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The correlation between pre-test probability and V/Q scan results in patients presenting with suspected pulmonary embolism

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CHAPTER 1

1 LITERATURE REVIEW

1.1 Introduction

Pulmonary embolism (PE) refers to the sudden blockage of a major vessel in the lungs due to a clot (Tabas & McNutt, 2005; Smith, 2008). If left untreated, the consequences can be disastrous. It is one of the major diagnostic challenges that a physician in the emergency department is faced with. The difficulty in making an accurate diagnosis leads to significant morbidity and mortality. This difficulty arises from the fact that the symptoms of PE are usually non-specific, and could range from a small, incidentally discovered PE to massive PE, which may ultimately be fatal.

Acute PE has been reported to occur in almost 600,000 patients every year in the United States alone (Ferretti *et al.*, 2005), although more recent estimates from the Centers for Disease Control and Prevention (CDC) suggest that almost 900,000 people are affected annually (Beckman *et al.*, 2010). Up to one-third of patients may succumb to the fatal effects of PE (Ferretti *et al.*, 2005). Various studies have estimated an overall incidence to be roughly 1 per 1000 people (Lake *et al.*, 2005; Ravenel *et al.*, 2005; Hoang *et al.*, 2008). A retrospective analysis spanning a period of 10 years from 1994-2004 investigated over 24 million patients in the state of New York (Burge *et al.*, 2008). The authors found that the incidence of PE had doubled during this period.

Despite the various diagnostic tools, reported mortality rates are extremely high at 15-30% if left untreated (Ravenel *et al.*, 2005; Hoang *et al.*, 2008). This significant mortality rate demands accurate, speedy diagnosis for effective treatment.

The development of PE is not restricted to a particular gender. There is no consensus regarding any specific gender conferring a higher risk of developing PE (Horlander *et al.*, 2003). A 25 year analysis by Silverstein et al. demonstrated that the elderly tend to have a higher rate of occurrence of PE (Silverstein *et al.*, 1998). One theory proposes that the cumulative risk factors that patients acquire in advancing age are some of the contributing causative factors (Silverstein *et al.*, 1998). The race of the patient also plays a significant role in inducing PE, whereby its incidence appears to be considerably higher in the black population compared to the white population (Horlander *et al.*, 2003; Schneider *et al.*, 2006; Meyer *et al.*, 2008).

1.2. Pathophysiology

Over the last several decades, it has increasingly been recognized that the pre-cursor to PE is underlying deep vein thrombosis (DVT). When a thrombus is acutely formed, it is usually soft and thus prone to embolisation.

Usually, the inherent thrombolytic system in the human body works to dissolve the thrombus. If this process fails, one of two outcomes may result. Either, the thrombus may be incorporated into the venous wall, causing contraction and scarring. This

may lead to some degree of occlusion of the vessel, as well as damage to the lower limb vasculature (Loud *et al.*, 2005). Collateral veins then form to bypass the area of occlusion. This is referred to as chronic DVT (Loud *et al.*, 2005). The other outcome is that the thrombus may separate from the vessel wall and enter the circulation as an embolus. It then travels through the right-sided chambers of the heart to reach the lungs, where it may completely obstruct a major vessel, leading to its most feared complication, i.e. fatal pulmonary embolus (Kline & Runyon, 2005; Tabas & McNutt, 2005; Smith, 2008).

Even though some of the pulmonary emboli come from the cardiac system or veins of the upper limb, the vast majority begin in the venous system of the lower limbs, extending into the inferior vena cava and thereby reaching the lungs. The risk of PE depends on the location of the DVT. If the thrombus is located in the small calf veins, the risk of PE is small (Loud *et al.*, 2005). However, if the thrombus is located in the larger veins, such as the popliteal, femoral or iliac veins, the risk of breaking off and embolising to a PE progressively increases (Loud *et al.*, 2005). This is true for both the initial PE as well as any recurrent episodes (Loud *et al.*, 2005). Up to one-third of patients may have recurring DVTs (Watts, 2004). The great challenge remains in trying to determine which patients fall into this recurrent category, so that appropriate prophylactic treatment may be offered.

Many risk factors have been shown to affect the development of a DVT. These include age over 40 years, a prior history of DVT, obesity, pregnancy, prolonged immobility, oestrogen use and underlying cancer, amongst others (Loud *et al.*, 2005).

1.3 Risk factors

DVTs can recur in 20-30% of patients (Watts, 2004). Great effort has been made in attempting to identify patients that may be at risk of recurrence. The most effective means has been to determine if patients have an underlying provocative event. The most commonly cited risk factors include prolonged inactivity/ bed rest, oral contraceptives, pregnancy, recent trauma or surgery, various cancers as well as some genetic risk factors including factor V Leiden, protein C & S deficiency and antithrombin deficiency (Watts, 2004; Ravenel *et al.*, 2005).

All these risk factors, in one way or another, directly have a bearing on the well-known Virchow's triad, leading to either venous stasis, vessel wall damage or a hypercoagulable state (Kline & Runyon, 2005; Tabas & McNutt, 2005; Smith, 2008). Long periods of sedentary behavior such as may occur in pregnancy or after recent major surgery, may lead to venous stasis. Trauma or infection may lead to endothelial injury to the wall of the vessel. Various genetic risk factors in the younger population lead to an overall hypercoagulable state thus promoting the development of DVT and subsequent PE. In the older population, many diseases, and particularly various cancers, have the same effect (Kline & Runyon, 2005; Tabas & McNutt, 2005; Smith, 2008).

Table 1.1: Virchow's triad and its association with the clinical risk factors in the development of DVT and PE

Venous stasis	* Prolonged immobility (e.g. stroke or prolonged bed rest,)
	* Congestive heart failure
	* HIV/AIDS, TB and Chronic obstructive pulmonary disease
Venous endothelial Damage	* Surgery within the past 3 months
	* Fractures of long bones or hip
	* Burns
	* Lower extremity trauma
Hypercoagulability	* Malignant neoplastic disease
	* Use of oral contraceptives
	* Marked obesity
	* Protein C or S deficiency
	* Factor V Leiden
	* Antithrombin deficiency

Adapted from (Goldhaber *et al.*, 1982; British Thoracic Society, 2003).

All the known risk factors can be classified as either hereditary or acquired (see Table 1.2).

Table 1.2: Risk factors for PE classified into either hereditary or acquired

GENETIC	ACQUIRED
Antithrombin III deficiency	Prior history of DVT or PE
Proteins C and S deficiency	Major surgery/ trauma (postoperative, indwelling catheters or injury to the spinal cord)
Factor V Leiden	Acute medical illness (HIV/AIDS, congestive cardiac failure, myocardial infarction)
Plasminogen abnormality and Plasminogen activator abnormality	Reduced mobility (fractures, immobilisation, obesity, burns)
Fibrinogen abnormality	Malignancy or chemotherapy
Resistance to activated protein C	Advanced age > 65 years
	Pregnancy (either during postpartum period, or as a result of being on oral contraceptives or oestrogen replacement therapy)
	Other

Adapted from (Kline & Runyon, 2005; Tabas & McNutt, 2005; Smith, 2008).

Ninety four percent of patients in the Prospective Investigation of Pulmonary Embolism Diagnosis II (PIOPED II) study had at least one of the following risk factors (Stein *et al.*, 2007):

- Previous pulmonary embolism
- Surgery within the last 3 months
- Heart failure
- Chronic obstructive pulmonary disease
- Travel of 4 hours or more in the past month
- Stroke, paresis, or paralysis
- Malignancy, especially lung cancer
- Central venous instrumentation within the past 3 months
- Current or past history of thrombophlebitis
- Trauma to the lower extremities and pelvis during the past 3 months
- Smoking
- Immobilisation

Identification of the above risk factors should enable physicians to predict which patients may be at high risk of developing venous thrombosis and subsequent PE. These factors have been incorporated into risk stratification scores such as the Wells' score. Decisions should then be made regarding prophylactic anticoagulation after a careful analysis of the risks and benefits in these patients to reduce mortality rates. A group of investigators have developed a risk prediction algorithm, called the QThrombosis algorithm (Hippisley-Cox & Coupland, 2011). This algorithm estimates

the future risk of a patient developing a DVT at 1 year and 5 years. They have utilized this information in guiding prophylaxis and medication decisions.

1.4 Clinical signs and symptoms

Patients with acute DVT usually present with a swollen and tender calf (Watts, 2004). If the DVT is long-standing, skin changes may manifest (Watts, 2004). If a DVT is suspected, it may be confirmed clinically by eliciting a positive Homan's or Pratt's sign. If there is pain in the calf region on dorsiflexion of the affected foot, this indicates a positive Homan's sign (Goodman & Boissonnault, 1998). This sign, however, is not specific for DVT only, and may be related to many other conditions, including Achilles tendonitis, injury to the gastrocnemius and plantar muscles or superficial phlebitis (Shafer & Duboff, 1971; Goodman & Boissonnault, 1998). However, if the Homan's sign is negative this does not imply that DVT is not present, as thrombi in the thigh and pelvic veins are often asymptomatic (McLachlin *et al.*, 1962). The Pratt's sign was described by the surgeon, Gerald Pratt. If the patient experiences pain while the posterior aspect of his/ her calf is being squeezed, this indicates a positive Pratt's (McLachlin *et al.*, 1962). However, this sign once again cannot be utilised exclusively for confirming a DVT (McLachlin *et al.*, 1962). Due to the low sensitivity and non-specific nature of the above signs, it is perhaps unsurprising that these are not included in the clinical prediction rules used in the risk-stratification of patients in the work-up for PE.

The clinical manifestation of an embolus depends on its size. Small emboli may be totally asymptomatic, and are discovered purely incidentally. A massive PE may ultimately be fatal.

Due to the nature of their size, the smaller thrombi tend to penetrate deeper into the lungs, thus occluding the vessels at the lung periphery. A thrombus large enough to cause an infarction may produce an inflammatory response of the parietal lining of the lung pleura. This leads to pleuritic chest pain (Tabas & McNutt, 2005; Smith, 2008). Due to the differential gradient in blood flow in the lungs as a result of gravity, the emboli tend to gravitate more toward the lower lobes as compared to the upper lobes. The smaller emboli also tend to be multiple (Tabas & McNutt, 2005; Smith, 2008).

Multiple pulmonary emboli may, over a period of time, result in the development of chronic thromboembolic pulmonary hypertension (CTEPH) and subsequent cor pulmonale. These manifest clinically as distended neck veins, systemic hypotension and a loud P_2 (which represents the pulmonary component of the second heart sound) (Kline & Runyon, 2005; Tabas & McNutt, 2005; Smith, 2008). Several authors have reported that the total affected area of the pulmonary vascular bed needs to be reduced by at least 60% for significant pulmonary hypertension to occur (Kline & Runyon, 2005; Tabas & McNutt, 2005; Smith, 2008). These patients may then progress to right ventricular failure, evident by a gallop rhythm and peripheral oedema (Kline & Runyon, 2005; Tabas & McNutt, 2005; Smith, 2008).

The pathophysiology of CTEPH is complex as a large number of patients have no known pre-existing coagulopathy. Intricate physical and neurohumoral factors have been implicated. Endothelin, which is a potent vasoconstrictor, is an example of a neurohumoral factor (O'Connell *et al.*, 2015). Furthermore, dysfunctional endothelial cells impair the resolution of already formed thrombus (O'Connell *et al.*, 2015). Both these factors exacerbate the CTEPH.

Two novel therapies have targeted these pathways. Endothelin receptor antagonists inhibit endothelin function, thus causing effective vasodilation (Robbins *et al.*, 2016). Riociguat on the other hand stimulates guanylate cyclase activity, thus promoting the synthesis of cyclic guanosine monophosphate (cGMP) (Robbins *et al.*, 2016; Smith *et al.*, 2016). This effectively reduces platelet aggregation and promotes vasodilation (Robbins *et al.*, 2016; Smith *et al.*, 2016). Furthermore, guanylate cyclase works synergistically with nitric oxide, another potent vasodilator (Robbins *et al.*, 2016; Smith *et al.*, 2016).

If the embolism has not caused an infarction, these patients usually present with non-specific signs and symptoms. However, some symptoms do occur more commonly than others. Pleuritic chest pain and shortness of breath are the most frequent complaints. The so-called pathognomic triad of symptoms—representing haemoptysis, pleuritic chest pain and dyspnoea—occurs in less than 20% of patients only (Kline & Runyon, 2005; Tabas & McNutt, 2005; Smith, 2008).

The most common symptoms of pulmonary embolism reported in the first PIOPED study were the following (Worsley & Alavi, 1995):

- Dyspnoea (73%)
- Pleuritic chest pain (66%)
- Cough (37%)
- Haemoptysis (13%)

Other symptoms include tachypnoea and tachycardia. On auscultation, crackles and even localised wheezes may be heard (Lake *et al.*, 2005; Ravenel *et al.*, 2005; Smith, 2008). However, it must be borne in mind that these symptoms are quite non-specific, and may be a result of many other disease processes. Thus, a high index of suspicion will direct the performance of appropriate diagnostic studies.

If the thrombus causes occlusion of a pulmonary artery, this may result in infarction of the lung parenchyma, with resultant ventilation–perfusion (V/Q) abnormalities and hypoxaemia. This, however, is an uncommon consequence and reportedly occurs in less than 10% of patients (Kline & Runyon, 2005; Smith, 2008). Patients having developed infarction will present with pleuritic chest pain of acute onset, which may sometimes be accompanied by dyspnoea and haemoptysis. The chest pain may be difficult to distinguish from chest pain of myocardial origin. Performance of an ECG tracing and monitoring response to nitroglycerine usually assists with this differential diagnosis (Kline & Runyon, 2005; Tabas & McNutt, 2005; Smith, 2008). A pleural rub or localised tenderness are suggestive of acute pulmonary infarction (Kline & Runyon, 2005; Tabas & McNutt, 2005; Smith, 2008). If a pleural effusion is also

present, decreased breath sounds may be heard. Dullness to percussion may be elicited (Kline & Runyon, 2005; Tabas & McNutt, 2005; Smith, 2008).

If the thrombus is large enough, it may become fused at the junction of the main pulmonary arteries, causing considerable haemodynamic compromise. A pulmonary embolus is defined as massive either when it occurs in both pulmonary arteries or when the result is arterial hypotension, defined as “systemic arterial pressure of <90 mmHg or a drop in systolic arterial pressure of at least 40 mmHg for at least 15 minutes” (Lohan *et al.*, 2007). Cardiogenic shock usually occurs, and manifests as poor perfusion of the extremities, impaired mentation, oliguria and cool, clammy extremities (Lohan *et al.*, 2007). With massive pulmonary embolism, death may occur in 30-60% of patients (Sandler & Martin, 1989; Goldhaber *et al.*, 1999; Wood, 2002; Worku *et al.*, 2014; Mostafa *et al.*, 2016). Thus, massive PE requires more aggressive therapeutic options. Such options include systemic thrombolysis, surgical pulmonary embolectomy and inferior vena cava (IVC) filter insertion (Worku *et al.*, 2014; Mostafa *et al.*, 2016; Wadhera & Piazza, 2016).

In view of the considerable morbidity and mortality associated with PE, patients with respiratory symptoms should be expeditiously worked up especially if they have significant risk factors for the disease.

1.5 Risk stratification

Due to the fact that many of the clinical signs and symptoms are non-specific, PE may not always be present in a patient presenting with respiratory symptoms suggestive of a PE. Thus, several structured clinical decision rules have been promoted to assist physicians especially in the setting of a patient with acute hypoxaemia (Kline & Runyon, 2005; Tabas & McNutt, 2005; Smith, 2008; Tapson, 2008; Bajc *et al.*, 2010). These include the models of Wells et al and Miniati et al (Wells et al., 2000; Miniati et al., 1996). These rules use a scoring system to determine the pre-test probability of the patient having PE.

According to Marika Bajc and colleagues, the Wells score is the most widely utilised rule for clinical decision making (Bajc *et al.*, 2010). Using this score, patients are classified as having a low, medium or high clinical probability of having PE based on a number of risk factors and physical findings. These three categories correspond to an increasing risk of having the disease (Quiroz & Schoepf, 2005). The diagnostic work-up is also subsequently based on the clinical probability. Clinical decision rules have been used together with D-dimer ELISA assays on an outpatient basis to reliably exclude PE without the additional need for more specific imaging tests (Ravenel *et al.*, 2005).

