant distinction between high and not high risk PE.[3]

The annual incidence of PE in South Africa (SA) is unknown but in the United States of America (USA) it is estimated at 600 000 cases. [2] The prevalence amongst hospitalized patients over a 21-year period (1979 -1999) in the USA was 0.4%.[2,4] Mortality figures for acute PE range from 7 – 11% .[2] In Sweden, an analysis of 2356 autopsies performed in 1987, showed venous thromboembolism in 595 (25%) and PE in 431 (18.3%). In 308 of

the autopsies, PE was considered to have caused or contributed to the deaths.[2,5] PE is regarded as the most common cause of preventable deaths in hospitalized patients and the annual healthcare cost attributable to treatment of venous thromboembolism (VTE) is estimated to be more than 1.5 billion US dollars.[6] These studies leave no doubt that PE is a prevalent condition, and is associated with a high, yet preventable mortality rate.

No similar studies focusing on the features and management of PE have been conducted in SA. The aim of this study was to assess the number of high risk and non high risk PE confirmed on computed tomography of the pulmonary arteries (CTPA) at Chris Hani Baragwanath Academic Hospital (CHBAH) over the period of one year and assess the significance of the various characteristics and the management of patients with confirmed PE.

Methods

Study population and sample

This was a retrospective study where all CTPA reports performed during the period of 1 January 2013 to 31 December 2013 were reviewed. The files of patients with confirmed PE on CTPA were pulled and further data was collected. The data analysed included demographics, admission ward, HIV status, CD4 count, anti-retroviral therapy (ART), D-dimer levels; mortality, the Wells and revised Geneva scores. The management of PE and possible complications thereof were also analysed. Other details collected included co-morbidities, Doppler ultrasounds and echocardiograms reports if available. There were no exclusion criteria.

Definitions

High risk PE was characterized by haemodynamic instability, which according to the ESC guidelines was defined as a systolic blood pressure of less than 90 or a drop in blood

pressure of ≥ 40mmHg for more than 15 minutes that could not be explained by another cause such as new-onset arrhythmia, hypovolaemia or sepsis.[2,3]

Non-high risk PE was further classified into moderate risk and low risk PE. Moderate risk PE was diagnosed when there was RV dysfunction and/or myocardial injury in a haemodynamically stable patient and low risk PE was when there was neither RV dysfunction nor myocardial injury. [2]

Statistical analysis

All the CTPA reports from the year 2013 were analysed and the ones with a confirmed PE were identified. A study number was allocated to each participant with a confirmed PE. A separate data sheet correlated names with a study number. All the captured data was recorded in Microsoft Excel sheets. The chi square test was used to compare categorical variables. For continuous variables the students t test was used when variables were normally distributed and where the variables were not variably distributed the McNemar's test was used. Univariate and multiple logistic regression analysis was used to determine predictors of in-hospital mortality for patients with PE.

Results

Overall incidence of PE

From the period of 1 January 2013 to 31 December 2013 there were 498 CTPA requests to exclude PEs at CHBAH, of these 147 CTPAs confirmed the diagnosis. The majority of the CTPAs were requested from the medical wards (79%) and 29% showed PE.

Demographics

A substantial proportion (78%) of the patients with PE comprised of females. The mean age of the patients was 47 ± 15.49 years. The mean age of patients who were

thrombolysed was 48.5 ± 14.6 years and of those not thrombolysed was 42.6 ± 11.5 (P=0.33). The study comprised of 137 black patients. (Table 3)

HIV, CD4 counts and ART

In this study 60 patients out of 147 (41%) with confirmed PE on CTPA were HIV positive. The HIV results of 37 patients were not available from either the files not being found or the test not being done. The CD4 counts of 45 HIV positive patients were found and over 60% of these patients had a CD4 count < 200 cells/mm^3. Amongst the HIV positive patients 24 were on ART, information was missing from 13 patients who were HIV positive regarding whether they were on ART or not.

Table 3: Demographics

Characteristics of the study sample	**Value N(%)**	**Missing value (N)**
Characteristics		
Patients with confirmed PE	147(29.5)	
High risk PE	33(22.4)	
Thrombolysed	6(18.2)	
General characteristics (Mean ± SD)		
Mean age (years)	46.82(15.2)	
SBP (mmHg)	118.2(24.7)	
DBP(mmHg)	73.9(15.5)	
HR b.p.m	111.5(17.0)	
Women	115(78.2)	
Blacks	137(93.2)	
HIV	60(40.8)	37
CD4 count < 200 cells/mm^3	28(62.2)	15
ARVs	24	13
Comorbidities		
↑BMI	24	29
TB	13	39
Malignancy	7	39
DVT	16	53
COPD/smoker	6	39

N= Number; SBP systolic blood pressure in mmHg; DBP diastolic blood pressure in mmHg; b.p.m beats per minute

Serum D-dimer levels

There were 70 patients who did not have a D-dimer result either because the files could not be found or the test was not done. The average serum D-dimer level was 3.7mg/l ±3.3. The serum D-dimer results of four patients which were specified but were only noted as raised and therefore could not be used to calculate the average D-dimer levels. There was only one result that was negative amongst the patients with a confirmed PE.

Mortality

There were 28 deaths (24%) amongst patients diagnosed with a PE on CTPA, this is excluding 28 patients where this data was missing. Thirteen (46%) of the 28 deaths were patients with high risk PE and 2 were thrombolysed. Malignancies were confirmed in three of these patients and two had suspected malignancies. There were six patients who had TB and one patient had PJP. There were nine HIV positive patients, five had a high body mass index (BMI) as noted in the files but a specific value was not specified. Univariate and multivariate analysis for independent predictors of mortality was performed on 88 patients where all the required data was available. The majority (79%) of the patients who died were female. On univariate logistic regression analysis, age in years after 40 was the only predictive factor of mortality with a p value=0.007 and an odds ratio of 1.04. Obesity, gender, thrombolysis and HIV were not found to be statistically significant in predicting mortality on univariate analysis. Age continued to be an independent predictor (odds ratio of 1.06 and p value=0.01) of mortality in a multivariate model when adjusted for other variables such as obesity, gender, HIV and thrombolysis. (Table 4)

Table 4: Multivariate analysis of predictors of mortality

Mortality	Odds Ratio	[95% Conf. Interval]
Obese	0.89	0.22 - 3.54
RVD	1.77	0.55 - 5.63
Age	1.06	1.01 - 1.12*
Gender	1.28	0.37 - 4.46
Thrombolysed	2.01	0.31 - 12.84

* $P \leq 0.05$

Wells and revised Geneva scores

According to the Wells score 31 (35%) patients with a confirmed PE on CTPA had a high probability, 54 (61%) had an intermediate probability, and 3(3%) had a low probability. Data regarding the Wells score was available from 88 of the 147 patients. Comparatively according to the revised Geneva score 31 (36%) had a high probability, 50 (58%) patients had an intermediate probability and 5 (6%) had a low probability of a PE. Data regarding the revised Geneva score was available from 86 of the 147 patients. This illustrates a close correlation between the two scores in this study. (Figure 1.)