Table 1.3: Criteria of Wells et al (2000) for assessment of pre-test probability for PE

Criteria	Points
Suspected DVT	3
An alternative diagnosis less likely than PE (by history, physical examination, CXR, ECG and blood results)	3
Heart rate >100 beats/min	1.5
Recent immobilisation or surgery	1.5
Previous DVT/PE	1.5
Haemoptysis	1
Malignancy (on treatment or treated in the past 6 months)	1

The traditional interpretation of the Wells score is as follows (Wells *et al.*, 2000; Wells *et al.*, 2001):

Table 1.4: Traditional interpretation of Wells score

Score range (points)	Interpretation of risk
<2	Low
2–6	Moderate
>6	High

A study by Stein and co-workers found that a Wells score of > 6 was associated with a 59% risk of PE, scores between 2 and 6 carried a 29% risk, and scores <2 were associated with a 15% risk of PE (Stein *et al.*, 2007).

An alternate interpretation of the Wells score has been suggested as follows (Wells *et al.*, 2000; Van Belle *et al.*, 2006):

- Score > 4 – PE likely. Diagnostic imaging should be considered.
- Score ≤ 4 – PE unlikely. D-dimer testing should be considered to rule it out completely.

The model proposed by Miniati et al does not rely on any laboratory tests (Miniati et al., 1996). Thus the pretest probability can be estimated quickly and easily at the patient's bedside, with the additional help of an ECG at most (Bajc *et al.*, 2010).

Some of the other scores that have been used include the Geneva score and its sequel, the revised Geneva score.

Table 1.5: Geneva score

Criteria	Points
Age (in years) • 60 – 79 • >80	 1 2
Previous PE or DVT	2
Recent surgery	3
Tachycardia (>100 beats/min)	1
$PaCO_2$ (in kPa) • <4.8 • 4.8 – 5.19	 2 1
PaO_2 (in kPa) • <6.5 • 6.5 – 7.99 • 8 – 9.49 • 9.5 – 10.99	 4 3 2 1
Chest x-ray • Atelectasis • Elevated hemidiaphragm	 1 1

Adapted from (Wicki et al., 2001)

Table 1.6: Revised Geneva score

Criteria	Points
Age > 65 years	1
Previous PE or DVT	3
Recent surgery or fracture of lower limbs	2
Active malignant condition	2
Unilateral lower limb pain	3
Haemoptysis	2
Tachycardia (beats/min) • 75-94 • >94	 3 5
Pain on palpation of lower limb and unilateral oedema	4

Adapted from (Le Gal *et al.*, 2006)

Table 1.7: Interpretation of revised Geneva score

Score range (points)	Interpretation of risk
<4	Low
4-10	Intermediate
>10	High

Adapted from (Le Gal *et al.*, 2006)

Pre-test probabilities have been used to augment the diagnostic utility of lung scans. The positive predictive value of 87% for a high probability lung scan in the PIOPED study increased to 96% positive predictive value after taking into account a high pretest probability (Stein *et al.*, 1993). In a similar manner, the positive predictive value of 14% for a low probability lung scan in the PIOPED study decreased to a mere 4% after taking into account a low pretest probability (Stein *et al.*, 1993).

1.6 Investigations

Without doubt, PE can be lethal. However, PE cannot be diagnosed solely on clinical features. Both the high mortality and the treatable nature of the disease warrant appropriate investigations to exclude this potentially fatal disease prior to discharging the patient from the emergency department.

Investigations should be carried out as soon as possible due to the variable rate of resolution of PE. Although PE may remain unresolved even six months after diagnosis (Nijkeuter *et al.*, 2006), many investigators have described complete resolution within days or even hours after anticoagulation treatment (James *et al.*, 1978; Fredin & Arborelius, 1982; Olsson *et al.*, 2006). Thus, the recommendation is to perform imaging tests within 24 hours from the onset of symptoms (Coakley, 1995).

1.6.1 Blood tests

1.6.1.1 Arterial Blood Gas

Efficient gas exchange in the lungs is coordinated by both adequate ventilation and adequate perfusion in that region. When one element is disturbed, this leads to hypoxaemia (King *et al.*, 2010). Although patients with PE often develop hypoxaemia (a decrease in P_aO_2), this is not specific for PE and is often seen in many other pulmonary conditions, such as pneumonia, congestive cardiac failure (CCF) and chronic obstructive pulmonary disease (COPD) (Lake *et al.*, 2005). On the other hand, even if the P_aO_2 is normal and the patient has a normal alveolar-arterial oxygen gradient, this does not entirely exclude the possibility of PE (Overton & Bock, 1988) . A normal alveolar-arterial gradient is reported to occur in up to 20% of patients (Stein *et al.*, 1995).

If cyanosis is detected though, this suggests a large pulmonary embolus causing systemic hypoxaemia (Kline & Runyon, 2005; Tabas & McNutt, 2005; Smith, 2008).

In light of the above, it has thus been suggested that arterial blood gas sampling may not be a very valuable test in the diagnostic algorithm in patients with suspected PE except in the setting of a normal chest xray (Stein *et al.*, 1996). Other biomarkers such as brain natriuretic peptide, pro-brain natriuretic peptide and troponin have shown greater promise in determining prognosis and clinical outcomes (Kucher, 2003; ten Wolde, 2003; Konstantinides, 2002).

1.6.1.2 Troponin levels

There is a significant association between elevated levels of certain biochemical markers and PE. These include serum troponin levels and brain-type natriuretic peptides.

The larger the size of the embolus, the higher the levels of serum troponin that have been reported (Konstantinides, 2008a). It has been postulated that stretching of the right ventricular myocardium may be responsible for the abnormally high levels of serum troponin that are released into the bloodstream (Aksay *et al.*, 2007; Becattini *et al.*, 2007; Becattini *et al.*, 2008; Kline *et al.*, 2008).

Different authors have expressed the concern that elevated levels of serum troponins correlate with up to a 4-fold increase in mortality (Meyer, Binder, Hruska, Luthe & Buchwald, 2000; Jiménez, Uresandi, Otero, Lobo, Monreal, Martí, Zamora, Muriel, Aujesky & Yusen, 2009). This has been confirmed in large studies with over 1300 patients enrolled (Jiménez *et al.*, 2009). Consequently, serum troponin levels may be useful in predicting the prognosis of patients, even though they are neither helpful in establishing the diagnosis of PE, nor are part of the established guidelines in the work-up of such patients.

1.6.1.3 Brain-type natriuretic peptide

Brain-type natriuretic peptide (BNP) is a polypeptide consisting of 32 amino acids. Excessive stretching of the myocardium causes this hormone to be released. It has been purported to play a role in vasodilation and fluid & sodium excretion, leading to hyponatraemia (Weber & Hamm, 2006).

As was the case with serum troponin levels, the larger the size of the embolus, the higher the levels of BNP that have been reported. High levels of BNP have been associated with an increased risk of complications and mortality (Kline *et al.*, 2008; Klok, Mos & Huisman, 2008; Scherz, Labarère, Méan, Ibrahim, Fine & Aujesky, 2010). This prognostic information is provided by elevated levels of either the BNP itself, or its precursor *N*-terminal pro-brain natriuretic peptide (NT-pro-BNP) (Kline *et al.*, 2008).

Although patients with confirmed with PE tend to have higher levels of BNP, the brain-type natriuretic peptide tests have been shown to be neither sensitive nor specific for pulmonary embolism. The study by Sohne et al, demonstrated in over 2000 patients that testing of BNP levels had a sensitivity and specificity of only 60% and 62%, respectively (Söhne, ten Wolde, Boomsma, Reitsma, Douketis & Büller, 2006). Thus, although BNP levels may provide essential information on the prognosis of the patient, routine BNP tests have not been included in the recommended diagnostic work-up of a patient with suspected PE.

1.6.1.4 D-Dimers

D-dimers are degradation products of cross-linked fibrin, and are therefore elevated in the blood during and immediately after a DVT (Watts, 2004; Bajc *et al.*, 2010). A negative D-dimer result, in combination with a low probability on the Wells prediction rule, has been utilised to safely rule out PE without further imaging (Lake *et al.*, 2005). This was proven by Kearon *et al*. in a large prospective, randomised trial which concluded that additional diagnostic testing can be safely withheld in patients with a low probability of PE who have negative D-dimer results (Kearon *et al.*, 2006). This finding has been corroborated by Freeman *et al.* who reports that none of the patients with a negative D-dimer level, accompanied by a low pre-test probability, were found to have a positive CTPA (Freeman *et al.*, 2012). This is as a result of its very high negative predictive value (NPV) of 99.6% (Lake *et al.*, 2005; Quiroz & Schoepf, 2005; Ravenel *et al.*, 2005).

D-dimers can be measured by various types of assays, including quantitative, semi-quantitative, and qualitative rapid enzyme-linked immunosorbent assays (ELISAs); quantitative and semi-quantitative latex as well as whole-blood assays (Kline & Runyon, 2005; Tabas & McNutt, 2005; Smith, 2008). The high sensitivity of the D-dimer ELISA (97%) as well as its extremely high NPV has led to the consensus that in the setting of a negative test, the likelihood of PE is very low and further diagnostic workup is usually superfluous (Lake *et al.*, 2005; Quiroz & Schoepf, 2005; Ravenel *et al.*, 2005).

A positive D-dimer assay on the other hand is non-specific, as levels are elevated in many other disease processes, including sepsis, pneumonia, pregnancy, various cancers, myocardial infarction, and even mere inflammation (Watts, 2004; Ravenel *et al.*, 2005; Bajc *et al.*, 2010). Thus, D-dimer testing has a limited role in a patient with significant co-morbidities (Watts, 2004; Lake *et al.*, 2005; Ravenel *et al.*, 2005). Its specificity is inversely proportional to age, making a positive D-dimer quite unhelpful in the elderly patients (Stein *et al.*, 2004). Thus, the real strength of a negative D-dimer testing lies in the evaluation of younger patients who have no associated co-morbidities (Qaseem *et al.*, 2007).

However, the recent ADJUST-PE study has proven that by using age-adjusted D-dimer levels, PE can be safely ruled out in a larger number of patients, especially the elderly (Righini *et al.*, 2014). In patients over the age of 75 years, using the age-adjusted cut-off values increased the diagnostic yield by a factor of 5 (from 6.4% to 29.7%) (Righini *et al.*, 2014). Thus, in a significant number of elderly patients, PE could be safely ruled out without the need for additional imaging (Righini *et al.*, 2014).

1.6.1.5 Ischemia-Modified Albumin

If the D-dimer assay is not available, a possible alternative is evaluation of the ischemia-modified albumin (IMA) levels. Although sensitivity of the IMA levels is slightly lower (93% vs 97%), its specificity is much higher at 75% (Turedi, Gunduz, Mentese, Topbas, Karahan, Yeniocak, Turan, Eroglu, Ucar, Karaca, Turkmen &

Russell, 2008). This is especially useful in the elderly patients, as well as patients with significant co-morbidities. Turedi et al. compared the two tests i.e. IMA and D-dimers in terms of their prognostic values (Turedi *et al.*, 2008). They discovered that due to the higher specificity, IMA had a better positive predictive value compared to the D-dimer test. At around the same time Tick et al. also studied the IMA (Tick *et al.*, 2008). Although their findings were similar, they strongly recommend that the IMA levels should not be utilized on their own to confirm or exclude PE.

1.6.2 Ancillary tests

These are tests that are of secondary importance in assisting at formulating a diagnosis.

1.6.2.1 Chest x-ray

It is mandatory for a chest x-ray to be obtained in patients with suspected PE prior to more advanced imaging tests, as it may provide important alternative diagnoses. Although there are no definitive findings indicative of PE, the American College of Radiology recommends the chest x-ray as “the most appropriate study for ruling out other causes of chest pain in patients with suspected pulmonary embolism”, namely, pneumothorax, pulmonary oedema, malignancy or pneumonia (Bettmann *et al.*, 2011).

The additional utility of the chest x-ray is in the triage of patients in the emergency department. Over and above being able to demonstrate other causes of chest pain, the chest x-ray also plays a role in deciding which imaging modality is given preference to. If the chest x-ray is normal, or near-normal, these patients are then referred for a V/Q scan (Roach *et al.*, 2010a). A normal chest x-ray, especially in the setting of an abnormal alveolar-arterial gradient, is highly suggestive of PE. If there are significant abnormalities on the chest x-ray, these patients are then referred for a CT pulmonary angiography instead, as the chances of the V/Q scan being non-diagnostic in this sub-group is high (Roach et al., 2010a; Ravenel et al., 2005).

The most common abnormality on the chest x-ray of a patient with PE is known to be cardiomegaly (Lake *et al.*, 2005). Other non-specific findings such as atelectasis, small effusions, an elevated hemidiaphragm or mild infiltrates may also be associated with the occurrence of PE (Kline & Runyon, 2005; Tabas & McNutt, 2005; Smith, 2008). If an infarction has occurred, the x-ray may demonstrate either the Westermark sign ("a prominent central pulmonary artery with decreased pulmonary vasculature distally") or the Hampton Hump sign ("a wedge-shaped, pleural-based triangular opacity with an apex pointing toward the hilum") (Kline & Runyon, 2005; Tabas & McNutt, 2005; Smith, 2008). A pleural effusion, if present, is also indicative of an infarction (Kline & Runyon, 2005; Tabas & McNutt, 2005; Smith, 2008).

1.6.2.2 Electrocardiogram

Similar to the chest x-ray, an electrocardiogram (ECG) is suggested prior to more advanced imaging tests as it may also provide important alternative diagnoses. Many disease processes may mimic PE and can be diagnosed on a simple ECG tracing – these include pericarditis and acute coronary syndromes.

In patients with PE, often quoted ECG abnormalities include tachycardia and nonspecific ST-T wave abnormalities. The widely publicised ECG finding of S1Q3T3 (consisting of an S wave in lead 1, and a Q wave with a flipped T wave in lead 3) has been found to be neither sensitive nor specific for PE (Kline & Runyon, 2005; Tabas & McNutt, 2005; Smith, 2008).

1.6.3 Diagnostic imaging

The diagnosis of PE remains a great challenge, as the clinical findings are nonspecific. Thus, PE cannot be confidently diagnosed clinically. Furthermore, the tests mentioned thus far are utilised mainly for finding an alternative diagnosis to PE. The diagnosis of PE eventually must be confirmed or excluded by a definitive imaging test. Ventilation-perfusion scanning, computed tomography and pulmonary angiography are all useful investigations in confirming the diagnosis of PE.

1.6.3.1 Pulmonary angiography

Pulmonary angiography is a procedure to visualise the pulmonary arteries directly in an attempt to identify pulmonary emboli. Historically, it has been described as the gold standard for the diagnosis of PE. This is due to its very high negative predictive value of over 90% (Ravenel *et al.*, 2005).

The clinician may directly visualise the embolus, or infer the presence of an embolus by other signs such as a filling defect or sharp cut-off of the affected artery indicating an obstruction to blood flow (Kline & Runyon, 2005; Tabas & McNutt, 2005; Smith, 2008). A positive pulmonary angiogram excludes the need for any further tests. A negative pulmonary angiogram has a very high negative predictive value if the entire pulmonary vasculature of both lungs is visualised. This is not always possible, as vessels smaller than third order branches are usually not visualised (Kline & Runyon, 2005; Tabas & McNutt, 2005; Smith, 2008).

Other challenges relating to pulmonary angiography include the fact that it is an invasive procedure, patients may be allergic to the iodinated contrast material and expertise in this procedure appears to be declining (Ravenel *et al.*, 2005; Smith, 2008). For these reasons, pulmonary angiography is rapidly being superseded by CT pulmonary angiography, which has a high sensitivity and specificity (Ravenel *et al.*, 2005; Smith, 2008). Despite its limitations, pulmonary angiography still remains a very useful investigation when CT angiography is not available or cannot be performed for various reasons explained later.

If performed correctly, pulmonary angiography is generally not an unsafe procedure, with reported morbidity and mortality rates of 5% and 0.5%, respectively (Kline & Runyon, 2005; Tabas & McNutt, 2005; Smith, 2008).

1.6.3.2 Computed Tomography and CT Pulmonary Angiography

Computed tomography with radiocontrast, also known as CT pulmonary angiography (CTPA) or CT angiography, was introduced in the early 1990s (Freeman & Blaufox, 2010; Leblanc & Paul, 2010). This is, in essence, a pulmonary angiogram which is imaged by CT, and is especially helpful in patients with an abnormal chest x-ray in whom the ventilation-perfusion results are more likely to be non-diagnostic (Tapson, 2008; Restrepo *et al.*, 2009). It quickly became popular as the investigation of choice for diagnosing PE (Wildberger *et al.*, 2005). This was as a result of its greater availability, as well as greater experience of radiologists with CT (Wildberger *et al.*, 2005).

Similar to pulmonary angiography, CT scanning has the advantage of direct visualisation of the emboli (Wildberger *et al.*, 2005). Other patterns have also been described to aid in the diagnosis of PE. These include a filling defect, a partial filling defect giving rise to the “lifesaver” sign and the “railway-track” sign (Lake *et al.*, 2005). If the embolus has completely occluded a vessel, a sharp cut-off may be visible (Lake *et al.*, 2005).

Quantitative analysis using the CT component may also provide additional information regarding prognosis. This includes assessment of the right ventricular/ left ventricular ratio (RV_D/LV_D). If the RV_D/LV_D ratio is >0.9, this has been shown to be associated with greater morbidity (Ravenel *et al.*, 2005).

The sub-optimal sensitivity of CTPA was attributed to the technology at that time being restricted to single-slice CT (Leblanc & Paul, 2010). The sensitivity has improved in more recent reviews with multislice CT (83% vs 73%), although the sensitivity for the more distal emboli remains low (Hoang *et al.*, 2008; Bailey & Roach, 2010; Leblanc & Paul, 2010; Morris, 2010; Freeman *et al.*, 2012). The specificity of CTPA in the diagnosis of PE has been shown to be around 96% (Hoang *et al.*, 2008; Leblanc & Paul, 2010). These figures were supported by the large prospective multi-centre PIOPED II study, which has advocated CTPA as an adequate test in diagnosing PE (Stein *et al.*, 2006). Recent studies have demonstrated the very good negative predictive value of CTPA to be around 95%

(Leblanc & Paul, 2010). Its positive predictive value centred around 86%, varying with the location of the thrombus (Leblanc & Paul, 2010).

The great advantage of CTPA especially over V/Q scintigraphy is its ability to detect alternative disease processes that may clinically present in a similar manner to PE. These include aortic dissection, pleural or pericardial effusions, oesophageal rupture, malignancies, pneumonias and abscesses (Leblanc & Paul, 2010; Roach *et al.*, 2010a). This imaging modality is reported to be the only test being able to provide an alternative diagnosis in 30-60% of patients (Remy-Jardin *et al.*, 1996; Lake *et al.*, 2005; Leblanc & Paul, 2010). This is a crucial advantage of CTPA over pulmonary angiography as well as ventilation-perfusion scans. Other factors that led to the popularity of this test include the low number of indeterminate readings, as well as the binary nature of CTPA reports (PE positive or negative) as opposed to the probabilistic reports of V/Q scans (low, intermediate or high probability) (Loud *et al.*, 2005; Leblanc & Paul, 2010). CTPA gives reliable results quickly and easily, and is generally available at all hours (Ferretti *et al.*, 2005).

In fact, investigators involved the large prospective multi-centre PIOPED II study as well as the Fleischner society have advocated the CTPA as “the initial imaging modality of choice for stable patients with suspected pulmonary embolism” (Remy-Jardin *et al.*, 2007; Stein *et al.*, 2007). Furthermore, the American College of Radiology (ACR) has also recommended CTPA as the standard of care in the diagnosis of PE (Bettmann *et al.*, 2011).

Challenges related to the performance of CTPA include the risk of complications from iodinated contrast due to allergic reactions, as well as the high thoracic radiation dose (Leblanc & Paul, 2010; Roach *et al.*, 2010a). This is a major concern especially in pregnant patients, and patients with impaired creatinine clearance (Leblanc & Paul, 2010; Roach *et al.*, 2010a). Although significant adverse events occur in less than 1% of patients, this incidence may increase up to 50% if the patient has severe chronic renal disease (Leblanc & Paul, 2010). Neonates that have been exposed in utero to iodinated contrast may develop depressed thyroid function (Leblanc & Paul, 2010). It is thus recommended to monitor thyroid functions in these patients.

The location of the emboli also appears to play a role, with higher sensitivities being demonstrated for the more proximal emboli and lower sensitivities for the more distally located emboli (Loud *et al.*, 2005; Morris, 2010). The significance of the more peripherally located emboli has been questioned, although their detection may indicate subclinical DVTs, which would then possibly require anticoagulation therapy or caval filtering to avert progression to fatal PE (Loud *et al.*, 2005). Furthermore, CTPA does not perform well when its results are discordant with the clinical probability, lowering both the positive and negative predictive values (Leblanc & Paul, 2010; Freeman *et al.*, 2012).

Having said that, the major concern with CTPA remains the high radiation exposure. This is especially problematic in women of childbearing age. The amount of radiation also makes CTPA an unsuitable imaging test in follow-up of patients.

Finally, inability to acquire a CTPA study due to technical factors occurs in 5-10% of patients (Leblanc & Paul, 2010). This may be related to streak artifacts or window setting artifacts (Lake *et al.*, 2005). Respiratory motion may also produce “stair-step” artifacts (Lake *et al.*, 2005).

Since PE and DVT are different stages of the same continuum, it has been suggested that these not be seen in isolation. This has led to the recent strategy of imaging the pulmonary vasculature in combination with imaging of the legs to assess for DVT. Various techniques have been devised, such as combined CT venography with pulmonary angiography, CTPA with leg sonography etc. (Loud *et al.*, 2005). A review of this strategy has revealed that if the combined imaging is negative, withholding anticoagulation treatment is a safe option, as the risk of recurrence in these patients is low (Loud *et al.*, 2005).

Excellent correlation has been reported between CTPA and conventional pulmonary angiography (Ferretti *et al.*, 2005). Thus, CTPA has replaced conventional pulmonary angiography in many centres.

1.6.3.3 Ventilation-perfusion scans (V/Q scan)

The original lung perfusion scan was introduced in the mid-1960s by Henry Wagner to confirm the diagnosis of PE (Bailey *et al.*, 2010; Bailey & Roach, 2010; Freeman & Blaufox, 2010; Roach *et al.*, 2010b; Schembri *et al.*, 2015). In the late 1960s, the

ventilation part of the study was added to increase the specificity of the procedure (Bailey & Roach, 2010; Freeman & Blaufox, 2010; Schembri *et al.*, 2015). The original PIOPED study propagated V/Q imaging as the standard of care at the time (The PIOPED Investigators., 1990). For years, the V/Q scan was the only non-invasive imaging method to diagnose PE until the introduction of the CTPA (Bailey *et al.*, 2010). More recently however, increasing recognition of the harmful effects of ionizing radiation from CT has switched interest back V/Q imaging (Freeman & Blaufox, 2010; Stein *et al.*, 2011).

The hallmark to confirm PE has been the demonstration of absent perfusion in segments with preserved ventilation i.e. V/Q mismatch, due to occlusion of blood flow by an embolus (Bailey & Roach, 2010; Bajc *et al.*, 2010; Roach *et al.*, 2010a). This mismatch is based at the pleural surface, with the apex pointing towards the hilum, conforming to a known segmental vascular territory (Bajc *et al.*, 2010). However, as the embolus resolves, some degree of perfusion may be restored and the V/Q mismatch appears less prominent (Bajc *et al.*, 2010).

The V/Q scan comprises of two distinct phases – a perfusion scan and a ventilation scan. The perfusion scan involves an intravenous injection of Technetium-99m-labeled albumin macroaggregates, which lodge in the pulmonary capillaries (Smith, 2008). The ventilation phase is determined by means of inhalation of radiolabelled aerosols or gases (Bajc *et al.*, 2010).

1.6.3.3.1 V/Q scan agents

Inert gases were the first ventilation agents to be used in V/Q imaging. These included ^{133}Xe and ^{81m}Kr (Bajc *et al.*, 2010). Their physical properties ensured that the gas washed out rapidly from the lungs. This was both advantageous as well as a shortcoming. Although the rapid washout reduced the radiation dose to the patient, it also meant that continuous inhalation was necessary to obtain adequate images, thus making the procedure quite costly (Bailey *et al.*, 2010).

Radio-aerosols were then introduced. These aerosol particles could be liquid, such as diethylene-triaminepentaacetic acid (DTPA), or solid namely Technegas. These radio-aerosols had the advantage that continuous inhalation was not required (Bailey *et al.*, 2010). However, turbulent flow resulted in deposition of especially the liquid particles of DTPA in the larger airways due to impaction (Bajc *et al.*, 2010). This created “hot-spot” artefacts, especially in patients with COPD making interpretation difficult (Bailey *et al.*, 2010; Bajc *et al.*, 2010). This drawback has been ameliorated to some extent with the SPECT technique (discussed later under section 1.6.3.3.5) (Bajc *et al.*, 2010; King *et al.*, 2010).

Technegas then entered the market. Due to the extremely small size of the particles as compared to the liquid radio-aerosols, excellent peripheral penetration was possible, as very little Technegas would stick to the larger airways (Bailey *et al.*, 2010). Thus, in patients with obstructive lung disease, Technegas is the agent of choice (Bajc *et al.*, 2010). This agent is also particularly suitable for SPECT imaging

as only minute amounts of the Technegas are cleared from the lungs over the duration of the imaging (Bailey *et al.*, 2010; King *et al.*, 2010).

Due to the different physical characteristics of the different ventilation agents used, there may be some variation in the images produced and associated artefacts.

Since inception, the perfusion tracer, viz. macro-aggregated albumin (MAA) is still widely utilised today (Bajc *et al.*, 2010). At least 60,000 particles must be injected to adequately image regional perfusion (Bajc *et al.*, 2010). Caution should be exercised in patients with pulmonary hypertension, a condition in which the number of particles needs to be reduced (Bajc *et al.*, 2010).

At least six views are required to allow adequate assessment of the various segments, although eight views from different angles are preferred (Bailey *et al.*, 2010). In a normally ventilated lung, there is uniform distribution of radiotracer. Due to gravitational effects, there may be less radiotracer at the apices and more at the lung bases (Schembri *et al.*, 2015). In a normally perfused lung, there is also uniform distribution of radiotracer. However, similar to the ventilation image, there may be less radiotracer at the apices and more at the lung bases (Schembri et al., 2015).

Since the ventilation scan is usually performed first, the radioactivity on the perfusion scan should be at least 3-4 times greater than the radioactivity on the ventilation scan (Bailey et al., 2010; Bajc et al., 2010; Schembri et al., 2015). This is to reduce

the chances of the interfering radioactivity from the ventilation scan obscuring the perfusion phase images (Schembri et al., 2015).

1.6.3.3.2 Usefulness of V/Q scan

In modern day practice, the V/Q scan is safe, especially with regards to the low radiation dose and has very few contra-indications (Schembri et al., 2015). It also has a high sensitivity of over 90%, although variable rates of specificity ranging from 58-91% have been reported (Bailey *et al.*, 2010; Bajc *et al.*, 2010; Schembri *et al.*, 2015). V/Q scan with the SPECT technique particularly has a very high negative predictive value of 97-99% (Bailey *et al.*, 2010; Bajc *et al.*, 2010; Roach *et al.*, 2010b; Schembri *et al.*, 2015).

Non-diagnostic findings occur in up to 40% of patients using the planar V/Q technique (Roach *et al.*, 2010b). These patients require further workup. In the study by Hull and co-workers, patients with a non-diagnostic V/Q scan were referred for non-invasive venous imaging (Hull *et al.*, 1989). If this venous imaging was negative, patients were not anti-coagulated. On follow-up, these patients had a very low incidence of developing thrombo-embolism. Based on this, current diagnostic algorithms advocate venous imaging in the setting of a non-diagnostic V/Q scan (Loud *et al.*, 2005).

Wells and colleagues, on the other hand, tested the safety of basing management decisions on a combination of V/Q scan results and the pre-test probability instead of venous imaging in a prospective study involving 1239 patients (Wells *et al.*, 1998).

Only 0.5% of patients with low or moderate pre-test probability and a non-high probability on V/Q scan developed a DVT or PE after being followed up for 90 days. Thus, they concluded that management of patients with suspected pulmonary embolism on the basis of pre-test probability and results of ventilation-perfusion scanning is safe.

This view was supported by the follow-up prospective study by Hull and co-workers involving 1564 patients, which revealed that only 1.9% of patients with non-diagnostic scans and not anti-coagulated had evidence of DVT or PE on follow-up (Hull *et al.*, 1996). Similar figures were obtained in a study conducted by Perrier and colleagues which included 1034 patients (Perrier *et al.*, 2000). Anticoagulant treatment was withheld in patients with a low clinical probability of PE and a non-diagnostic lung scan. Only 1.7% of patients had DVT or PE on follow-up.

1.6.3.3.3 V/Q scan interpretation criteria

Criteria have been devised for the interpretation of V/Q scan results so that common terminologies may be understood by both referring physicians and nuclear medicine doctors (Bailey *et al.*, 2010).

The results of the V/Q scan are classified on the basis of probability of a PE – i.e. very low, low, intermediate or high, or no typical evidence. Different criteria have been defined depending on the performance of a ventilation scan and/or chest x-ray, and are summarised below.

Table 1.8: Interpretation criteria for the diagnosis of pulmonary embolism based on the ventilation-perfusion scan with or without a chest X-ray.

Enhanced PIOPED criteria	Perfusion-only modified PIOPED II
High	PE present
≥2 large mismatched segmental defects (>75% of a segment)	≥2 large mismatched segmental defects (>75% of a segment)
Non-diagnostic	Non-diagnostic
All other findings	All other findings
Very low	PE absent
Non-segmental perfusion defect smaller than CXR lesion	Non-segmental perfusion defect smaller than CXR lesion
1-3 small segmental defects	1-3 small segmental defects
Solitary matched defect (≤1 segment) in mid or upper lung with corresponding CXR lesion	Solitary matched defect (≤1 segment) in mid or upper lung with corresponding CXR lesion
Stripe sign	Stripe sign
Solitary large pleural effusion	Solitary large pleural effusion
≥2 matched defects, with regionally normal CXR	Very low probability
Normal	
No perfusion defects	

Adapted from (Parker *et al.*, 2012)

As with most tests, the V/Q scan should be interpreted within the context of pre-test probability. A low pre-test probability with a low probability V/Q scan makes pulmonary embolism unlikely (Gottschalk *et al.*, 2007), and a high probability scan with a high pre-test probability is considered diagnostic for PE (Kline & Runyon, 2005; Tabas & McNutt, 2005; Gottschalk *et al.*, 2007; Smith, 2008). A normal or near normal result is 98% sensitive for the exclusion of PE.

1.6.3.3.4 Utility of V/Q scans

Although the most common indication for the performance of a V/Q scan is to detect the presence of PE, many other disease processes can affect both ventilation and perfusion of the lungs. Pathologies which may produce a V/Q mismatch include radiation therapy induced changes, veno-occlusive disease, vasculitis, congenital pulmonary vascular abnormalities as well as extrinsic vascular compression from a neoplasm or mediastinal lymphadenopathy (Roach *et al.*, 2010a).

1.6.3.3.5 V/Q scan with SPECT technique

Traditionally, the V/Q scan has used planar techniques due to its ease of access and acceptance internationally (Bailey *et al.*, 2010). In the last few decades, major improvements have been made in image acquisition, reconstruction and analysis, including the single-photon emission computed tomography (SPECT) technique (Hofman *et al.*, 2011).

With rapidly advancing technology, many procedures in the nuclear medicine arena have swapped over to the more sophisticated single-photon emission computed tomography (SPECT) imaging rather than simple planar imaging. These include cardiac imaging, brain imaging and tumour scintigraphy (Reinartz *et al.*, 2004; Roach *et al.*, 2010b; Freeman *et al.*, 2012). The main difference is 3-dimensional images that are produced with the SPECT technique as opposed to 2-dimensional images. The additional advantage it confers is that SPECT can be combined with CT to either provide attenuation correction and thus reduce artefacts, or to enhance fusion imaging and thereby increase specificity (Freeman & Blaufox, 2012).

Planar V/Q scintigraphy is restricted to 2-dimenstional images. This is problematic as there may be significant overlap of anatomical segments, leading to underestimation of the extent of a perfusion defect due to shine through from adjacent normal lung (Bailey *et al.*, 2010; Roach *et al.*, 2010b). Furthermore, the medial basal segment of the right lower lobe is not visualised on routine planar V/Q scintigraphy (Bailey *et al.*, 2010; Roach *et al.*, 2010b).

SPECT scanning solves the above limitations due to its improved image resolution and better anatomical detail without overlapping structures (Bailey *et al.*, 2010; King *et al.*, 2010; Leblanc & Paul, 2010; Roach *et al.*, 2010b; Freeman *et al.*, 2012). These factors, together with the reduced attenuation artefacts, allow smaller lesions to be detected more easily (Bajc *et al.*, 2010; Freeman & Blaufox, 2010; King *et al.*, 2010; Leblanc & Paul, 2010; Roach *et al.*, 2010b; Freeman *et al.*, 2012). Although some authors are convinced of the superiority of V/Q SPECT over planar V/Q (Bajc

et al., 2009; Bajc *et al.*, 2010; Bailey *et al.*, 2010; Bailey & Roach, 2010; Leblanc & Paul, 2010), there is considerable debate as to whether the additional lesions detected are clinically significant (Freeman & Blaufox, 2010; Freeman *et al.*, 2012). Opponents of V/Q SPECT cite the fact that the negative predictive value of a simple planar study is similar to that of CTPA (Freeman *et al.*, 2012). Secondly, the false negative rates are comparable for all the imaging modalities, viz. CTPA, planar V/Q and SPECT V/Q (Freeman *et al.*, 2012).