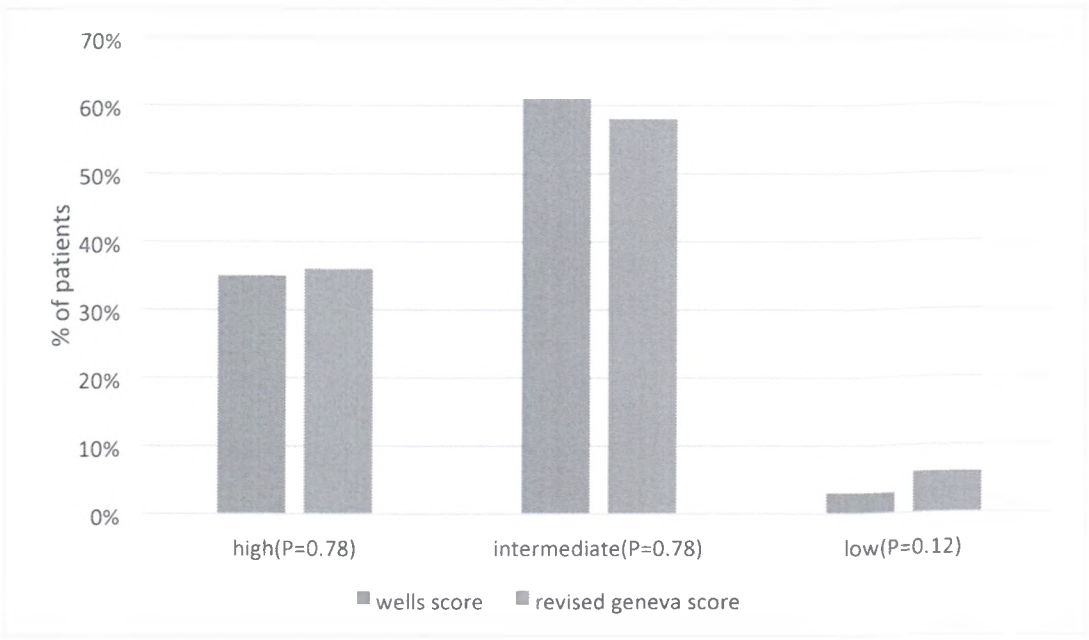

Figure 1: Comparison between the Wells and revised Geneva scores

Thrombolysis and embolectomy

There were 33 patients out of the 147 with confirmed PE (22.4%) who met the criteria for a high-risk PE according to the definition outlined by the ESC guidelines. Of these, five (15%) patients received thrombolysis. One patient did not meet the criteria of a high-risk PE but was thrombolysed based on echocardiographic findings of RV dysfunction. There was a 39% mortality amongst patients with a high-risk PE (table 5). There were no documented complications of thrombolysis. None of the patients had a surgical or percutaneous embolectomy but one had an IVC filter implanted and was being considered for a surgical embolectomy which was still to be done upon discharge.

Table 5: Incidence of thrombolysis of high risk PE at CHBAH in 2013

Number of CTPAs requested in 2013	Number of confirmed PE on CTPA	Number of high risk PE	Number of high risk PE thrombolysed
498	147(29.5%)	33 (22.4%)	5 (15.2%)

Discussion

Incidence and demographics

A study conducted in New Jersey between 1998 -2000, found the incidence of PE to be higher in black Americans compared to white patients. This study yielded similar results but it's difficult to comment on the increased incidence in blacks compared to whites as the majority of the patient population at CHBH were black.[7]

In a comparable study conducted in Sweden in 2006, 343 patients from a total of 517 with potential VTE, were found to have a confirmed VTE. Of the 343, 161 had a PE (31.1%). The mean age of diagnosis was 67.6 for men and 72.5 for women. The commonest risk factors were recent hospital admission and malignancy. The incidence in this study was similar but the mean age of diagnosis was much lower, which is not surprising as the majority of patients admitted at CHBAH have HIV associated conditions and are much younger.[8]

Inter-departmental incidence analysis

In a study that looked at the trends of outcomes for PE in the US it was found that 28.8% of the patients were classified as surgical and 71% as non-surgical.[6] We found that 78% of the patients in this study were non-surgical, possibly due to increased vigilance amongst physicians of the risk of PE but this is worrisome due to the obvious risk factors for PE in surgical wards.

HIV infection

HIV infection is an independent risk factor for VTE which explains that 41% of patients with PE in this study were HIV positive. There is a higher incidence of VTE in HIV patients with lower CD4 counts which is related to an increasing hypercoagulable state which occurs

with progressive immune suppression associated with HIV disease progression.[9,10,11] The bulk of the HIV infected patients diagnosed with PE in this study had a CD4 count less than 200cells/mm^3 which is known to cause a higher risk of thrombosis compared to patients with higher CD4 counts.

Advancing age is a risk factor for thrombosis in the general population in the developed world but the mean age of HIV infected patients at the time of VTE is 40 years which is 20 years less than their non-infected counterparts.[11] This finding also held true in this study but the difference was more exaggerated with the mean age of patients with HIV infection and a confirmed PE was 24 years.