1.6.3.3.6 Advantages of V/Q SPECT over planar V/Q scintigraphy

Although no large multicentre studies have directly compared V/Q planar scintigraphy head-to-head with V/Q SPECT imaging, many small studies have shown SPECT to be superior to planar imaging (Bajc *et al.*, 2004; Gutte *et al.*, 2010). Both the sensitivity and specificity of the test appeared to be improved with the SPECT technique (97% vs 76% and 91% vs 85%, respectively) (Bailey *et al.*, 2010; Freeman & Blaufox, 2010; Roach *et al.*, 2010b). SPECT was able to demonstrate more defects as compared to planar imaging (Roach *et al.*, 2010b).

The most impressive observation was the drastic reduction in rate of non-diagnostic studies with the use SPECT (from 39% to 4%) (Roach *et al.*, 2010b). Even though the accuracy of V/Q SPECT is similar to CTPA (94% vs 93%), V/Q SPECT has the additional advantage of a lower radiation dose (Bailey *et al.*, 2010). Thus, the EANM guidelines have prudently advised that V/Q SPECT “should be the preferred modality whenever possible” (Bajc *et al.*, 2009).

1.6.3.3.7 V/Q SPECT/CT

Since V/Q SPECT is performed in 3-D, it is possible to add a 3-D anatomical component to the acquisition. Adding a low-dose CT to the V/Q SPECT scintigraphy may have certain advantages. Although the sensitivity has remained similar, the specificity increased from 88% to 100% (Roach *et al.*, 2010a). Addition of anatomical data also improved the overall accuracy by reducing the false positive rate – since the CT component could differentiate pulmonary vessels and fissures, which also produce defects on V/Q perfusion scintigraphy (Roach *et al.*, 2010a). Adding the CT component also reduced the non-diagnostic rate of V/Q SPECT from about 4% to 0% (Roach *et al.*, 2010a).

Besides PE, a V/Q SPECT/CT study may be helpful in other conditions, such as modifying radiation therapy fields in the treatment of lung cancer so as to allow delivery of the maximum dose to the cancer while sparing normal well-perfused adjacent lung tissue (Roach *et al.*, 2010a). It can also be used to assess the consequences of lung surgery on the patient's pulmonary reserve prior to resection (Roach *et al.*, 2010a).

1.6.3.3.8 V/Q vs CTPA

For years, the V/Q scan was the only non-invasive imaging method to diagnose PE until the introduction of the CTPA (Bailey *et al.*, 2010). Recently however, increasing recognition of the harmful effects of radiation from CT has switched interest back V/Q imaging (Freeman & Blaufox, 2010; Stein *et al.*, 2011).

Comparisons have been made between CTPA and V/Q SPECT. Studies have demonstrated that the diagnostic accuracy of both tests was identical (Reinartz *et al.*, 2004; Miles *et al.*, 2009); however, V/Q with added SPECT showed a better sensitivity while CTPA had a better specificity (Reinartz *et al.*, 2004; Suga *et al.*, 2008; Gutte *et al.*, 2009). The better sensitivity of V/Q SPECT may be due to the better visualisation of more peripheral emboli, while the better specificity of CTPA is due to the fact that it allows for the direct visualisation of pulmonary emboli (Leblanc & Paul, 2010). The negative predictive value of both tests has been shown to be high (Leblanc & Paul, 2010; Roach *et al.*, 2010b; Freeman *et al.*, 2012).

CTPA may offer an alternative diagnosis in many patients because of the detailed anatomy provided by this technique (Freeman *et al.*, 2012). An alternative diagnosis is hardly ever provided by V/Q scintigraphy, although if the SPECT technique is used pleural effusions, pneumonias and COPD may be recognised (Leblanc & Paul, 2010).

Advantages of the V/Q scan include the fact that there is no real risk of renal toxicity or allergic reactions (Roach *et al.*, 2010a). Added to this, the technical success rate of V/Q scan acquisition is extremely high at around 99% compared to CTPA at 90-95% (Leblanc & Paul, 2010; Roach *et al.*, 2010a).

Radiation to the breast tissue of females is a concern with CTPA (Freeman *et al.*, 2012). This is of special concern during the reproductive years and during pregnancy (Bajc *et al.*, 2010). This radiation may be sufficiently high to increase the lifetime risk

of developing cancer (Leblanc & Paul, 2010). In light of the harmful effects of ionizing radiation, V/Q scintigraphy has been advocated as the imaging modality of choice in the serial follow-up of patients even if the initial diagnosis was made on CTPA (Freeman *et al.*, 2012). In fact, many protocols advocate V/Q scintigraphy as the diagnostic modality of choice for most patients in the setting of a normal or near-normal chest x-ray; although the CTPA remains crucial in the setting of a severely abnormal chest x-ray (Leblanc & Paul, 2010; Freeman *et al.*, 2012).

Perhaps the best diagnostic accuracy would be obtained by adding the functional data provided by SPECT to the anatomical information provided by CT. This would mean combining V/Q SPECT imaging acquisition with either low-dose CT or CTPA. Both cases would result in a high sensitivity due to the SPECT technique as well as a high specificity due to the CT component (Roach *et al.*, 2010b). Thus, V/Q SPECT imaging and CTPA should be seen as complementary rather than competitive diagnostic modalities.

1.6.3.3.9 VQ Positron Emission Tomography (PET/CT)

Ventilation-perfusion SPECT studies are performed with tracers labelled with Technetium-99m. For VQ PET studies, the Technetium-99m is substituted with Gallium-68, a positron-emitting radionuclide. The PET tracers have a more homogenous distribution in the lungs for both ventilation and perfusion studies, thus producing better quality images (Hofman *et al.*, 2011). This, together with the higher resolution, may translate into improved accuracy with the PET tracers, although this remains to be proven in large studies.

The short half-life of Gallium-68 of only 68 minutes allows the perfusion study to be performed first, with the option of proceeding to the ventilation part only if required (Hofman *et al.*, 2011). This ultimately would reduce the radiation exposure to the patient. Furthermore, since most PET scanners have built-in CT capabilities, the nuclear medicine physician has the option of performing V/Q PET/CT studies, in an attempt to increase the diagnostic accuracy even further.

Similar to SPECT, V/Q PET may be used over and above confirming the diagnosis of PE, by playing a role in researching pulmonary physiology, more specifically in airways diseases (Hofman *et al.*, 2011). These roles have been discussed previously under SPECT in section 1.6.3.3.5.

V/Q PET/CT may become an essential consideration in centres that have a PET scanner available, more so in the light of the recent shortages of Technetium-99m, as PET radionuclides can be substituted for Technetium-99m based agents in PET imaging.

1.6.3.4 Magnetic Resonance (MR) Imaging and MR angiography

Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) are possible options in patients with contraindications to CT, such as renal failure or pregnancy (Gupta *et al.*, 1999; Ravenel *et al.*, 2005; Gottschalk *et al.*, 2007). However, these imaging modalities are not commonly found in resource-poor settings. Other challenges include the requirement for the patients to hold their

breaths for a long period of time (Lake *et al.*, 2005; Ravenel *et al.*, 2005). Similarly, acquisition times are quite lengthy (Lake *et al.*, 2005; Ravenel *et al.*, 2005). However, with improvements in technology, these challenges are likely to be overcome.

Studies have shown excellent correlation between MRI and V/Q SPECT studies in the evaluation of PE (Schibany *et al.*, 2001; Kluge *et al.*, 2006).

1.6.3.5 Echocardiography

If the patient is clinically unstable, as is usually the case with a massive PE, they may not tolerate most of the above-mentioned imaging procedures. In these cases, a transthoracic or transoesophageal echocardiography (echo) may be helpful in the identification of PE (Konstantinides, 2008b). Both the subcostal and the parasternal views should be examined, as the thrombus itself may be visualised directly.

1.6.4 Auxiliary investigations

These differ from ancillary investigations in that these are supplementary or additional investigations that may support the diagnosis of a PE. Since an embolus normally originates in the deep venous system of the legs, diagnostic algorithms include imaging of the deep venous system. These imaging tests comprise of duplex ultrasonography or the more invasive venography. They play an essential role in the workup of patients whose V/Q scan or CTPA is non-diagnostic. Without detailed discussions these investigations include the Duplex Ultrasonography, Venography and Thrombus specific imaging agents (TSIAs).

1.7 Treatment

If the PE is left untreated, acute circulatory failure and subsequent death may result. It is thus imperative that the diagnosis is made expeditiously and treatment initiated timeously. Clinical findings usually help the clinician to decide on the appropriate treatment to offer, i.e. anticoagulation or thrombolysis (Ferretti *et al.*, 2005).

Initial management of PE consists of rapid assessment and stabilisation for immediate life-threatening conditions. As with any critically ill patient, the emergency physician should start with the basic “ABC’s” i.e. Airway, Breathing, Circulation. Intravenous access, cardiopulmonary monitoring and oxygen therapy should be initiated.

1.7.1 Anticoagulation

Anticoagulation is an essential treatment for patients with PE. This may be initiated even prior to the completion of more definitive studies if the pre-test probability is moderate-to-high (Kline & Runyon, 2005; Tabas & McNutt, 2005; Smith, 2008). Anticoagulation can be withheld in patients with subsegmental PE only if the risk of recurrence is low (Kearon *et al.*, 2016).

The anticoagulation agents recommended in the latest guideline of the American College of Chest Physicians include low-molecular-weight heparin (LMWH), vitamin K antagonists (VKA) such as warfarin and the new/novel oral anticoagulants (NOACs) such as dabigatran, rivaroxaban, apixaban, or edoxaban (Kearon *et al.*, 2016).

1.7.1.1 NOACs

NOACs are a new class of anticoagulant medications that inhibit the coagulation cascade directly, either by inhibiting thrombin (via inhibiting factor II) or inhibiting factor Xa directly (Sardar *et al.*, 2015). Thus, they are also known as DOACs (direct oral anticoagulants).

The NOACs have been recommended as the preferred agents in patients without a history of cancer (Kearon *et al.*, 2016). In such patients, treatment should continue for at least 3 months. In patients with concomitant cancer, the NOACs have been proposed as a last resort (Kearon *et al.*, 2016).

1.7.1.2 Vitamin K antagonists (VKA) such as warfarin

The mechanism of action of warfarin includes the inhibition of vitamin K–dependent factors, namely factors II, VII, IX, and X, protein C and protein S. Warfarin has been propagated as a secondary alternative for the treatment of PE in patients both with concomitant cancer as well as having no history of cancer (Kearon *et al.*, 2016).

It is advised that patients are prescribed anticoagulants for at least three months after initial diagnosis. Studies conducted to evaluate whether 3 or 6 months of anticoagulation proved more efficacious, demonstrated no additional benefit from 6 months of treatment compared to 3 months (Pinede *et al.*, 2001; Campbell *et al.*, 2007).

Patients placed on warfarin should be monitored to maintain an INR between 2.0-3.0 (Watts, 2004). During the anticoagulation period, if the PE recurs, some authors suggest that these patients can then be maintained at a higher INR ratio of up to 4.5 (Watts, 2004). However, an INR outside the therapeutic range increases the risk of bleeding or thrombosis.

1.7.1.3 Low-molecular-weight heparin therapy

This is the recommended first line treatment for treatment of PE in patients with concomitant cancer (Kearon *et al.*, 2016). It is also believed to be a reasonable alternative therapeutic option in patients that develop recurrent VTE despite being on VKA or NOAC therapy (Kearon *et al.*, 2016).

The two types of LMWH that have obtained approval by the U.S. Food and Drug Administration (FDA) for treating PE and/ or DVT are enoxaparin and tinzaparin (Kearon *et al.*, 2008).

1.7.1.4 Aspirin

This has not found favour as an actual treatment modality in patients presenting with PE. Instead it may be administered on a chronic basis to prevent the recurrence of VTE.

1.7.2 Thrombolysis

Systemic thrombolysis is generally not necessary in patients presenting with acute PE, unless this is complicated by hypotension (Kearon *et al.*, 2016). However, if the patient deteriorates after starting anticoagulant therapy, systemic thrombolytic therapy should be administered even if there is no associated hypotension, as long as the risk of bleeding is low (Kearon *et al.*, 2016).

If a thrombolytic agent is used, this should be administered via a peripheral vein rather than catheter-directed thrombolysis (Kearon *et al.*, 2016). Catheter-directed thrombolysis is the preferred option if there is a high risk of bleeding or the patient has gone into severe shock (Kearon *et al.*, 2016). Immense caution needs to be exercised if this treatment option is used in patients with recent haemorrhage, surgery or trauma (Lohan *et al.*, 2007).

1.7.3 Pulmonary thromboendarterectomy

This may be an option in selected patients with chronic thromboembolic pulmonary hypertension if adequate expertise is available (Kearon *et al.*, 2016).

1.8 Supportive Care

Numerous strategies have been advocated to prevent the occurrence of a DVT, as well as to prevent the progression if a thrombus has already formed. These include physical activities and graded compression stockings, with varying success rates

(Kline & Runyon, 2005; Tabas & McNutt, 2005; Smith, 2008). The latest guidelines discourage the routine use of compression stockings to prevent post thrombotic syndrome (Kearon *et al.*, 2016).

1.9 Prognosis

The high rates of morbidity and mortality warrant prompt diagnosis. In the PIOPED study, the mortality rate at 1 year was found to be 24% (Worsley & Alavi, 1995). Patients that survive the initial episode of PE warrant appropriate treatment to prevent recurrences. The rate of recurrent thromboembolism is less than 5% during the first 3-6 months of anticoagulant (Meyer *et al.*, 2008).

The aim of this study was to evaluate the correlation between pre-test probability (determined clinically via the Wells score) and ventilation-perfusion (V/Q) scan results in patients presenting with suspected pulmonary embolism at a University Hospital (namely, Charlotte Maxeke Johannesburg Academic Hospital and Chris Hani Baragwanath Academic Hospital), and thus to indirectly evaluate the appropriateness of clinician referrals for suspected PE.

CHAPTER 2

2 MATERIALS AND METHODS

2.1 Study population

The study is a retrospective analysis of 120 adult patients (>18 years of age), who were sequentially referred for a V/Q scan for suspected pulmonary embolism at Charlotte Maxeke Johannesburg Academic Hospital and Chris Hani Baragwanath Academic Hospital. The time frame spanned a period of 16 months (1 January 2008 to 30 April 2009).

This study was approved by the Human Research Ethics Committee, University of the Witwatersrand (Clearance Certificate Protocol Number – M090903 / Reference Number R14/49).

The inclusion criteria were as follows:-

- Age greater than 18 years
- Patients referred for a V/Q scan for suspected PE

The exclusion criterion was as follows:-

- Patients referred for a follow-up V/Q scan after anticoagulation

2.2 Materials and methods

Clinical notes were obtained from the request forms to ascertain risk factors, presenting symptoms and other data (as per Appendix A) to determine pre-test probability of having a pulmonary embolus. All the patients studied were categorised as low risk, moderate risk or high risk based on the Wells score.

All the patients subsequently underwent a V/Q scan. The V/Q scan results were obtained from the database of the Nuclear Medicine Department at both above-mentioned academic hospitals. Based on the results, all the patients were categorised as no typical evidence of PE, very low probability, low probability, intermediate probability or high probability. The result of the Wells score was subsequently compared to the V/Q scan result to assess a correlation between the two parameters, i.e. clinician data vs V/Q scan results.

All patients were allocated a patient code. This list was kept separately from the data in order to maintain confidentiality (see Appendix B).

2.3 Statistical analysis

The sample size of 120 patients was obtained from calculation by a statistician who used a power of 80% and a level of significance of 5%.

The data obtained was analysed with the assistance of a statistician. Phase 1 involved a descriptive analysis of data. This included drawing up of medians,

percentages and frequency of the study variables. Thereafter, cross tabulation of certain variables was performed e.g. age, gender against the V/Q scan results etc.

In phase 2, a test of association was conducted between the Wells score and the V/Q scan results, using the Cohen's kappa values. Tests were conducted at 5% significance level. The statistical analysis was carried out using the SAS software version 9.1 (SAS Institute, Cary, NC, USA).

CHAPTER 3

3 RESULTS

The study included 120 patients, 74 patients from Charlotte Maxeke Johannesburg Academic Hospital (62%) and 46 from Chris Hani Baragwanath Hospital (38%).

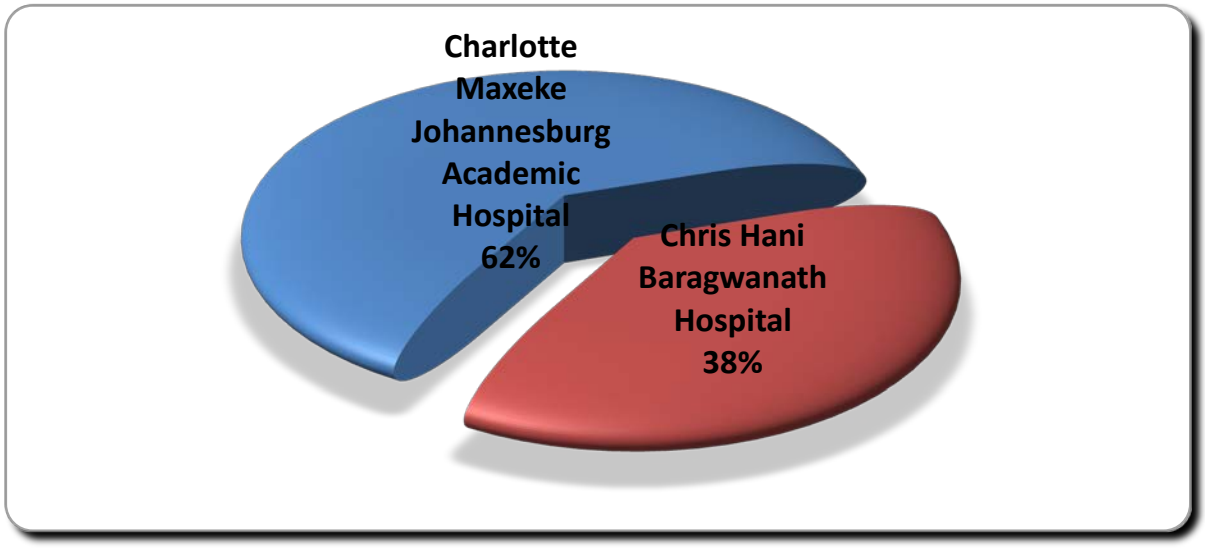


Figure 3.1: Distribution of patients from the two hospitals

There were 85 females and 35 males, with a female:male ratio of 2.5:1.

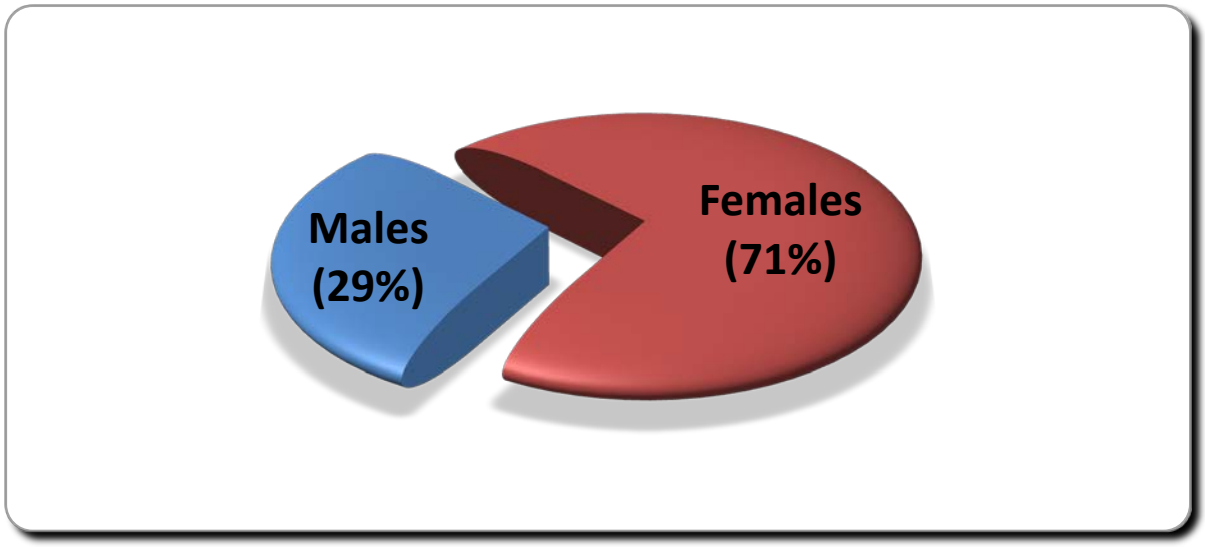


Figure 3.2: Female to male ratio

The median age was 55 years, with a range from 18 to 86 years. The mean age was calculated as 53.3 years. The majority of the patients were in the 6th and 7th decades (see figure 3).

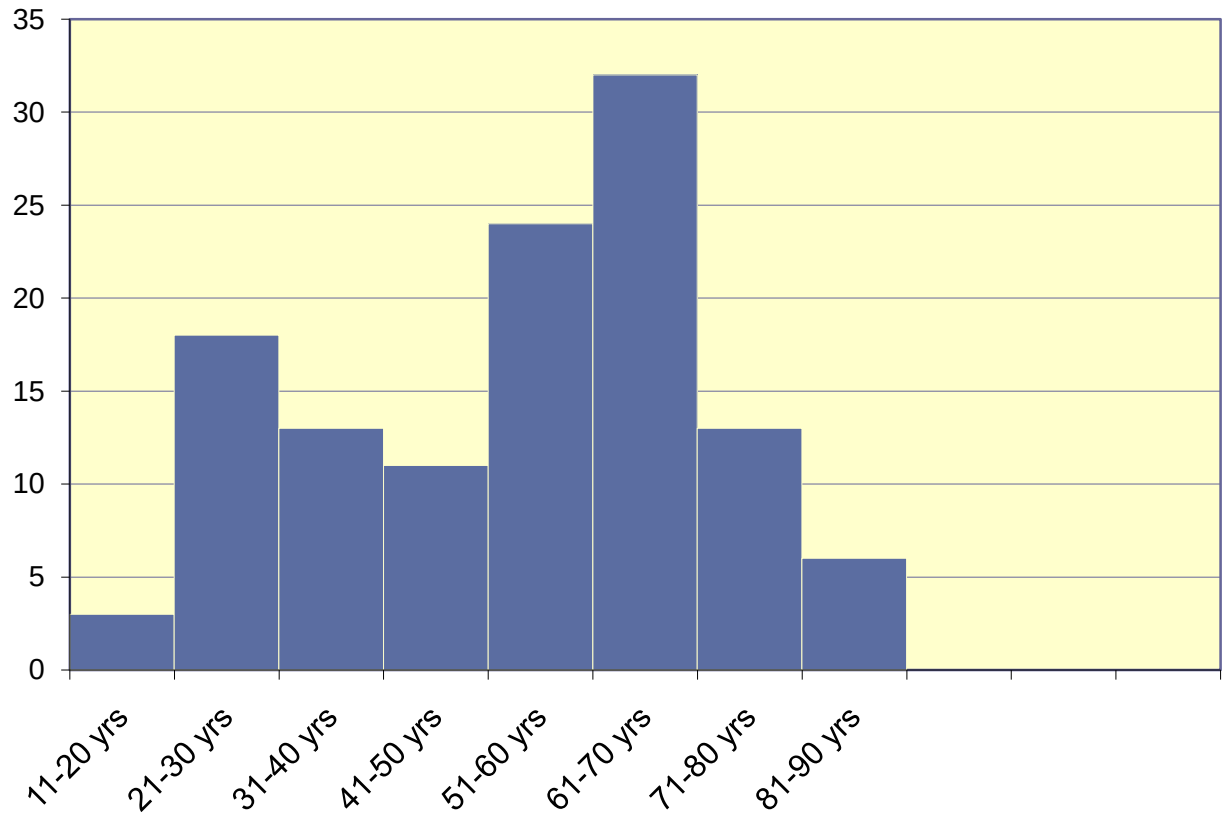


Figure 3.3: Distribution of patient numbers over the various age groups. Although the first column is labelled as 11-20 years for the sake of consistency in the histogram, this age group included only patients between the ages of 18 and 20 years.

Dyspnoea was the most common symptom, occurring in 94/120 patients (78%), while chest pain was observed in 57/120 patients (48%). Only 11/120 patients (9%) had complained of haemoptysis.

The most common presenting sign was tachycardia, occurring in 49/120 patients (41%), followed by tachypnoea, occurring in 37/120 patients (31%). Both systemic hypotension and shock were rarely observed – only 1/120 patient each (<1%).

The so-called pathognomic triad of symptoms—represented by haemoptysis, pleuritic chest pain and dyspnoea—occurred in only 7/120 patients (6%). None of these patients had a high probability on VQ scan, making this triad an unreliable indicator of pulmonary embolism.

In our study population, DVT was suspected in 19/120 patients (16%) and was confirmed in 11/120 patients (9%) on duplex doppler ultrasound. Of these 11 patients, 2 had a high probability on VQ scan (18%), 3 had a low probability (27%), while 6 had an intermediate probability (55%) and required further imaging.

Seven of the 120 patients referred for a scan (6%) had a previous history of DVT or PE. In these 7 patients, only 1 patient had a high probability on the VQ scan. Two of the patients had a very low probability, 3 demonstrated a low probability and in 1 patient the scan revealed an intermediate probability for PE.

In the sample population studied, only 2 patients had thrombophilic risk factors for PE, namely the presence of a lupus anticoagulant in both patients. Acquired risk factors are listed in Table 3.1 below.

Table 3.1: Acquired risk factors in the sample population of 120 patients

Risk factors	Number of patients (percentage)
Age older than 65 years	38 (32%)
Acute medical illness, including HIV/AIDS, CCF, MI	34 (28%)
History of recent immobilisation	30 (25%)
Previous DVT or PE	7 (6%)
Pregnancy/ post-partum	6 (5%)
Known malignancy	5 (4%)

The 30 patients with a history of immobilisation were immobilised either due to major surgery, or due to the legs being in a plaster cast as a result of a fracture.

In the 5 patients with a history of known malignancy, the VQ scan revealed a high probability in 2 patients (40%), while in another 2 patients the scan demonstrated no typical evidence of a PE (40%). These numbers are too low to draw any significant statistical conclusions. A specific malignancy was documented in two of the five patients, namely oesophageal carcinoma and rectal carcinoma. Two other patients with a known malignancy had recently received chemotherapy, although the specific type of malignancy was not mentioned.

Of the 34 patients suffering from an acute medical illness, the majority of the patients had presented with CCF (23/34 or 68%), while just more than a third of patients (12/34 or 35%) had been diagnosed with HIV/AIDS. Three of these patients had both co-morbidities i.e. HIV/AIDS and CCF. COPD had been confirmed in 10 patients, while another 9 patients had a history of smoking. It is not clear if the smoking history in these 9 patients was significant enough to lead to COPD. The specific diagnosis for the type of medical illness was not documented in one patient.

The P_aO_2 value was recorded in 3/120 patients in our study (~2.5%), and showed all three patients to be hypoxic. This may have been the main reason for suspecting PE in these patients, and one of the patients turned out to have a high probability on the VQ scan.

The result of the D-dimer test was recorded in almost half of the patients (57/120 or 48%) in our study. Of these patients, 4 had normal values, while 53 patients had raised D-dimer levels. Of the 4 patients with normal values, the VQ scan failed to demonstrate any evidence of PE (3 had very low probability and 1 had a low probability of PE). Of the 53 patients with raised D-dimer levels, the majority of the patients (40/53 or 75%) still had low probability, while 7 patients (13%) had intermediate probability and only 6 patients (11%) had high probability of PE on the V/Q scan.

Fourteen of the 120 patients (12%) in our study demonstrated the typical $S_1Q_3T_3$ pattern.

Taking all these above factors into account a Wells score was calculated for each patient. A score of 3 was given in Wells criteria under “alternative diagnosis less likely” either if the clinician specifically indicated this or this was based on the clinical history and other notes in the file indicating that another diagnosis was less likely. An alternative diagnosis being less likely was thus recorded in 80/120 patients (67%).

It is interesting to note that although an alternative diagnosis was unlikely in 80/120 patients (67%) in our study, the risk based on the total Wells score was found to be high in 13/120 patients (11%), while the VQ scan demonstrated a high probability in only 15/120 patients (13%).

Based on the total of the Wells’ score, the pre-test probability was calculated as follows: 36/120 patients (30%) were classified as low risk, 71/120 patients (59%) as moderate risk and 13/120 patients (11%) as high risk for having a PE.

Table 3.2: Results of the Wells score

Risk stratification based on Wells score	Number of patients (percentage)
Low risk	36 (30%)
Moderate risk	71 (59%)
High risk	13 (11%)

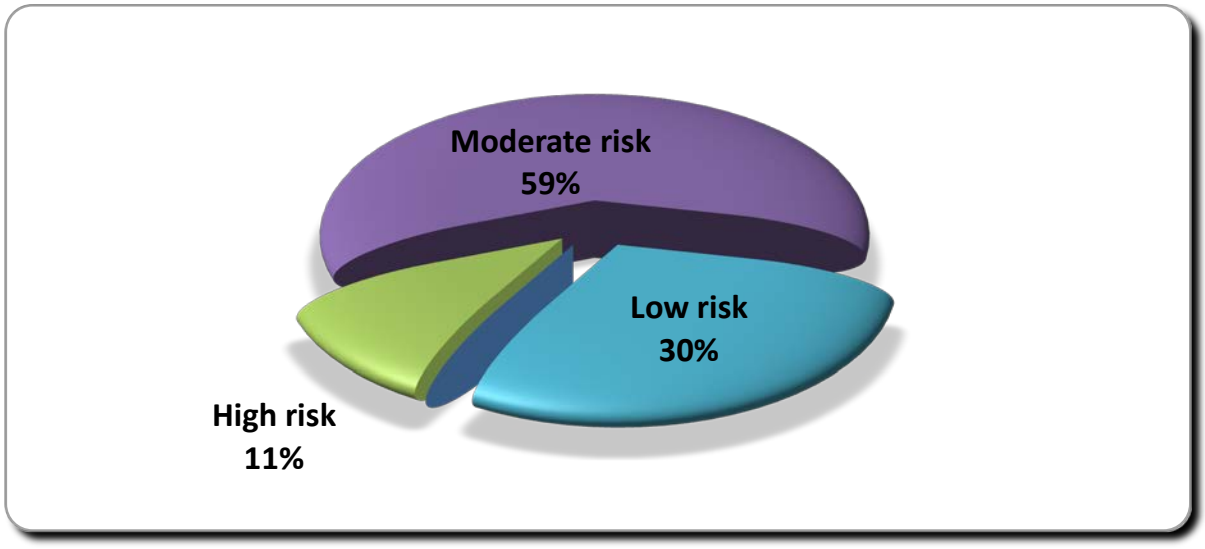


Figure 3.4: Risk stratification of patients according to the Wells score

The VQ scan was performed in all the patients studied. This comprised of two distinct phases – a perfusion scan and a ventilation scan. The perfusion scan involved an intravenous injection of Technetium-99m-labeled albumin macroaggregates, which lodge in the pulmonary capillaries. The ventilation phase was determined by means of inhalation of a radiolabelled aerosol, viz. Tc99m-DTPA. Since the ventilation scan was performed first, the radioactivity on the perfusion scan was 3-4 times greater than the radioactivity on the ventilation scan to reduce the chances of the interfering radioactivity from the ventilation scan obscuring the perfusion phase images. At least six views were required to allow adequate assessment of the various segments. The results of the VQ scan are shown in Table 3.3 and Figure 3.5 below.

Table 3.3: Results of the VQ scan

VQ scan results	Number of patients (percentage)
No typical evidence for PE	17 (14%)
Very low probability	26 (22%)
Low probability	46 (38%)
Intermediate probability	16 (13%)
High probability	15 (13%)

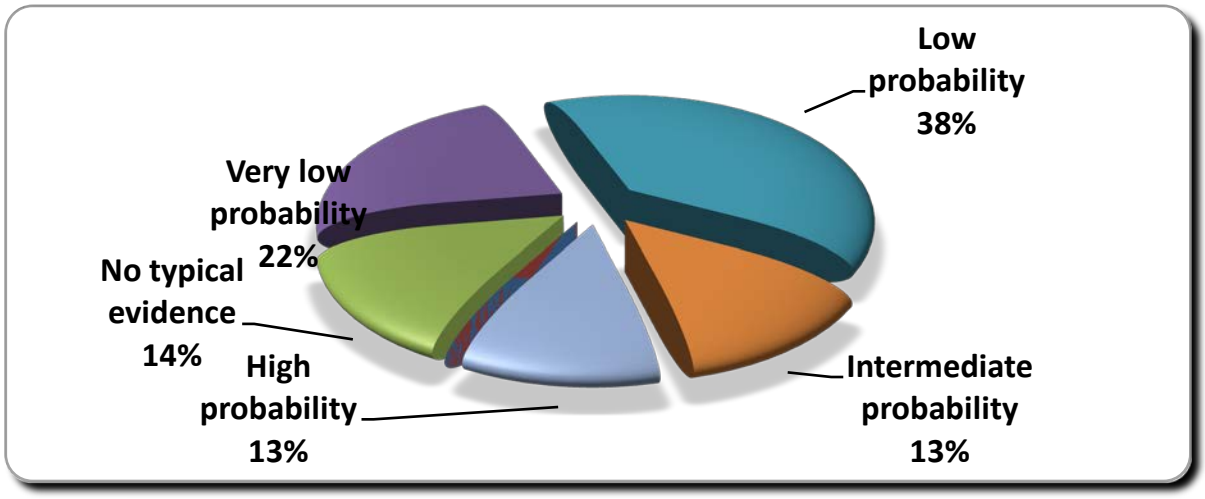


Figure 3.5: Graphical representation of VQ scans results

Many sources in the literature combine very low probability and low probability into one category simply labelled as low probability. When these two categories are combined in our study, the total number of patients falling into this category amounts to 72/120 patients (60%).

Of the 36/120 patients that were categorised as low risk based on the Wells criteria, only 2/36 patients (6%) had high probability on the VQ scan. Five patients (14%) had an intermediate probability and further imaging was suggested, either a CTPA or a “treat and repeat” regimen was advocated. The “treat and repeat” regimen refers to treating the patient for 7-10 days and a repeat VQ scan is performed thereafter to confirm resolution. The rest of the 29/36 patients (81%) demonstrated a low probability, very low probability or no typical evidence of PE (see Table 3.4).

Of the 71/120 patients that were categorised as moderate risk based on the Wells criteria, 11 patients (16%) had high probability on the VQ scan. Seven patients (10%) had an intermediate probability and further imaging was suggested, either a CTPA or “treat and repeat” regimen. A “treat and repeat” regimen may be considered if the VQ scan is equivocal (intermediate probability). This includes commencing therapeutic anticoagulation, and repeating the perfusion scan after about a week. If there is resolution of the perfusion defects, this would confirm the diagnosis of PE and thus support long-term anticoagulation. However, if there is no resolution despite anticoagulation therapy, the underlying pathology is unlikely to be PE and anticoagulation can be safely terminated. The rest of the 53 patients (75%) demonstrated a low probability, very low probability or no typical evidence of PE.

Of the 13/120 patients that were initially categorised as high risk based on the Wells criteria, 2 patients (15%) had high probability on the VQ scan. Four patients (31%) had an intermediate probability and further imaging was suggested, either a CTPA or “treat and repeat” regimen. The rest of the 7 patients (54%) demonstrated a low probability, very low probability or no typical evidence of PE.

The 16/120 patients in our study (13%) that demonstrated an intermediate probability on the VQ scan were subsequently referred for further imaging, either a CTPA or a repeat VQ scan 7-10 days post treatment to evaluate for resolution of the defects initially visualised.

In summary, 80% of the patients initially categorised as low risk had a low probability of PE on the V/Q scan. Ten percent of the patients initially classified as moderate risk had an intermediate probability on the V/Q scan. Only fifteen percent of the patients initially classified as high risk had a high probability on the V/Q scan.

Table 3.4 overleaf summarises these pre-test probabilities assigned to the patients and their correlation with the V/Q scan results.

Table 3.4: Correlation of Wells score with VQ scan results

Risk of PE on Wells score	Probability of PE on VQ scan	Number of patients (percentage)
Low risk (36 patients – 30%)	Low probability, very low probability or no typical evidence	29 (80%)
	Intermediate probability	5 (14%)
	High probability	2 (6%)
Moderate risk (71 patients – 59%)	Low probability, very low probability or no typical evidence	53 (75%)
	Intermediate probability	7 (10%)
	High probability	11 (15%)
High risk (13 patients – 11%)	Low probability, very low probability or no typical evidence	7 (54%)
	Intermediate probability	4 (31%)
	High probability	2 (15%)

For the purposes of statistical analysis, the group showing no typical evidence of PE was removed from the sample, as PE had reliably been excluded in this group. Further, the very low probability and low probability categories were combined and labelled as low probability.

The total sample population now consisted of 103 patients. Thirty one of these patients were categorised as low risk based on the Wells score, and 77% of these (24/31 patients) were also classified as low probability on the V/Q scan. Sixty patients were categorised as moderate risk based on the Wells score, and 12% of these (7/60 patients) were also classified as intermediate probability on the V/Q scan. Twelve patients were categorised as high risk based on the Wells score, and 17% of these (2/12 patients) were also classified as high probability on the V/Q scan. These results are re-interpreted in table 3.5 below.

Of the 17 patients that had been removed from the sample due to demonstrating no typical evidence of PE on the V/Q scan, 5 patients had initially been assigned as low risk based on the Wells score, 11 patients as moderate risk and only 1 patient as having a high risk of having PE.

Table 3.5: Statistical correlation of Wells score with V/Q scan results

WELLS' CRITERIA	VQ SCAN RESULTS				
	Low and very low probability	Intermediate probability	High probability	TOTAL	PERCENTAGE
Low risk	24	5	2	31	30.10%
Moderate risk	42	7	11	60	58.25%
High risk	6	4	2	12	11.65%
TOTAL	72	16	15	103	
PERCENTAGE	69.90%	15.53%	14.56%		

The kappa value has been validated as a reliable indicator of agreement when comparing two data sets statistically (Bowers, 2008). The specific values and their interpretation are charted in table 3.6 below.

Table 3.6: Interpretation of the kappa values

Kappa value	Interpretation
0.00 – 0.20	Poor agreement
0.21 – 0.40	Fair agreement
0.41 – 0.60	Moderate agreement
0.61 – 0.80	Good agreement
0.80 – 0.99	Very good agreement

Adapted from Bowers, 2008.

The data was subsequently analysed in light of the kappa values. Of the total sample population of 103 patients submitted for statistical analysis, 77% of the patients (24/31) initially categorised as low risk based on the Wells score were also classified as low probability on the V/Q scan, thus demonstrating good agreement between these variables. Twelve percent of the patients (7/60) initially categorised as moderate risk were classified as intermediate probability on the V/Q scan, demonstrating poor agreement between these variables. Seventeen percent of patients (2/12) initially categorised as high risk were also classified as high probability on the V/Q scan, also demonstrating poor agreement between these variables. These results are summarised in table 3.7.

Table 3.7: Kappa statistics

Comparing Wells score to V/Q scan results	No. of patients	Kappa value	Interpretation
Low risk AND low probability	24/31	77%	Good agreement
Moderate risk AND intermediate probability	7/60	12%	Poor agreement
High risk AND high probability	2/12	17%	Poor agreement

CHAPTER 4

4 DISCUSSION

The diagnosis of PE is a major challenge to the emergency care physician. In the United States, it is the third most common cause of death, with an incidence estimated at 600,000 patients per year (Ferretti *et al.*, 2005). Only two-thirds of the patients affected are alive one month after the diagnosis, while only half live to about a year (Heit *et al.*, 1999; Horlander *et al.*, 2003). Despite its significant mortality rate, PE was found in less than one-third of the patients in the PIOPED study (The PIOPED Investigators., 1990). Therefore, carrying out blanket investigations on all patients with respiratory symptoms would result in enormous costs to the health care system. It is thus prudent to utilize clinical scoring systems to direct diagnostic pathways. This study aimed to evaluate the appropriateness of clinician referrals for suspected PE by evaluating the correlation between pre-test probability (determined clinically via the Wells score) and the V/Q scan results.

The sample population for our study included patients that had undergone a V/Q scan for suspected PE in academic hospitals. As these are the two largest public sector hospitals in the southern Gauteng region, it was hoped that patients included in the study would be representative of a variety of different backgrounds and with different socio-economic circumstances.

It was impossible to determine the incidence of PE from our study as it is well known that many patients are diagnosed clinically and treatment initiated without diagnostic

imaging. As this was a retrospective study, these patients would not have been included in our study. Furthermore, our study looked solely at patients undergoing a V/Q scan. Thus, patients referred for other diagnostic imaging modalities such as a CTPA would also not be included in our study.

Although the race of the patient appears to play a role in the development of PE, where the incidence appears to be significantly higher in the black population compared to the white population (Horlander *et al.*, 2003; Schneider *et al.*, 2006; Meyer *et al.*, 2008), it was not possible to ascertain this in our retrospective study population as the specific race of the patients was not documented in the records.

The sample population comprised of patients ranging from 18 years to 86 years of age. The median age was 55 years, with almost half of the patients being in the 6^{th} and 7^{th} decades of life, while the mean age of the patients in our sample was calculated as 53.3 years. This concurs with reports from Silverstein et al. who demonstrated a higher incidence of PE in older patients (Silverstein *et al.*, 1998). Almost one-third of the sample population referred for a V/Q scan were over 65 years of age (39/120), with approximately two-thirds of the patients being over the age of 50 (75/120). Eighteen percent (7/39) of the patients in the over-65 age group had a high probability of PE on the V/Q scan compared to 7% (6/81) of patients in the under-65 age category. This is of concern since the diagnosis may often be missed in the older age group due to their many co-morbidities. It thus requires an astute clinician not to simply dismiss the symptoms as being non-specific and

chronic. A further confounding factor in this age category is that therapeutic anticoagulation may be inappropriately withheld due to bleeding concerns.

In the sub-group of patients over 65 years of age, 64% (25/39) were females and 36% (14/39) were males. Although advancing age is in itself often cited as an independent risk factor for the development of PE (Silverstein *et al.*, 1998), the general consensus is that the cumulative risk factors patients acquire with advancing age are the cause rather than the age itself. At least half of the patients studied in this sub-category (20/39) had co-morbidities. This included CCF (8/39 patients), obesity (12/39 patients), COPD (7/39 patients) and recent surgery (3/39 patients). All three patients in the last group had undergone major surgery – the first patient had a triple vessel bypass procedure, the second patient a total hip replacement and the third patient had prostate surgery. All these co-morbidities lead to reduced mobility and eventual venous stasis, thus further increasing the risk of developing PE.

Three other patients had a previous history of DVT or PE. None of the patients had a history of malignancy.

Most of the patients in this sub-category presented with dyspnoea (34/39). This is a very non-specific symptom, also occurring in CCF and COPD, thus making clinical diagnosis in such patients extremely difficult. Three patients had concomitant haemoptysis, while only 2 patients had the classical triad of dyspnoea, haemoptysis as well as chest pain.

Seventeen of the 39 patients had D-dimers measured as part of the diagnostic workup. Even though this value was high in all these patients, it did not prove to be very helpful as D-dimers are non specific and are often raised in patients with CCF (Watts, 2004; Ravenel *et al.*, 2005; Bajc *et al.*, 2010). Consequently, only 2 of the patients with high D-dimer values had a high probability on the V/Q scan.

It is interesting to note in this age group (i.e. > 65 years), 7/39 patients, despite their co-morbidities, had a high probability of PE demonstrated on the V/Q scan. This constituted almost half of all patients in the sample population in whom the V/Q scan demonstrated a high probability of PE (7/15 patients).

On examining patients on the other side of the age spectrum i.e. patients less than 50 years of age, this again showed a preponderance of females (35 females and 10 males). Only 3 patients were younger than 20 years of age, again alluding to advancing age as an independent risk factor for the development of PE (Silverstein *et al.*, 1998).

In patients younger than 50 years of age, our histogram (figure 3.3) showed a surprisingly increased incidence (15%) in patients in the 3rd decade of life presenting for a V/Q scan (18/120 patients). The reasons are, however, different to those in the older age group. Seventy two percent of these patients (13/18 patients) had a history of recent immobilisation, making this a significant risk factor in the younger population. A closer look revealed 14 of the 18 patients (78%) were females. Six of the 14 females (43%) were either pregnant or in the postpartum period. Two of these

patients had an additional history of oral contraceptive use, which is known to further increase the risk of developing PE by promoting a hypercoagulable state (Watts, 2004; Ravenel *et al.*, 2005). All these risk factors have been documented in the literature to disrupt the equilibrium of Virchow's triad (Kline & Runyon, 2005; Tabas & McNutt, 2005; Smith, 2008).

Other significant risk factors in patients younger than 50 years of age included history of recent surgery (2 patients had a Caesarean section while another patient had a laparotomy for an ectopic pregnancy), and obesity leading to reduced mobility (9/45 patients). Patients undergoing surgery also have endothelial damage to the vessel wall, thus further disrupting Virchow's triad, while obesity promotes a hypercoagulable state (Watts, 2004; Kline & Runyon, 2005; Ravenel *et al.*, 2005; Tabas & McNutt, 2005; Smith, 2008).

Two of the 45 patients had a history of malignancy although the exact malignancy was not documented. An association between malignancies and the occurrence of pulmonary embolism is well documented as malignancies promote a hypercoagulable state (Watts, 2004; Kline & Runyon, 2005; Ravenel *et al.*, 2005; Tabas & McNutt, 2005; Smith, 2008). Specific neoplasms which may lead to the development of pulmonary embolism include bronchogenic carcinoma; pancreatic carcinoma and carcinomas of the genitourinary tract, colon, stomach, and breast (Watts, 2004; Kline & Runyon, 2005; Ravenel *et al.*, 2005; Tabas & McNutt, 2005; Smith, 2008).

A further 2 of the 45 younger patients had a history of previous DVT or PE, while another four patients presented in CCF, although the cause of the CCF was not clearly documented.

It is also noteworthy that 27% (12/45) of the patients in the younger age category had been diagnosed with HIV/AIDS. This is indeed of concern as this dreaded disease not only predisposes a patient to other co-morbidities in addition to a hypercoagulable state at a young age, but also increases the health-care cost to the economy. Extensive awareness campaigns may be crucial in attempting to control this scourge and its complications.

With regards to genetic risk factors, 2 patients had documented anti-phospholipid syndrome with a lupus anticoagulant, which is known to lead to a hypercoagulable state.

It is important to note that in our study the most common risk factor in both the younger and the older age category was immobility. This was also the most common risk factor found in the PIOPED II study (Stein *et al.*, 2007). Other common risk factors were a history of CCF in the older age category and AIDS in the younger age category.

In the sub-group of patients under the age of 50 years, most of the patients presented with dyspnoea (30/45), while 6/45 patients had complained of haemoptysis. Only 3/45 patients had the classical triad of concomitant dyspnoea,

haemoptysis and chest pain. These results are similar to those found in the older age group.

Eighteen of the 45 patients (40%) had raised D-dimer levels. Only 1 of these patients had a high probability on the V/Q scan. Although it has been suggested that D-dimer testing should mostly be used to exclude PE in young patients with no co-morbidities (Qaseem *et al.*, 2007), in our population sample, many of the patients with high D-dimer values did in fact have other co-morbidities.

Of the 2 D-dimer values that were within the normal range, it is not surprising that both these patients had a low probability on the V/Q scan. Since D-dimers have a very high negative predictive value (Lake *et al.*, 2005; Quiroz & Schoepf, 2005; Ravenel *et al.*, 2005), the V/Q scan could have been omitted in both these patients and in the older age group if age corrected D-dimer had been used.

Although the development of PE is not restricted to a particular gender, it has been recorded that the incidence of PE is greater in females if the sample population is under 55 years of age (Horlander *et al.*, 2003). This may explain the higher female-to-male ratio in our study group, as a large portion of the patients (69/120 patients making up 57.5% of our sample population) were under 60 years of age. Risk factors specific to the female gender, such as pregnancy, post-partum state and history of oral contraceptive use, may account to some degree for this increased incidence in young females. Of note though, it has been found that females have a lower probability of developing recurrent PE (Horlander *et al.*, 2003).

Twenty five percent of the total sample population across all age groups (30/120 patients) presented with a history of immobility. Since immobilisation leads to local venous stasis, it is a significant contributor to the formation of a thrombus, as described in the literature (Watts, 2004; Kline & Runyon, 2005; Ravenel *et al.*, 2005; Tabas & McNutt, 2005; Smith, 2008).

Besides advancing age and a history of immobilisation, the other significant risk factor in our total sample population was an acute medical illness, affecting 28% of the patients (34/120 patients). Of these patients, 65% (22/34) presented with CCF. Eighty two percent of the patients (18/22) were older than 50 years of age. Although co-morbidities are generally associated with advancing age, it must be noted that in the 3 patients younger than 40 that presented with CCF, all 3 patients had been diagnosed with HIV/AIDS, thus alluding to the complex co-morbidities associated with HIV/AIDS.

It is surprising that patients with known CCF were referred for a V/Q scan, since such patients are known to have a low cardio-pulmonary reserve. This reduces the likelihood of a PE causing the patient's symptoms. This is evidenced by the majority of patients with CCF that were found to have a low probability on V/Q scan – 14/19 patients (74%). Of the patients with CCF that had a high probability on a V/Q scan, the majority had concomitant HIV/AIDS, thus increasing the likelihood of thromboembolic events. However, if the symptoms are out of keeping with the degree of heart failure, these patients should be investigated for a PE.

Overall, twelve of the 34 patients (35%) had been diagnosed with HIV/AIDS. Eighty three percent of these patients (10/12 patients) were younger than 40 years of age. This conforms to the hypothesis of Malek *et al.* that HIV-infected patients possess a greater risk of almost 40% of developing thromboembolic disease (Malek *et al.*, 2011).

As far as the other thrombophilic risk factors mentioned in the literature are concerned, only two patients in our sample population had been diagnosed with a lupus anticoagulant (anti-phospholipid syndrome). The absence of other risk factors may be due to the very low incidence of the genetic abnormalities such as Factor V Leiden in the non-caucasian population (Watts, 2004; Ravenel *et al.*, 2005). Thus routine testing of genetic abnormalities is not performed in our public sector hospitals unless clinically indicated. Some of the clinical scenarios that may encourage an astute physician to perform these tests include young females (<40 years of age), a positive family history of thrombosis, thrombosis in unusual sites or recurrent thrombosis. It is imperative to identify patients at high risk of developing venous thrombosis and PE, as implementation of a prophylactic strategy in these patients may reduce mortality.

All the risk factors mentioned thus far contribute to the development of a DVT, by affecting one of the elements of Virchow's triad i.e. nature of blood flow, quality of vessel wall and/or composition of the blood. In our sample population though, only 11/120 patients (9%) had a confirmed DVT on Doppler studies, while only 7/120 patients (6%) had a history of previous DVT or PE.

This is surprising since the literature mentions clearly that PE is a complication of underlying DVT (Watts, 2004; Loud *et al.*, 2005). It is unclear in our sample population whether the remainder of the patients did not undergo a duplex Doppler ultrasonography, or whether a duplex Doppler ultrasonography was indeed performed in these patients but failed to demonstrate a DVT. This was indeed disappointing as it has been said that PE can also be suggested by demonstrating a DVT at any site. Although the results of Doppler studies are highly dependent on the experience of the operator, this is a non-invasive and widely available modality with high sensitivity and specificity for proximal DVT of the lower limbs (Loud *et al.*, 2005).

Although venography is the gold standard for diagnosing a DVT, its clinical utility has become less common with the advent of non-invasive Doppler studies (Loud *et al.*, 2005). Furthermore, venography necessitates the injection of a special dye. Since some patients may exhibit an adverse reaction to this dye, this complication has also contributed to its decline in popularity (Loud *et al.*, 2005). None of the patients in our study population had a venography performed.

It is well known that many of the signs and symptoms of PE are non-specific. Patients may present with various symptoms, ranging from a sudden onset of catastrophic haemodynamic instability to progressively worsening dyspnoea. In our sample population, systemic hypotension as well as shock were rarely observed. Both these signs are associated with a massive PE. It is thus likely that the majority

of the patients presenting as such may have demised prior to the performance of a V/Q scan. Thus, they were not included in our sample population.

In our sample population, dyspnoea was the most frequent complaint, followed by chest pain and haemoptysis. This order of frequency concurs exactly with the incidence of common symptoms reported in the PIOPED study (Worsley and Alavi, 1995).

It has been reported that the so-called pathognomic triad of symptoms—represented by haemoptysis, pleuritic chest pain and dyspnoea—occurs in less than 20% of patients (Kline & Runyon, 2005; Tabas & McNutt, 2005; Smith, 2008). In our sample population, this figure was even lower – 7/120 (6%) of patients. None of these patients had a high probability on VQ scan, making this triad an unreliable indicator. It has been suggested, however, that this triad of symptoms may occur only if a PE is complicated by a pulmonary infarction (Kline & Runyon, 2005; Tabas & McNutt, 2005; Smith, 2008). It is thus possible that in many patients the PE had not progressed to a pulmonary infarction, thus very few patients actually presented with all these symptoms concurrently.

Patients with acute pulmonary infarction may also develop a pleural effusion (Kline & Runyon, 2005; Tabas & McNutt, 2005; Smith, 2008). Even though a pleural effusion may mask the typical segmental defect of PE, a VQ scan may still show defects in other regions where there is no effusion. In our sample population, 4 patients had a documented pleural effusion on the chest x-ray. However, none of these patients

had the classical triad of symptoms. It is possible though, that in the patients that did present with the classical triad of symptoms, the presence of an effusion was not documented.

In patients with an acute embolism without infarction, the most frequently detected signs are tachypnoea and tachycardia (Kline & Runyon, 2005; Lake *et al.*, 2005; Ravenel *et al.*, 2005; Tabas & McNutt, 2005; Smith, 2008). This was not supported in our study. Of the 22/120 patients in our sample population that presented with concomitant tachypnoea and tachycardia, only 2 patients had a high probability of PE on the V/Q scan. On the other hand, of the 15 patients that had a high probability of PE, 12 of the patients (80%) presented with dyspnoea.

Patients with multiple pulmonary emboli may eventually develop pulmonary hypertension. This manifests clinically as a loud component of the second heart sound, distended neck veins and systemic hypotension (Kline & Runyon, 2005; Tabas & McNutt, 2005; Smith, 2008). The only patient in our study population that had documented systemic hypotension also had a high probability of PE on the V/Q scan. Of the patients in our study population that had documented pulmonary hypertension, right ventricular failure, palpable P2 or cor pulmonale, only 1 patient had a high probability on the V/Q scan. This patient had a raised systolic pulmonary artery pressure of greater than 40mmHg on echocardiogram.

Overall, the incidence of common symptoms in our study population was as follows:-

- Dyspnoea (78%)
- Chest pain (48%)
- Haemoptysis (9%)

This order of frequency concurs with that reported by Worsley and Alavi in the PIOPED study (Worsley & Alavi, 1995).

The incidence of the common signs in our study population was as follows:-

- Tachycardia (41%)
- Tachypnoea (31%)

It was not documented if the Homan's sign or the Pratt's sign was performed on any of the patients in our sample population.

Review of the literature brings forth conflicting data regarding the utility of P_aO_2 in the workup of PE. Hypoxaemia is characteristic of acute PE, yet many other aetiologies that masquerade as PE may also lower the P_aO_2, such as COPD, pneumonia, CCF (Lake *et al.*, 2005). It is surprising that the P_aO_2 value was recorded in less than 3% of patients in our study population. This may be due to the referring physicians questioning its objective utility since hypoxaemia occurs inconsistently in patients with PE (Overton & Bock, 1988). Furthermore, since many of the patients in the older age category had other co-morbidities such as CCF and COPD, this would reduce the specificity of P_aO_2 measurement in this sub-group of patients. Despite its

limitations, the P_aO_2 levels definitely have a role to play in high risk patients in whom other respiratory conditions have been excluded, and its routine measurement in this category of patients should be encouraged.

Cyanosis may be present, although it is not a prominent feature of pulmonary embolism – unless it is a massive embolism causing significant ventilation-perfusion (V/Q) mismatch and systemic hypoxaemia (Kline & Runyon, 2005; Tabas & McNutt, 2005; Smith, 2008). In our study population, only one patient had cyanosis. This patient did not turn out to have a high probability of PE on the V/Q scan.

Measurement of the D-dimer values may be more beneficial due to its high negative predictive value. This important test was not documented in at least half of the patients in our sample population. This is unfortunate in view of the large randomised trial by Kearon *et al.* in which no additional diagnostic testing was performed in patients with a low pre-test probability of PE and a negative D-dimer result (Kearon *et al.*, 2006). In this trial the authors did not find a higher rate of symptomatic venous thrombo-embolism during follow-up for 6 months. Of the 36 patients in our population sample that had been categorised as low probability, in almost two thirds (23 patients) D-dimer testing was not performed!

Of the patients in whom D-dimer testing had been performed, in 3 patients the value was within the normal range. All these patients went on to have a low probability of PE on the V/Q scan. This corroborates the study of Kearon *et al.* demonstrating that a negative D-dimer test in a patient with a low pretest probability reliably excludes

PE without the need for further diagnostic imaging (Kearon *et al.*, 2006). Thus, the V/Q scan could have been entirely avoided in these 3 patients. It is important to bear in mind that this number may have been higher if the D-dimer values had been recorded in all the patients in our sample population.

We do acknowledge that a high D-dimer value is non-specific, being elevated in many other clinical conditions such as cancer, pregnancy, recent trauma and CCF (Watts, 2004; Ravenel *et al.*, 2005; Bajc *et al.*, 2010). Since many of the patients in our study population had these co-morbidities, the D-dimer values may have been raised as a result of the co-morbidities rather than due to PE. Qaseem *et al.* documented that D-dimer testing should mostly be used to exclude PE in young patients with no co-morbidities (Qaseem *et al.*, 2007).

Assessment of the ischaemia-modified albumin (IMA) levels offers an alternative to D-dimer testing. Turedi *et al.* compared the two tests i.e. IMA and D-dimers in terms of their prognostic values (Turedi *et al.*, 2008). They discovered that due to the higher specificity, IMA had a better positive predictive value compared to the D-dimer test. However, this test is not available in our institution and was therefore not performed in our patients in this study.

Although there are no definitive findings indicative of PE on a chest x-ray, the American College of Radiology recommends this investigation as “the most appropriate study for ruling out other causes of chest pain in patients with suspected

PE", namely, pneumothorax, pulmonary oedema, malignancy or pneumonia (Bettmann *et al.,* 2011).

It was thus disappointing to note that in our study population, the chest x-ray findings were documented in only 5% (6/120) patients. Two of the x-rays demonstrated consolidation, suggesting pneumonia as the cause of the patient's symptoms. It is unclear why these patients were subsequently referred for a V/Q scan. Four of the chest x-rays demonstrated a pleural effusion. Although a pleural effusion may indicate the presence of PE complicated by a pulmonary infarction, these patients did not have the classical triad of symptoms suggesting infarction. None of these patients demonstrated the typical x-ray findings of a pulmonary infarction, namely the Westermark sign or the Hampton Hump sign described earlier. Furthermore, only 1 of these 4 patients had a high probability of PE on the V/Q scan. Perhaps these numbers would have been more significant, had the chest x-ray findings been recorded in all the patients.

It must be noted that a normal-appearing chest x-ray may also be helpful in such patients. In a patient who presents with severe dyspnoea and hypoxaemia, with no evidence of bronchospasm or a cardiac shunt, a normal-appearing chest x-ray is strongly suggestive of pulmonary embolism (Kline & Runyon, 2005; Tabas & McNutt, 2005; Smith, 2008).

The role of ECG is mainly to exclude other clinical entities which may mimic the presentation of PE. The widely quoted ECG finding of S1Q3T3 is neither sensitive

nor specific, occurring in less than 20% of patients with proven PE (Kline & Runyon, 2005; Tabas & McNutt, 2005; Smith, 2008). Once again, the documentation of ECG findings in our study population was poor. Of the documented findings, only 14/120 (12%) patients demonstrated this typical pattern. Of these however, 6/14 (43%) patients had a high probability of PE on the V/Q scan, making this a significant finding in patients that do have PE.

Evidence-based literature suggests that clinical prediction rules be utilised to assess the clinical probability of PE before proceeding with imaging tests (Qaseem *et al.*, 2007; Tapson, 2008; Bajc *et al.*, 2010). Several clinical decision rules have been promoted to assist physicians (Miniati *et al.*, 1996; Wells *et al.*, 2000). The clinical practice guideline developed by the American Academy of Family Physicians and the American College of Physicians advocates the use of the Wells prediction rule for this purpose (Qaseem *et al.*, 2007).

Based on the history, and presenting signs and symptoms, all the patients were initially categorised into low, moderate or high pre-test probability based on the Wells score. The majority of the patients were categorised as moderate risk (59%). Thirty percent (36 patients) were categorised as low risk, and the remainder (11%) as high risk for having a PE. As mentioned previously, if D-dimer tests had been performed and found to be negative in all the 36 patients categorised as low risk, these patients would not have required further imaging to confirm or exclude the diagnosis of PE.

An alternate interpretation of the Wells score has been suggested as follows (Van Belle et al, 2006; Wells et al, 2000):-

- Score > 4 – PE likely. Diagnostic imaging should be considered.
- Score ≤ 4 – PE unlikely. D-dimer testing should be considered to rule it out completely.

If this pathway had been followed, 48% (57/120) of the patients had a score of ≤4. Of these 57 patients, 3 had a normal D-dimer levels and the V/Q scan could have been avoided in these 3 patients. Furthermore, in 60% (34/57) of these patients, the D-dimer levels had not been checked. Had these values been checked and were within the normal range, the V/Q scan could have been avoided in another 34 patients!

Many diagnostic imaging modalities have been used to confirm or exclude PE, such as a pulmonary angiogram, CTPA, MRI, MR angiography and echocardiogram. Together with different sensitivities and specificities, each modality has its own inherent advantages and disadvantages, which have been discussed previously. Availability of equipment in different settings as well as the clinical condition of the patient also plays a role in determining which imaging modality is employed.

Despite the pulmonary angiogram being classified as the gold standard in diagnosing PE, V/Q scans have established a crucial role in the diagnosis of PE due to their lower radiation exposure. V/Q scans have been validated in large prospective studies against PA and proven to have high sensitivity (Miniati et al, 1996; The PIOPED Investigators, 1990).

V/Q scanning of the lungs was performed on all the patients in our sample population. The results of the V/Q scan were also categorised into low, medium or high probability of having a PE.

A total of 74% of patients scanned fell into the low probability, very low probability or no typical evidence category. Thirteen percent of the patients were classified as intermediate probability and the remaining thirteen percent as high probability on the V/Q scan.

The 16/120 patients in our study (13%) that demonstrated an intermediate probability on the VQ scan were subsequently referred for further imaging, either a CTPA or a repeat VQ scan 7-10 days post treatment to evaluate for resolution of the defects initially visualised.

As demonstrated above, in a significant proportion of patients, the V/Q scan results may be non-diagnostic. The results of the V/Q scan should be interpreted in the context of pre-test probability. The safety of basing management decisions on pre-test probability and V/Q scan results has been well proven by Wells and colleagues (Wells *et al.*, 1998).

In our study population, 6% of patients with a low pre-test probability, 15% of patients with a moderate pre-test probability and 15% of patients with a high pre-test

probability were classified as high probability on the V/Q scan results, respectively (see table 3.4).

These results are substantially different to those obtained by Stein *et al.* who found that a low pre-test probability was associated with a 15% risk of PE, moderate pre-test probability with a 29% risk, and a high pre-test probability with a 59% risk of PE (Stein *et al.*, 2007). This difference in the results may be due to the retrospective evaluation of the Wells' score in our study as it is possible that not all the parameters had been documented in the case files.

In terms of correlating the Wells score with the V/Q scan results, of the patients initially allocated to the low-risk subgroup based on the Wells score, the V/Q scan demonstrated low probability in 80%, while 15% of patients initially allocated to the high-risk subgroup based on the Wells score, were also classified as high probability on the V/Q scan (see table 3.4).

Of the 36/120 patients that were categorised as low risk based on the Wells criteria, only 2/36 patients (6%) had high probability on the VQ scan. Five patients (14%) had an intermediate probability and further imaging was suggested, either a CTPA or a "treat and repeat" regimen was advocated. This requires anticoagulation for 7-10 days and a repeat VQ scan thereafter to confirm resolution of the defects visualised initially. This allows for confirmation of PE as the cause of the defects in retrospect. The rest of the 29/36 patients (81%) demonstrated a low probability, very low probability or no typical evidence of PE.

Of the 71/120 patients that were categorised as moderate risk based on the Wells criteria, 11 patients (16%) had high probability on the VQ scan. Seven patients (10%) had an intermediate probability and further imaging was suggested, either a CTPA or treatment for 7-10 days and a repeat VQ scan thereafter to confirm resolution. The rest of the 53 patients (75%) demonstrated a low probability, very low probability or no typical evidence of PE.

Of the 13/120 patients that were initially categorised as high risk based on the Wells criteria, 2 patients (15%) had high probability on the VQ scan. Four patients (31%) had an intermediate probability and further imaging was suggested, either a CTPA or treatment for 7-10 days and a repeat VQ scan thereafter to confirm resolution. The rest of the 7 patients (54%) demonstrated a low probability, very low probability or no typical evidence of PE.

Overall, 80% of the patients initially categorised as low risk had a low probability of PE on the V/Q scan. Ten percent of the patients initially classified as moderate risk had an intermediate probability on the V/Q scan. Fifteen percent of the patients initially classified as high risk had a high probability on the V/Q scan results (see table 3.4).

As mentioned previously, for the purposes of statistical analysis, the group showing no typical evidence of PE was removed from the sample, as PE had reliably been

excluded in this group. Further, the very low probability and low probability categories were combined and called low probability.

Of the total sample population of 103 patients submitted for statistical analysis, there was good agreement between the low risk of PE on the Wells score compared to the low probability of PE on the V/Q scan results. Practically this implies that if a physician finds himself in a health care centre lacking a nuclear medicine facility, he may safely base management decisions in patients with a low pre-test risk of PE on the Wells' score. However, there was poor agreement between the moderate and high risk patients compared to the intermediate and high probability of PE on the V/Q scan results, respectively. These patients would require a V/Q scan to guide management decisions.

Many factors may have contributed to the poor correlation in these sub-categories in our setting. The first factor is the diagnostic workup and inappropriate investigation of patients in the public sector hospitals. Since the patients were referred based solely on presenting signs and symptoms, it is possible that some patients were referred inappropriately for V/Q scans. We do acknowledge that this diagnosis is not always easy clinically in the light of the non-specific signs and symptoms. It is for this very reason that clinical decision rules, such as the Wells prediction rule, have been developed in an attempt to improve implicit clinical judgement. The patients in our sample population may not have been referred for a V/Q scan primarily based on the Wells score. In actual fact, the Wells score was often calculated in retrospect by the investigating departments.

Furthermore, this being a retrospective analysis, no formal diagnostic pathways were followed prior to requesting a V/Q scan. This is evident from the fact that some patients had been subjected to a V/Q scan unnecessarily, despite having a low pre-test probability as well as negative D-dimer results.

As mentioned previously, carrying out blanket investigations on all patients with respiratory symptoms would result in enormous costs to the health care system. It is thus prudent to utilize clinical scoring systems to direct diagnostic pathways. To help quantify the pre-test probability of PE, clinical scoring systems such as the Wells score should be utilised to avoid unnecessary radiation exposure to the patient as well as reduce unnecessary costs to the health care sector.

CHAPTER 5

CONCLUSION

A patient presenting with possible PE may become a nightmare for the treating physician. It may culminate in significant morbidity and mortality, yet is difficult to diagnose. The wide range of non-specific signs and symptoms may result in the diagnosis being missed. As many as 400,000 cases may be missed annually in the United States (Kline and Runyon, 2005).

Although anticoagulation is an effective treatment, it has its inherent side-effects and associated morbidity. Thus, it is prudent to utilize clinical scoring systems to direct diagnostic pathways prior to instituting treatment.

The diagnostic challenge is that the so-called pathognomic triad of symptoms—representing haemoptysis, pleuritic chest pain and dyspnoea—is rarely being seen.

Furthermore, D-dimer determinations are only of value in certain clinical settings. However, if the D-dimer value is within the normal range in low and moderate risk patients, a diagnosis of PE can be excluded with a margin of safety, without further imaging and subjecting the patient to unwarranted radiation exposure.

Chest x-ray and ECG findings alone are non-specific. These, however, may be crucial to diagnose other conditions that can clinically mimic PE.

Although pulmonary angiography offers the only definitive means of establishing a diagnosis of PE, it is not practical to employ such an invasive and expensive technique as a screening test. Interposed between clinical suspicion and angiography is the V/Q scan, which is an effective non-invasive procedure for the imaging of PE. In addition, a normal scan essentially rules out the diagnosis of PE. Even in patients in whom the V/Q scan is non-diagnostic, it may be used to guide selective pulmonary angiography, thus increasing the sensitivity of the test.

Our study demonstrated good agreement between patients with low risk of PE on the Wells score compared to the low probability of PE on the V/Q scan results. Practically this implies that if a physician finds himself in a health care centre lacking a nuclear medicine facility, he may safely base management decisions in patients with a low pre-test risk of PE on the Wells score. However, there was poor agreement between the moderate and high risk patients compared to the intermediate and high probability of PE on the V/Q scan results, respectively. These patients would require a V/Q scan or other imaging modalities to guide management decisions.

RECOMMENDATIONS

- In remote areas where logistics may not permit imaging, normal D-dimer value in low and moderate risk patients, may be enogh to exclude the diagnosis of PE
- To help quantify the pre-test probability of PE, clinical scoring systems such as the Wells score should be utilised to direct diagnostic pathways. This may avoid unnecessary radiation exposure to the patient as well as reduce unnecessary costs to the health care sector.
- A further prospective study with a larger patient base may yield more conclusive results. If this is done, a three to six month follow-up period of these patients should be used as a clinical end point. Such study should consider adding the SPECT acquisition following planar imaging for direct comparison.

LIMITATIONS OF THE STUDY

Some of the limitations of the study include the following:-

1. The number of patients studied was small. Thus the conclusions drawn from this pilot study may not be entirely accurate.
2. Selection bias. Since the study concentrated on inpatients presenting to a University Hospital, the patient sample is not entirely representative of the South African cross-sectional population.
3. The study also did not include patients that demised outside of a hospital setting, such as at home or in a nursing facility. We believe, however, that most individuals who suffer a PE are likely to seek medical care and will probably be hospitalised.
4. As this was a retrospective analysis, there were no pre-defined criteria in place for the clinicians to refer patients for a VQ scan.
5. Similarly, the study did not include patients where the clinical diagnosis of PE was missed.
6. We further acknowledge that the information was obtained from patient records. Thus incomplete or incorrect data may skew the results.

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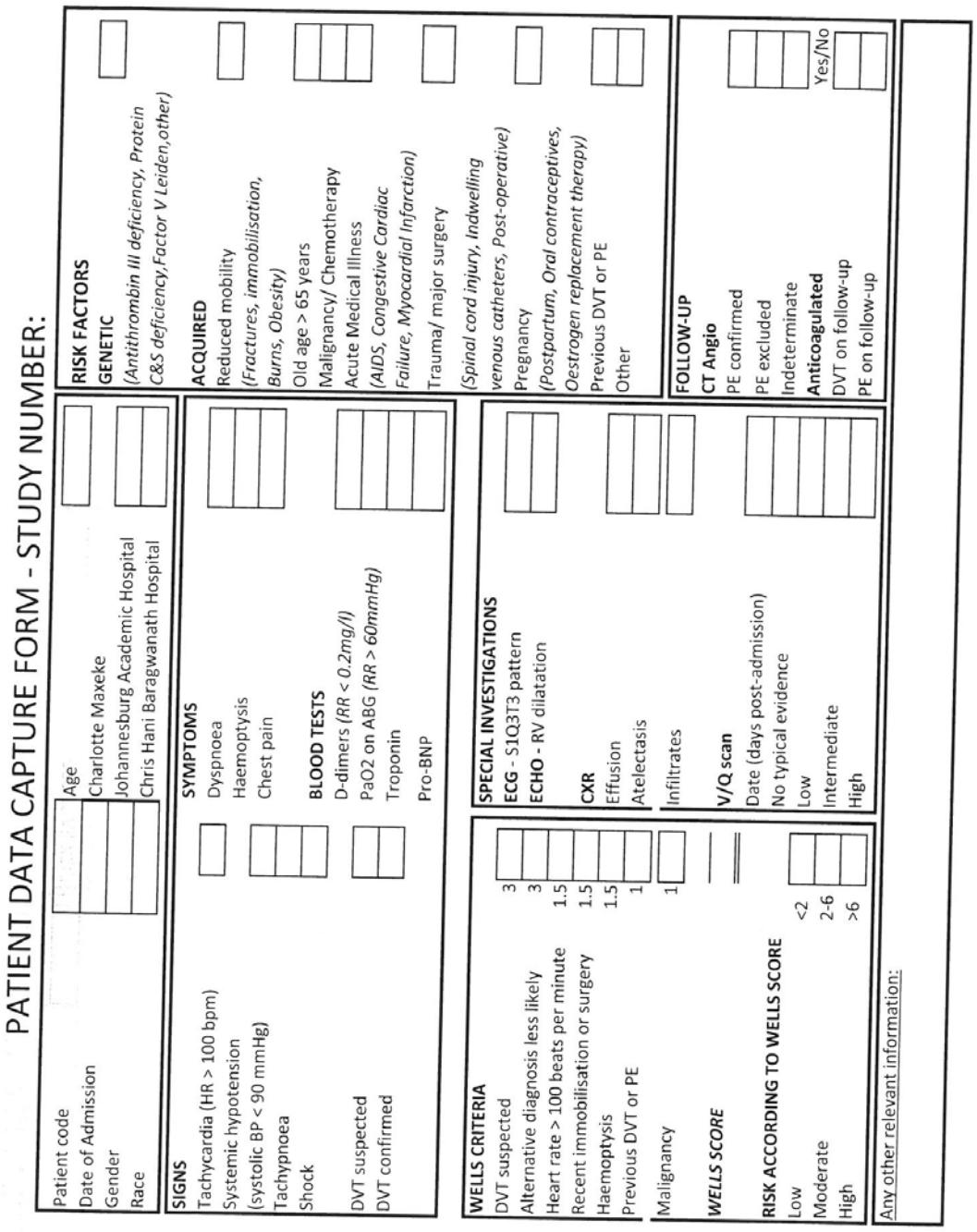
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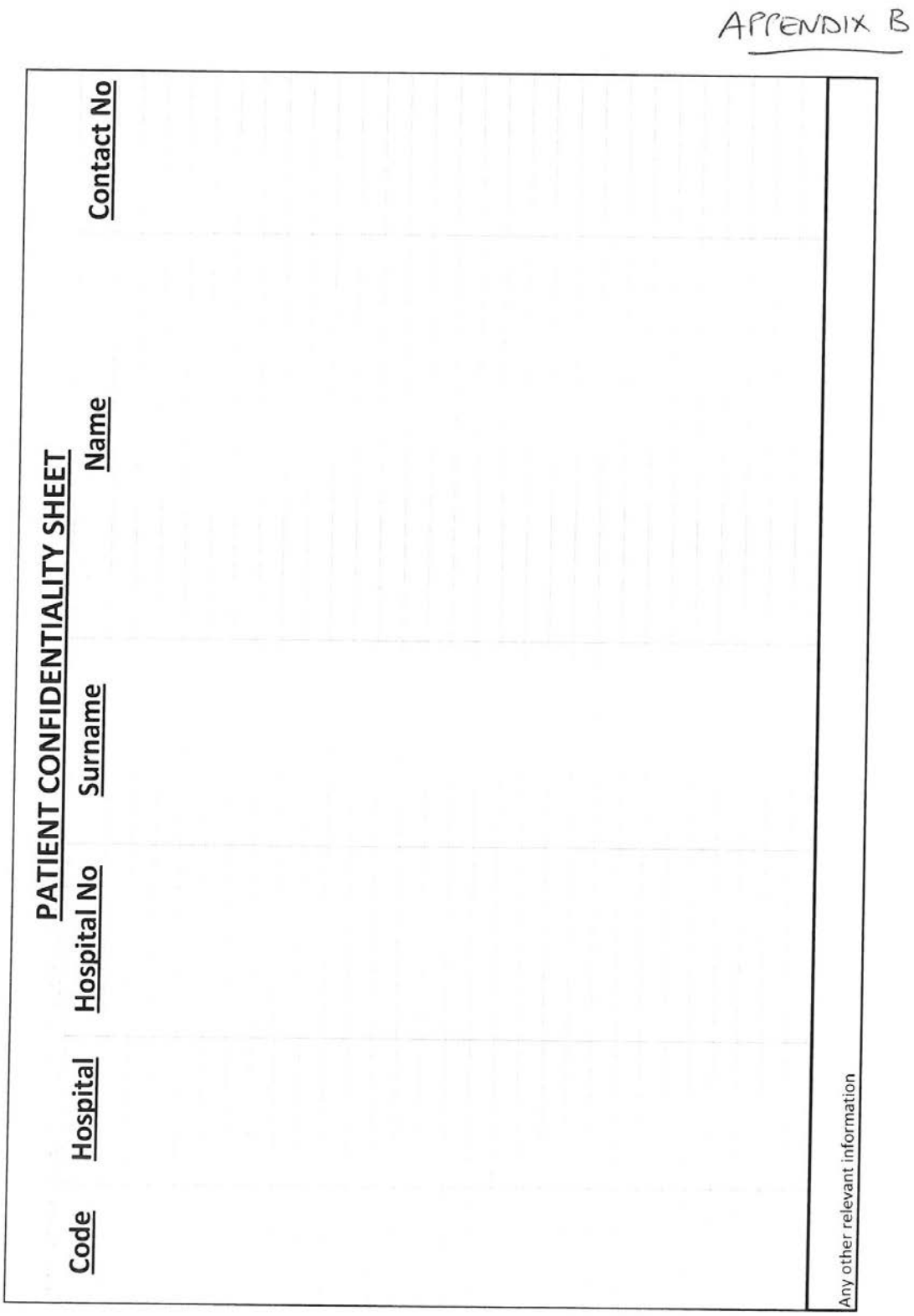
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APPENDIX A


PATIENT DATA CAPTURE FORM - STUDY NUMBER:
Patient code
Date of Admission
Gender
Age
Charlotte Maxeke Johannesburg Academic Hospital
Chris Hani Baragwanath Hospital
RISK FACTORS
GENETIC
(Antithrombin III deficiency, Protein C&S deficiency,Factor V Leiden,other)
ACQUIRED
Reduced mobility (Fractures, immobilisation, Burns, Obesity)
Old age > 65 years
Malignancy/ Chemotherapy
Acute Medical Illness (AIDS, Congestive Cardiac Failure, Myocardial Infarction)
Trauma/ major surgery (Spinal cord injury, indwelling venous catheters, Post-operative)
Pregnancy (Postpartum, Oral contraceptives, Oestrogen replacement therapy)
Previous DVT or PE
Other
SIGNS
Tachycardia (HR > 100 bpm)
Systemic hypotension (systolic BP < 90 mmHg)
Tachypnoea
Shock
DVT suspected
DVT confirmed
SYMPTOMS
Dyspnoea
Haemoptysis
Chest pain
BLOOD TESTS
D-dimers (RR < 0.2mg/l)
PaO2 on ABG (RR > 60mmHg)
Troponin
Pro-BNP
SPECIAL INVESTIGATIONS
ECG - S1Q3T3 pattern
ECHO - RV dilatation
CXR
Effusion
Atelectasis
Infiltrates
V/Q scan
Date (days post-admission)
No typical evidence
Low
Intermediate
High
FOLLOW-UP
CT Angio
PE confirmed
PE excluded
Indeterminate
Anticoagulated
DVT on follow-up
PE on follow-up
Yes/No
WELLS CRITERIA
DVT suspected 3
Alternative diagnosis less likely 3
Heart rate > 100 beats per minute 1.5
Recent immobilisation or surgery 1.5
Haemoptysis 1.5
Previous DVT or PE 1
Malignancy 1
WELLS SCORE
RISK ACCORDING TO WELLS SCORE
Low <2
Moderate 2-6
High >6
Any other relevant information:


APPENDIX B
PATIENT CONFIDENTIALITY SHEET
Code
Hospital
Hospital No
Surname
Name
Contact No
Any other relevant information

Appendix C – Human Research Ethics Committee Clearance Number

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Academic & Research)

MEMORANDUM

TO: **Dr Abdul-Basit Rahmani**
Department of Emergency
EMAIL dr.rahmani247@gmail.com

FROM: Ms Anisa Keshav
Secretary: Human Research Ethics Committee (Medical)
Tel 717-1234 fax 011 717 1265
e-mail: anisa.keshav@wits.ac.za

DATE: 12 October 2009

REF: ***R14/49***

The protocol below was considered at a meeting of the Human Research Ethics Committee (Medical) **on Friday 2 October 2009. Please see the Committee's decision:**

M090903
The Correlation between Pre-Test Probability V/Q Scan Results in Patients Presenting with Suspected Pulmonary Embolism at a University Hospital (CM JOhannesburg Academic Hospital or CH Baragwanath Hospital)
APPROVED UNCONDITIONALLY

A copy of your clearance certificate will be e-mailed to you in due course.

Appendix D – Turnitin report