Some studies have shown that the introduction of HAART has increased the incidence of VTE in HIV positive patients, protease inhibitors (PIs) in particular have been implicated, at least 40% of the HIV positive patients in this study were on HAART, although the exact regimen was not documented.[10,11] As PIs form part of second line therapy in HIV patients, the increased risk for PE in these patients might also be partly due to the poor general state of these patients with lower CD4 counts and possibly other opportunistic co-morbidities.

Thrombolysis and embolectomy

Only 15% of patients with high risk PE were thrombolysed in this study, one patient with an intermediate risk PE was thrombolysed because of features of RV strain on echocardiogram. One patient was not thrombolysed due to recent spinal surgery, another was a 19-year old patient with primary anti-phospholipid syndrome who was out of the window period for thrombolysis She had an IVC filter inserted and was planned for a surgical embolectomy but was not yet done upon discharge. There were no documented

complications of thrombolysis noted in any of these cases. The mortality rate was 39% amongst high risk PE patients. The average age of patients in the thrombolysis versus the non-thrombolysis group was very similar ranging from 42 to 43 years, therefore age clearly did not play much of a role in the decision regarding management. According to a study comparing mortality rates between patients with high risk PE who received and did not receive thrombolytic therapy, it was found that the fatality rates were lower in the thrombolysed group.[12] It was also found that the addition of a vena cava filter and thrombolysis further reduced the fatality rate.[12] This emphasizes the underutilization of thrombolysis at CHBAH, the reasons for this may be a reluctance on the part of the treating doctor to thrombolyse due to its potential complications and the need for close monitoring during and post thrombolysis or possibly a lack of awareness , regarding its short and long term benefits and the window period of 14 days since beginning of symptoms where it can still be utilized. IVC filters also are underutilized and may have added benefit on top of thrombolysis in improving clinical outcomes of patients with high risk PE.[12] Surgical and percutaneous embolectomy is evidently not considered often enough as a treatment modality in patients where thrombolysis might be contraindicated.

The Wells and revised Geneva scores

The Wells and revised Geneva score both have similar accuracy in predicting the likelihood of PE in the high, intermediate and low category.[2] These scores were not always documented in the files of these patients and were calculated based on information in the file where they were otherwise missing. This study showed strong similarities between the two scoring systems and both placed the majority of patients in the intermediate category. This can be explained partly in the context of the population at CHBAH where the mean population is much lower than 65 which is a component of the Wells score. Only 16 patients had DVTs confirmed on Doppler ultrasound, three did not show a DVT and for the

remaining patients either the data could not be found or the ultrasounds were not done. Most records made a comment on the suspicion of a DVT and the possibility of proximal DVTs cannot be excluded.

In this study, seven patients had a confirmed malignancy, one had a low grade squamous intra-epithelial lesion (LGSIL) and 2 had suspected malignancies. Of the confirmed malignancies 4 were lymphomas and the remaining three were Kaposi's sarcoma, breast carcinoma and bronchial carcinoma. This is in keeping with studies which have shown that haematological, lung, gastro-intestinal, pancreatic and brain malignancies carry higher risk of VTE. [3] A large proportion of the patients were HIV positive and had active TB which are both well known as a risk factors for VTE but are not included in either one of these scores, further study using a control group would prove valuable to perhaps decide on the inclusion of these risk factors in these scores in areas where they are endemic.

A recently published study from the Western Cape investigated the increase in yield of positive CTPAs when an electronic clinical decision support (CDS) system, which comprised of the modified Wells score and the D-dimer test result, was implemented. The percentage of positive CTPAs increased by 14.3% after using this system.[13] In our study the incidence of positive CTPAs was almost 30% despite the lack of a strict protocol to obtain a CTPA.

Although the importance of clinical probability is undeniable in risk assessment for PE, the more popular original Well's score has a subjective criterion "alterative diagnosis less likely than PE" which carries a score of 3 and together with a non-specific criteria of a heart rate more than 100 beats per minute which carries 1.5 points and already puts the probability of PE as "likely". There are numerous clinical confounders resembling PE in the South

African population which in turn also increase their risk for a PE. This in turn makes the overutilization of CTPA far less harmful than its underutilization considering the associated morbidity and mortality of missing the diagnosis of a PE.

The importance of clinical presentation cannot be overemphasized and as risk stratification scores are merely tools to improve the specificity of a certain diagnosis, the clinical condition of the patient is paramount in deciding on further investigations. Although there are many confounders with similar presentation to a PE, especially in the South African setting, it must be born in mind that the South African population is the very population at highest risk for PE with the HIV pandemic and the various associated prothrombotic conditions.

D-dimer levels

The sensitivity of D-dimer levels is well acknowledged and this study did not dispute this, with all the D-dimer levels in patient with confirmed PE being raised except for one. This was a 52 year old male patient with multiple myeloma for more than 20 years and on thalidomide since 2010. He also had a previous history of right leg deep vein thrombosis (DVT) in 2007 for which he received warfarin for six month. He had presented on the current admission with a DVT in the left leg confirmed on Doppler ultrasound and his CTPA showed chronic PTED. This might be attributed to the time from onset of symptoms to presentation which is known to significantly decrease the D-dimer levels, but more importantly this case highlights the importance of clinical suspicion as being the main driver of aggressive investigation for a possible PE regardless of the D-dimer result as the Wells and revised Geneva score both put this patient in a high-risk category for a PE.

Predictors of mortality

In this study the only variable found to be a statistically significant predictor of mortality was age. This is not surprising due to the many co-morbidities that are present in the older population and this finding was shared in a study which looked at the predictors of in-hospital and long term mortality in patients with acute PE and found older age to be a significant factor with a p value=0.031.[14]

A recently published study from the Western Cape investigated the increase in yield of positive CTPAs when an electronic clinical decision support (CDS) system, which comprised of the modified Wells score and the D-dimer test result, was implemented. The percentage of positive CTPAs increased by 14.3% after using this system.[13] In this study the incidence of positive CTPAs was almost 30% despite the lack of a strict protocol to obtain a CTPA.

Limitations

This was a retrospective study and the data collection was reliant on the manual record keeping system at CHBAH, therefore not all the relevant information were available for all cases. This compromised the accuracy of some of the objectives of the study especially the D- dimer levels, but from the proportion of the other results the findings most likely would have been exaggerated if all the data were available.

Conclusion

PE occurs frequently at CHBAH and is more common in middle aged, HIV positive females. The majority of the CTPAs are requested from the medical wards. The Wells and the revised Geneva score are comparable in predicting the likelihood of PE. Thrombolysis is gravely underutilized where it is clinically indicated in high risk PE. There is a significant mortality in patients diagnosed with PE and age was found to be the only significant

predictor of mortality. Surgical and percutaneous embolectomy are rarely considered as treatment modalities in patients who have contraindications to thrombolysis and IVC filters are also infrequently utilized. No complications of thrombolysis were reported.

The way forward

The purpose of this study was to statistically define the impact of the diagnosis and management of PE at CHBAH so that improvement can be made in areas where problems were identified. Thrombolysis is grossly underutilized and this needs to change to optimize the short and long term outcomes of patients with PE. A greater use must be made of surgical and percutaneous embolectomy where thrombolysis is contraindicated and close collaboration between medical and surgical doctors is needed to implement this.

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Chapter 3: APPENDICES

3.1 Data collection form

Case no	Risk		Thrombolysis		Anticoagulated		RVD		CD4 count	D-dimer
	High	Not high	Yes	No	Yes	No	Positive	Negative		

Wells score	Revised Geneva score	Mortality	
		Yes	No

3.2 Ethics clearance

R14/49 Dr Swati Meel

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140925

NAME: (Principal Investigator)	Dr Swati Meel
DEPARTMENT:	Internal Medicine Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Features and Management of Pulmonary Embolism at Chris hani Baragwanath Academic Hospital
DATE CONSIDERED:	03/10/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Alan Peter
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	06/10/2014

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES