THE UNIVERSITY *of* EDINBURGH

NEW INSIGHTS INTO THE NATURAL HISTORY OF THROMBO-EMBOLIC DISEASE PROVIDED BY IMAGING AND DISEASE QUANTIFICATION

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Only a life lived for others is a life worthwhile.

Albert Einstein

To, Helen
Andrew, David, James,
Rachel and Christopher,
my father and in
remembrance of my mother

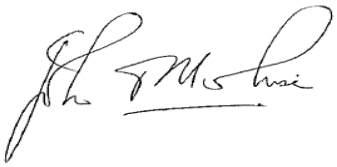
Contents

Declaration

I declare that the research described within this thesis is my own work and that this thesis was composed by myself unless otherwise stated.

The papers selected for this thesis were all papers that I was instrumental in writing. I was involved in their preparation from concept to final publication. The initial idea behind all these papers was mine although several were developed in conjunction with colleagues. The papers others were involved in the initial design of were chapter III which, as a follow on from the paper in chapter II, was suggested by Dr John O'Neill, chapter IV where Dr John Simpson and I co-supervised two medical students on a prospective project and chapter XII which developed out of collaboration with Dr John Reid. Where CT scans were reviewed to confirm a diagnosis, to look for unsuspected PE or to score thrombus load or calculate RV/LV ratio, I did this myself in chapters III, IV, and V. Such cases in chapters VI and XII were reviewed by radiology trainees, whom I supervised, and I adjudicated on cases where a doubt existed as well as confirming the presence of identified unsuspected PE in chapter VI. I also scored a cohort of cases in chapter XII to provide an inter-observer Bland-Altman analysis. Chapter VII was based on results from a venous thrombo-embolism imaging database that I ran and Chapter IX,X and XI were all projects that I devised based on the Scottish Hospital In-Patient Statistics where I approached

Information Statistics Division of the Scottish Health Service and, in conjunction with their staff, devised the projects. The data analysis and statistics for these projects was mainly performed by ISD Scotland but I oversaw the writing up and submission of the papers. Neither this thesis nor any part thereof has been submitted for any other degree or professional qualification.



Dr John Tallach Murchison

25.01.13

Chapter I

Introduction

Venous thromboembolism (VTE) is a common disease with a myriad of presentation. It is often difficult to diagnosis with symptoms which are shared with many other disorders. Because of the overlap in symptomatology with other pathologies it is both commonly overlooked when present and commonly considered when absent. The threshold for investigating suspected VTE has dropped over time, in part due to a greater awareness of the disease among clinicians, but also because of the greater availability of diagnostic tests which are both accurate at positively diagnosing VTE and are patient friendly. This has resulted in a mushrooming of the number of diagnostic tests being performed for suspected VTE in radiology departments. As such radiology provides a window into the disease in a way that no other speciality can. All branches of medicine having their share of VTE patients but radiology provides a unique opportunity to study VTE patients as, no matter from which speciality they arise when the disease is suspected, they will almost inevitably end up undergoing a definitive radiological test. There is much still to learn about VTE however developments in modern imaging and computerised databases have advanced our understanding of this common disease. The window that radiology provides into VTE has contributed towards those advances.

Historical background of the thesis.

When I started as a consultant radiologist the isotope lung scan (ILS) was the imaging method of choice for investigating suspected pulmonary embolism (PE) and contrast venography the principle investigation for suspected deep vein thrombosis (DVT). The main drawback with the ILS is that it uses indirect imaging to detect perfusion abnormalities, for which there are numerous causes, resulting in many diagnostically indeterminate studies.[1] I first developed an interest in VTE in the early 1990s and the first paper which I published on venous thromboembolism addressed the thorny issue of how to managed indeterminate ILS.[2] Imaging for suspected VTE has evolved dramatically over the past two decades. Doppler ultrasound scanning (US), which does not use ionising radiation, and which is quick, easy and patient friendly has now replaced contrast venography for the diagnosis of DVT, and more importantly CT Pulmonary Angiography (CTPA) has replaced the ILS. This single factors more than anything else has revolutionized the diagnosis and understanding of venous thromboembolism. A factor made possible by the advent of helical or volume CT scanning and enhanced by the development in recent years of multi-slice CT scanning. Replacing indirect imaging, with all its inherent uncertainties, with direct imaging, enables confirmation or exclusion of PE with much greater certainty and permits more accurate quantification of thrombus load. It also allows detection of PE in situations where it hasn't been clinically suspected. The

papers which comprise this thesis span this period of cosmic change in VTE diagnosis. Access to a test with a high specificity which enables quantification has opened the door to many new insights into the disease process of venous thrombo-embolism.

Future Directions

Understanding of VTE has improved over recent years and better diagnosis using modern imaging modalities has been the foundation for much of the progress that has been made. Diagnosis of VTE and standards of care for VTE patients are increasingly evidence based but there is still much to learn. Not all cases of VTE are the same and there are many questions about the optimal type of treatment and optimum length of treatment for patients diagnosed with VTE still to be answered. With increasing numbers of cases being diagnosed the pattern of disease has changed and maxims, previously laid down, do not necessarily still apply. Much of the evidence on outcome and treatment is based on historical data where many of the PEs identified were large. With the lowering of thresholds for investigation many more smaller isolated segmental and sub-segmental PEs are being found and it may turn out that these do not need such prolonged treatment or indeed may not need treatment at all. This may be particularly true for the smaller PEs that are detected 'incidentally' during contrast enhanced scans for other indications as demonstrated in chapters VII and VIII. The significance of below knee DVTs is still unclear. These are detected less frequently now that we have moved from contrast

venography to Doppler ultrasound and there is a school of thought that smaller isolated below knee DVTs do not need treated. When we published the paper in Chapter X of this thesis on the distribution of DVT as demonstrated by contrast venography the reviewers suggested that we look at the long term outcome of these patients to cast more light on the significance of below knee DVT, and the need or otherwise for active treatment, particularly to look at the risk of recurrent DVT and of the risk of venous insufficiency syndrome in this cohort. We took this advice and have shown a significant incidence of both conditions in our isolated below knee DVT cohort over time, work which is under preparation for publication. Another area of current uncertainly is how to manage the pregnant patient with suspected PE. Our present protocol uses a combination of isotope lung scan and CTPA with triage depending on CXR findings with this scheme based on radiation dose to mother and child. This is a field where the evidence base is limited and which is likely to be impacted by advances in Magnetic Resonance pulmonary angiography where ionising radiation is avoided and which I am sure will play an increasing part in the imaging of suspected PE. MR Pulmonary angiography is not the only cross-sectional imaging advance. There is now the opportunity for 4D imaging of patients who have suffered a PE with both Volumetric CT and MRI imaging. This allows assessment of residual thrombus load and evaluation of perfusion abnormalities which occur and persist due to micro-vascular occlusion even when there is no morphological imaging evidence of residual thrombus. This has the potential advantage of identifying patients at longer term risk of developing pulmonary hypertension at an earlier stage

permitting tailoring of therapy and earlier therapeutic intervention. This is a field which we are currently actively exploring having attracted a pilot grant and for which we are seeking further funding.

There are many questions still to be answered about VTE. The papers included in this thesis have cast light upon some of the questions that exist but it is hoped that, in collaboration with academic and thoracic clinical colleagues, to further advance the frontiers of VTE understanding for the benefit of patients and of the wider medical community.

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Chapter II

HELICAL CTPA IN THE INVESTIGATION OF PULMONARY EMBOLISM: A 6 YEAR REVIEW

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Clinical Radiology 2004 ;59: 819-825

Abstract.

Purpose: To assess the change in practice and resulting diagnostic outcome in the radiological investigation of pulmonary embolism since the introduction of helical CTPA in a large teaching hospital.

Methods and Materials: A retrospective review was undertaken of all radiological investigations performed over a 6-year period before and after the introduction of CTPA (protocols 1 and 2, respectively) as an integral part of the imaging protocol in the investigation of clinically suspected PE. The total numbers and results of all investigations are assessed for each protocol.

Results: A substantive increase in both the total number of patients and the number of investigations performed for the investigation of PE since the introduction of CTPA occurred. Five hundred and twenty-six patients underwent 617 investigations performed in 1995/1996 with 760 patients undergoing 805 in 2001/2002. There was a significant decrease in the number of investigations per patient, 1.17 in 1995/1996 versus 1.06 in 2001/2002. Primary investigation showed a significant decrease in indeterminate examinations from 25.7% to 8.5% and an increase in positive results for pulmonary embolism from 18% to 24%.

Conclusion: In the study population there was a significant increase in the number of patients being investigated for PE, with a decrease in both the number of non-diagnostic investigations and the total investigations per patient since the introduction of helical *C*TPA. This is probably due to the ready availability of a new imaging technique and

physicians awareness, that CTPA has significantly improved specificity, which encourages the referral of patients for investigation.

Introduction

Pulmonary thromboembolism (PE) is a common condition with significant morbidity and mortality; the latter reaching 30% in some series in untreated cases [1,2]. Appropriate use of anticoagulation or thrombolytic therapy improves outcome with a reduction in mortality to as little as 2.5 %[3]. Therapy however is not risk free and serious complications may occur [4]. Identifying the correct patients to treat is therefore essential. Unfortunately the clinical manifestations of PE are variable and lack specificity to reliably diagnose or exclude clinically significant PE [5]. Imaging is mandatory to confirm the diagnosis but there is no general agreement on the best strategies.

Although chest radiographs are non-specific for PE they are essential in the interpretation of lung scintigrams and may allow an alternative diagnosis that may account for the clinical presentation [6,7]. Lung scintigraphy is a safe and sensitive investigation for suspected acute PE [8]. The main drawback with this technique is the high proportion of indeterminate examinations requiring further investigations [8,9]. Pulmonary angiography has been considered the gold standard in the investigation of PE but is usually reserved for those cases deemed indeterminate by first line non-invasive tests. It is an invasive investigation, is not universally available and has a small

but recognised morbidity and mortality [8]. This may account for its low utilisation; less than 2% in some studies [10,11]. Helical computed tomographic pulmonary angiogaphy (CTPA) and the newer multi-slice CTPA have changed the investigation of PE. Multiple studies have reviewed CTPA against both formal pulmonary angiography and ventilation/perfusion nuclear imaging(V/Q) and have consistently demonstrated a high sensitivity and specificity [12-17, 20] with good inter-observer agreement [18]. It is only minimally invasive and allows direct visualization of the thrombus and thrombus load. Single slice helical CTPA is largely limited to demonstrating PE to segmental artery level at present whereas multi-slice CTPA can show subsegmental PE. Whether subsegmental emboli contribute significantly to morbidity and mortality is debatable [19]. Multi-slice CTPA can visualize subsegmental PE, is minimally invasive, and is replacing conventional pulmonary angiogram as the gold standard [24].

Previous studies have reviewed different protocols for the investigation of PE with a combination of CTPA and lung scintigrams [21,23]. Within our centre we use a combined protocol incorporating both perfusion (Q) lung imaging and CTPA. The purpose of the present study was to assess the change in practice and resulting diagnostic outcome in the radiological investigation of pulmonary embolism since the introduction of CTPA.

Materials and Method

A retrospective review was carried out of all radiological investigations performed in patients with clinically suspected PE. In total six years were reviewed, commencing one year prior to the introduction of CTPA as an integral part of the imaging protocol in the investigation of PE, thereby allowing assessment of two protocols (Fig 1&2). Protocol 1 was employed before the introduction of CTPA and protocol 2 after it was introduced into the diagnostic algorithm. The total number and results of all investigations in both protocols were reviewed for the first and last years. Local population served remained unchanged throughout the study.

Lung scintigrams were obtained using a GE MaxiCamera 400 (Single Head) Gamma camera. 80MBq technetium-99m macroaggegated albumin (MAA) was injected via a peripheral intravenous cannula with saline flush. Images were acquired in anterior, posterior, right and left anterior and posterior oblique projections, with 400,000 counts per image. Those patients requiring ventilation as part of this study (protocol 1) received 160MBq of Xenon133 via aerosol. Reports were divided into three groups, normal, indeterminate and high probability with the first and last as described in PIOPED [8] and all other findings grouped as indeterminate. CTPA was performed on a GE HiSpeed Advance CT (Milwaukee, WI, USA).

100 millilitres of non-ionic contrast media (Niopam 300mg/ml), diluted with 40mls of saline, was injected via a 16 or 18G needle in the antecubital fossa at a rate of 4mls/sec.

Images were obtained with a delay of between 10 and15 seconds, depending on the patients cardiac status, from diaphragm to aortic arch (pitch of 1.7, 3mm slice thickness with image reconstruction at 1.5mm intervals). Venography and Doppler examinations are well recognized investigations for deep venous thrombotic disease and were performed using standard protocols. Conventional pulmonary angiography was performed using a femoral approach and 100cm 5F pigtail catheter. Selective right and left main pulmonary artery runs with AP and 30^0 anterior oblique views were performed. Coned segmental runs were acquired when indicated.

Results

In the first year 526 patients were investigated for PE, using protocol 1, with 617 examinations performed, equivalent to 1.17 per patient. All patients had chest radiographs as part of their investigation in both protocols. These have not been included in the assessment of the number of investigations each patient underwent. Five hundred and twenty six lung scintigrams studies demonstrated a combined positive or normal result in 74% with the remaining 26% being indeterminate. Additional investigations were performed in 63% in the latter group or 17% of the total number of patients (Table 1). Pulmonary angiography was performed in only 7.4% of indeterminate cases and is in line with other studies[10,11]. In 9% of second line investigations results were not available for the study.

In the final year of the study 760 patients were investigated for clinically suspected PE, using protocol 2, with 805 investigations, equivalent to 1.06 per patient. This is a 44.5% increase in the total number of patients being investigated. CTPA was the primary investigation in 59% of patients and was diagnostic, i.e. positive or negative for PE in 97.6%. Q was performed in the remaining 41%. This examination was diagnostic in 80% with 21% indeterminate. Further investigations included CTPA in 48% of the indeterminate group from the perfusion arm with 26% of these secondary investigations being positive (Table 2).

All statistical analysis was performed comparing proportions using Chi-square with SAS/STAT version 8.2 (SAS Institute, Cary, NC, USA). Forty-four percent more patients were investigated for PE in the year 2001/2002 with protocol 2 versus the year 1995/1996 with protocol 1, $p<0.001$. Our hypothesis is that with the advent of CPTA more physicians were referring their patients for diagnostic tests.

When comparing patients being investigated with protocol 2 vs protocol 1, patients in protocol 2 had a statistically significant higher initial diagnostic test (either positive or negative) 90% versus 74 % in protocol one ($p<0.0001$). This result supports our finding that patients being investigated under protocol 2 had overall less diagnostic tests performed 1.06 compared to 1.17 tests per patient with protocol 1.

Total CTPA and lung scintigram, combined ventilation/perfusion and sole ventilation, examinations were reviewed over the six-year period, 1995-2002 (fig 3). This demonstrates a 51% increase in the total number of investigations during this time.

From its first year of introduction CTPA has increased rapidly with significant more CPTAs performed now than lung scintigrams. Lung perfusion examinations have decreased but at a slower rate than the increase in CTPA, reflecting the significant rise in patients being investigated.

The first year of the study had a male/female ratio of 48/52% with a mean age of 51.8/52.5 years respectively with the same age range (17-98). The final year had a male/female ratio of 51/49 with a mean age of 60.4/56 respectively and an age range of 19-98.

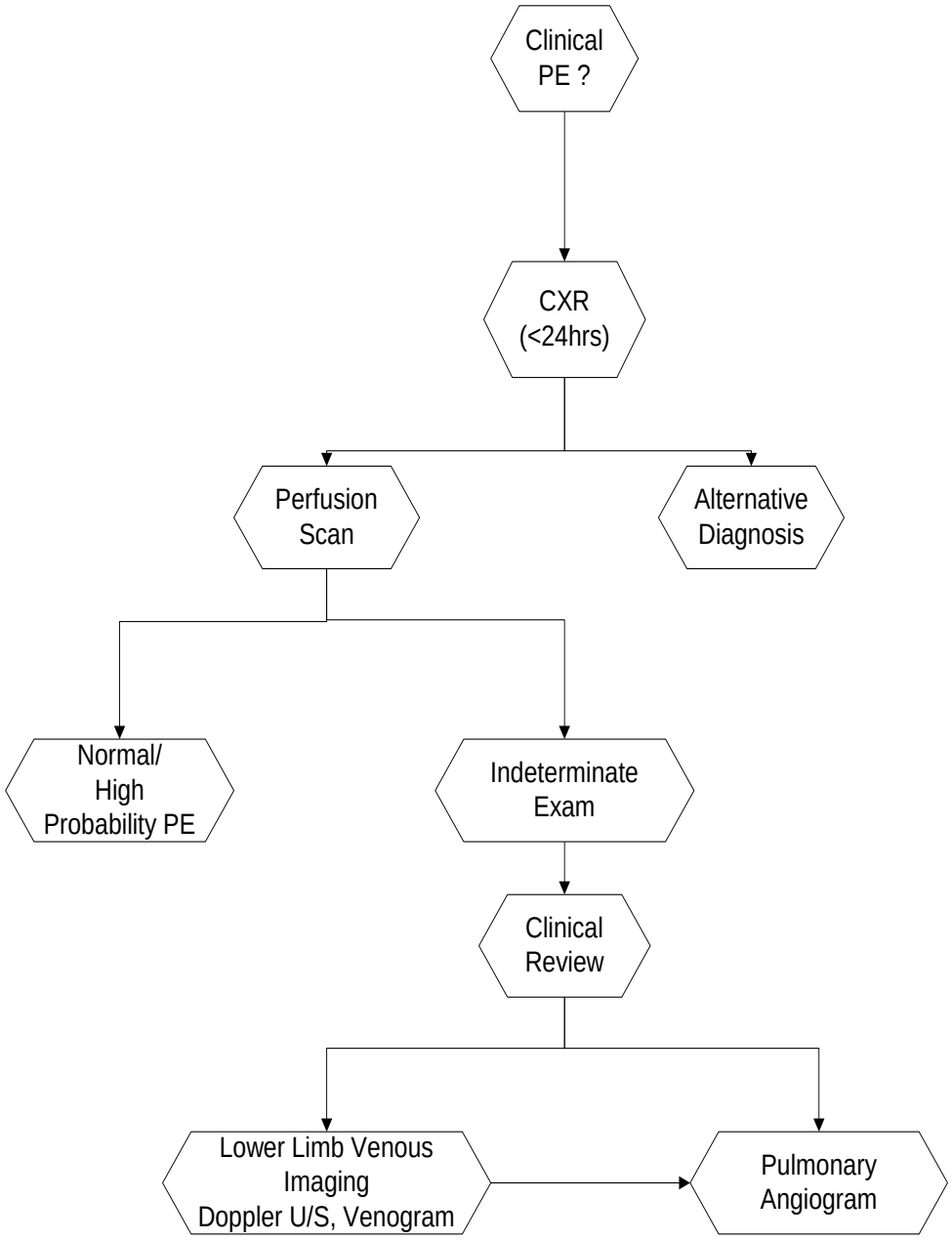


Figure 1 Protocol 1

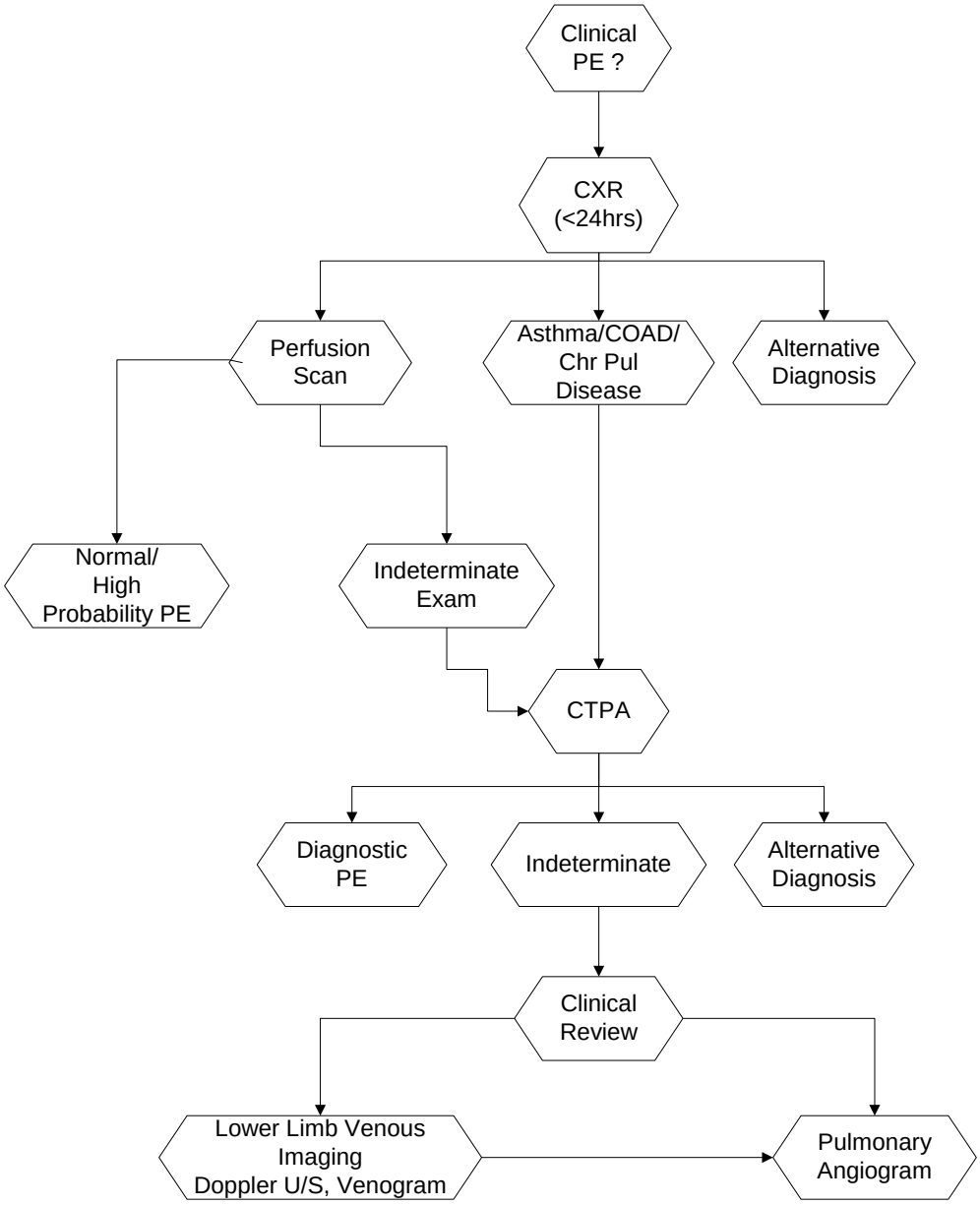
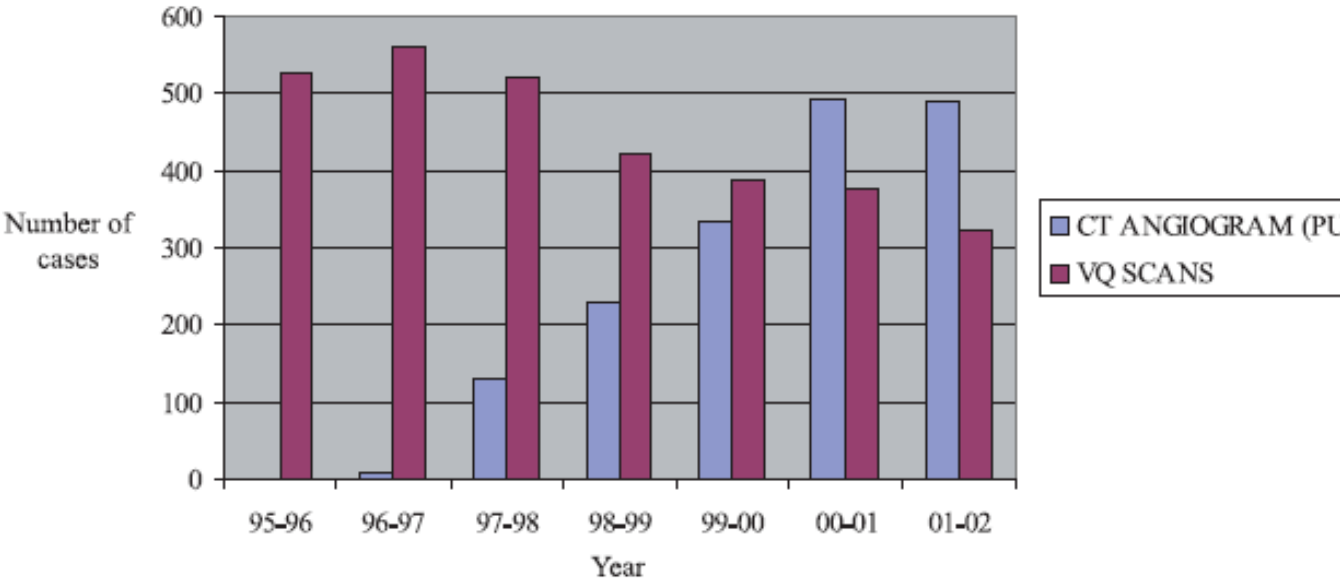


Figure 2 Protocol 2

Figure 3 Comparison of CTPA/CPA and lung scintigrams



Discussion

The current debate in the diagnostic imaging of pulmonary embolism focuses on whether CTPA should be a primary or secondary investigation. In the majority of hospitals it is established as an integral part of the algorithm for investigation suspected pulmonary embolus although its role varies from institution to institution. Our current protocol incorporates its use depending on both the clinical presentation and chest radiograph findings. This may change with the introduction of multi-slice CT as the increased sensitivity of CTPA is likely to result in even greater utilization of CTPA as a primary investigative tool.

All diagnostic imaging tests for PE have their limitations. CXR demonstrate abnormalities in the vast majority of patients with clinically suspected PE regardless of the final diagnosis. Chest radiographs are normal in 12 and 18% of patients with and without PE respectively in those patients who are clinically suspected to have PE and have a negative predictive value of 74%[8]. They do however present alternative diagnoses, a baseline from which to follow the patient radiologically, and in our institution a simple method to assess which arm of the protocol a patient enters [19]. In this study, after the introduction of CTPA, patients who had a normal CXR without a history of chronic lung disease received a perfusion scan (protocol 2), the remaining patients were allocated to CTPA. The ventilation scintigraphy was not performed in the former group as it provides no significant change in sensitivity and specificity [9,13,22].

Table 1 Results from protocol 1

Primary Investigation	V/Q	Secondary Investigations (Indeterminate group)	Conventional Pul Angio	Venography	Doppler Ultrasound
Positive	18%		40%	28 %	41%
Normal	56.3%		60%	59%	59%
Indeterminate	25.6%		0%	13%Result navailable	0%
Total	100%(526)		100% (10)	100% (64)	100%(17)

Numbers of patients given in parenthesis. venography, conventional pulmonary angiography, lower limb Doppler imaging

The percentage of patients referred for lung scintigraphy changed dramatically in protocol 2 with the majority of patients (59.3%), allocated to CTPA. Decreases in the

indeterminate results in scintigraphy occurred, 25.6% and 20.7% in protocol 1 & 2 respectively, which can be accounted by the exclusion of patients with an abnormal CXR and/or chronic lung disease who are more likely to have a non-diagnostic lung scan[19]. In addition however there was a significant drop in the total number of indeterminate investigations from 25.6% to 9.9%. The corresponding increase in diagnostic outcome rose from 74.3% to 90.1% of first line radiological investigations. Second line investigations decreased from 17.3% in protocol 1 to 5.9% in protocol 2 in line with the dramatic decrease in indeterminate results.

Comparison with previous studies was not directly possible because, on review of the relevant literature on Medline, no study incorporated our second diagnostic protocol. Our first protocol however can be compared. The number of positive scintigraphic studies is compatible with previous studies [8,9,21], but there is a notable increase in the number of negative studies that is present in both protocol arms. This finding may be due to a lower clinical threshold for referral.

Table 2a Results protocol 2 initial imaging

	CTPA	Perfusion nuclear imaging
Positive	30%	15%
Normal	68%	64%
Indeterminate	2%	21%
Total	100% (451)	100% (309)

Table 2b secondary investigations for the indeterminate group with protocol 2.

	Conventional Pulmonary Angiogram	Venography	Doppler	CTPA (Q indeterminate)	Q (CTPA indeterminate)
Pos	0	43%	67%	26%	0
Neg	100%	57%	33%	74%	100%
Indet	0	0	0	0	0
Total	100%(1)	100% (7)	100%(6)	100%(31)	100%(1)

Numbers patients given in parenthesis. CTPA, pulmonary angiography, venography, conventional lower limb venography, lower limb venous Doppler imaging, Q, perfusion nuclear imaging

The expected increase in referrals with the introduction of a new imaging technique, CTPA, took place with a year on year rise for the first four years with a temporary plateau in the latter two years. Review of the most recent figures (April 2003) has demonstrated a further significant rise in utilization of CTPA to 707 for the twelve months since the end of the study. This rise is likely due to greater access to our CT scanner and a lower clinical threshold. The corresponding drop in perfusion examinations, 41%, showed a slower decline in the last year, 299 in the most recent figures, but may continue to decrease further with longer term follow-up.

The steadily increasing demand for CTPA within our institution needs to be addressed. Recently published British Thoracic Society guidelines for the management of suspected PE stresses the importance of clinical probability assessment in the initial patient review and highlights the role of D-dimer testing [25]. We intend to adopt these guidelines in a locally tailored version and commence D-dimer testing. Lung scintigraphy, in those with a normal CXR, remains an integral part of our protocol and thus reduces the demand that would be placed on CTPA if the latter were the sole primary imaging investigation.

In conclusion our results demonstrate a significant increase in the number of patients being investigated for pulmonary embolism in our institution with a decrease in the number of non-diagnostic investigations since the introduction of helical CTPA. This may be due to a combination of factors. The introduction of a new imaging technique has focused both physicians and radiologists on a potentially lethal and relatively common condition. This increased awareness, combined with the knowledge that CTPA has a significantly improved specificity, encourages physicians to refer patients for investigation. The introduction of CTPA and a new investigative protocol has produced more clinically diagnostic studies giving clinicians a firmer basis for making therapeutic decisions.

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Chapter III

EFFECT OF THE INTRODUCTION OF HELICAL COMPUTED TOMOGRAPHY ON RADIATION DOSE IN THE INVESTIGATION OF PULMONARY EMBOLISM

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ABSTRACT

Aim:

To assess the change in patient radiation dose in the radiological investigation of pulmonary embolism since the introduction of helical Computed Tomography Pulmonary Angiogram (CTPA) in a large teaching hospital.

Methods and Materials:

All radiological investigations performed as an integral part of the imaging protocol in the investigation of clinically suspected pulmonary embolism (PE) over a six year period before and after the introduction of CTPA were retrospectively reviewed. The protocol for investigation of PE changed in our institution after the introduction of CTPA. Protocols 1 and 2 were protocols in place before and after the introduction of CTPA, respectively. An In-depth evaluation was made of the imaging records and radiation dose for 30 consecutive patients investigated for clinically suspected PE in 1995 (protocol 1) and 2002 (protocol 2). Radiation doses were then extrapolated for the total number of patients investigated in each year.

Results:

The number of radiological investigations performed per patient decreased from a mean of 1.17 in protocol 1 to 1.06 in protocol 2. There was a 44% increase in the total number

of patients investigated. The effective dose per patient increased from 1.30mSv to 1.35mSv with the introduction of CTPA into the imaging protocol, an increase of only 4%. First line investigations showed a significant decrease in indeterminate examinations from 25.7% to 8.5%.

Conclusion:

Two different imaging protocols are reviewed with respect to type and number of procedures required for the investigation of PE and the resulting patient effective dose incurred. Results demonstrate an increase in the number of patients being investigated for suspected PE and a small increase in effective dose per patient since the introduction of helical CTPA. Although CTPA in itself incurs a higher effective dose, this is offset by the significant decrease in the number of non-diagnostic and total number of investigations per patient. We hope that this paper will serve as a stimulus for the radiological community to examine current protocols in all areas of diagnostic imaging. We stress the importance of assessing new and established imaging protocols to maximise the benefit and reduce the risk to patients.

Introduction

The introduction of a new diagnostic imaging test in the investigative protocol for the diagnosis and management of patient pathology requires the fulfilment of several criteria. The predominant criteria is that the benefit of the test outweigh any incurred risks and

that this benefit/risk ratio is equal to or greater than the imaging tests already in place. In the investigation of pulmonary embolism (PE) helical computed tomographic pulmonary angiogaphy (CTPA) and the newer multi-slice CTPA require both the use of ionising radiation and intravenous contrast material (IVCM) which can be considered risk factors. The risk of adverse reactions from IVCM is established but to our knowledge there has been no review of the radiation dose incurred in this new investigation as part of a diagnostic imaging protocol with direct comparison to those imaging tests previously available. The purpose of our study is to assess what impact the introduction of helical CTPA in the investigation protocol of pulmonary embolism has had on patient radiation dose. In addition we review the measurement of this radiation dose and the significance of this to the patient.

Pulmonary embolism is a common condition with significant morbidity and mortality, the latter reaching 30% in some series in untreated cases.[1,2] Appropriate use of anticoagulation or thrombolytic therapy improves outcome with a reduction in mortality to as little as 2.5%. [3] Therapy however is not risk free and serious complications may occur. [4] Identifying the correct patients to treat is therefore essential. Unfortunately the clinical manifestations of PE are variable and lack specificity to reliably diagnose or exclude clinically significant PE. [5] Imaging is mandatory to confirm the diagnosis but conventional strategies have been imprecise. [6]

Multiple studies have reviewed CTPA against both formal pulmonary angiography and radionuclide ventilation/ perfusion (V/Q) imaging and have consistently demonstrated a

high sensitivity and specificity.[7-12] It is only minimally invasive, allows direct visualization of the thrombus and thrombus load. However demonstration of PE in vessels beyond segmental artery level is limited at present for single slice CT. Whether sub-segmental emboli contribute significantly to morbidity and mortality is debatable. [13]

The dosimetric measurement that provides a direct relationship to the radiation hazard is the effective dose (ED). This was introduced in 1990 by the International Commission on radiation protection and is defined by the sum of the products of the equivalent organ dose and its relevant organ weighting factor for all tissues and organs within the body. It is therefore not measured directly. Expressing the dose in the form of an effective dose allows the relative biological effect and therefore the relative risk of different radiation doses to be compared directly. It is the most appropriate measurement for use in this study due to the use of different imaging modalities which employ different types of radiation

Materials and Method

A retrospective review of imaging protocols for the investigation of PE pre and post the introduction of CTPA was performed. Protocol 1 and 2 were assigned to the imaging protocols in place in our centre before and after the introduction of CTPA, respectively (figures 1 and 2). Imaging records and radiation dose for 30 consecutive patients investigated for clinically suspected PE in 1995 were reviewed. Plain radiographs were a necessary part of both protocols and therefore were excluded from further calculations assessing the change, if any, in effective dose. Radionuclide lung scintigrams (V/Q) and

where appropriate lower limb venography and conventional pulmonary angiograms were assessed. The process was repeated in 2002 using the same parameters with the addition of CTPA. Due to the small number of conventional pulmonary angiograms, each of these studies was separately assessed for ED. The same applies to the seven cases of lower limb venography in protocol 2, with 20 cases assessed for protocol 1. Both years were then assessed with respect to the total number of radiological investigations performed for clinically suspected PE and the total effective doses involved. Patients in protocol 2 had a perfusion scan performed if the chest radiograph was normal and there was no history of chronic pulmonary disease. If the chest radiograph provided an alternative diagnosis, no further imaging was performed with respect to PE unless there was a high clinical suspicion of concurrent PE. Otherwise the remaining patients proceeded to CTPA.

Radio-nuclide lung scintigrams were obtained using a GE Maxi Camera 400 (Single Head) Gamma camera. 80MBq technetium-99m macro-aggregated albumin (MAA) was injected via a peripheral intravenous cannula with saline flush. Images were obtained in anterior, posterior, right and left anterior and posterior oblique, with 400,000 counts per image. Those patients requiring ventilation as part of this study, protocol1, received 160MBq of xenon-133 via aerosol. Reports were divided into three groups, normal, indeterminate and high probability and assessed in conjunction with the clinical presentation.

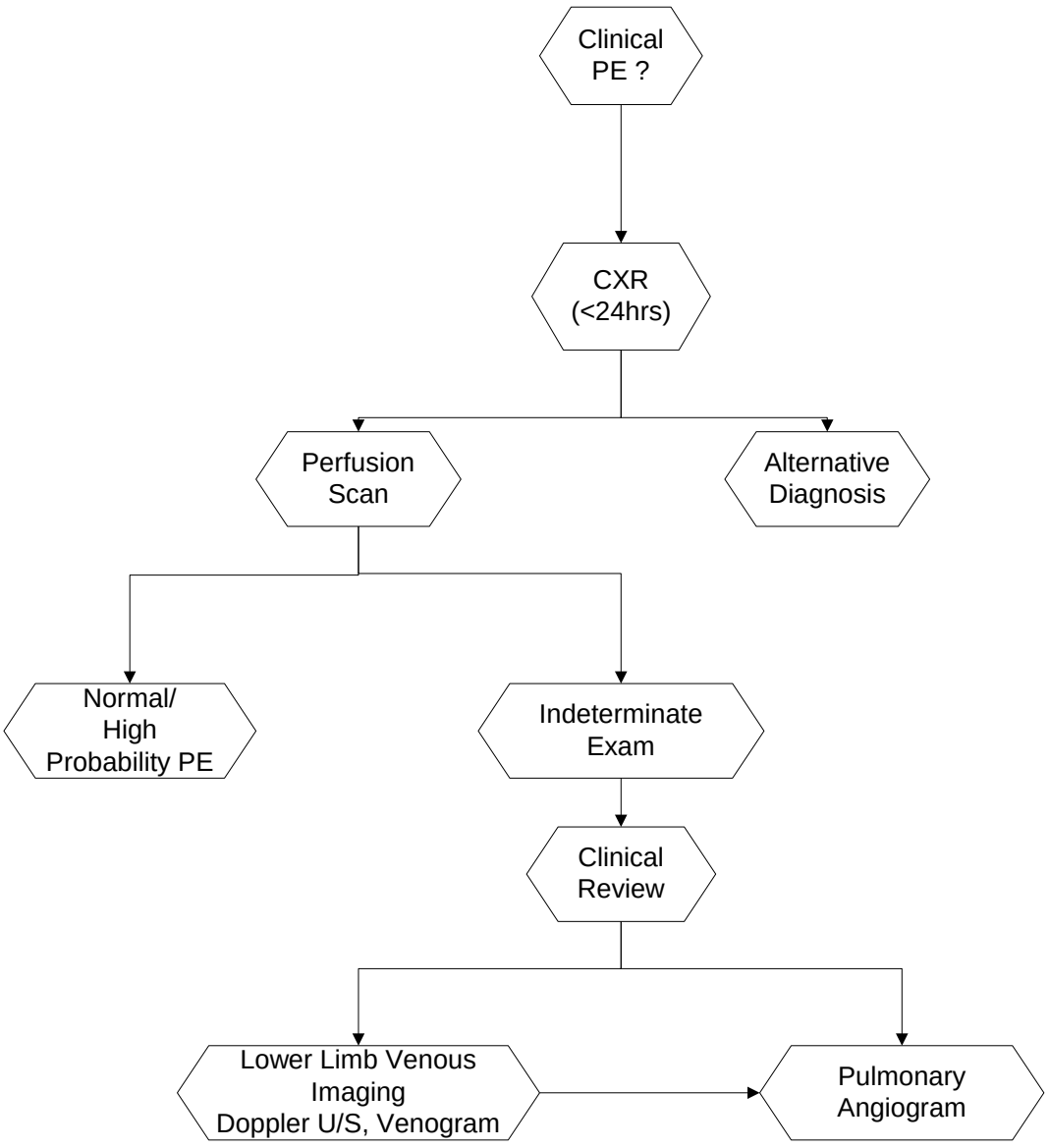

Fig 1-Protocol 1 radiological investigation clinically suspected pulmonary embolism (PE) pre CT pulmonary angiography (CTPA). CXR, chest radiograph; U/S, ultrasound.

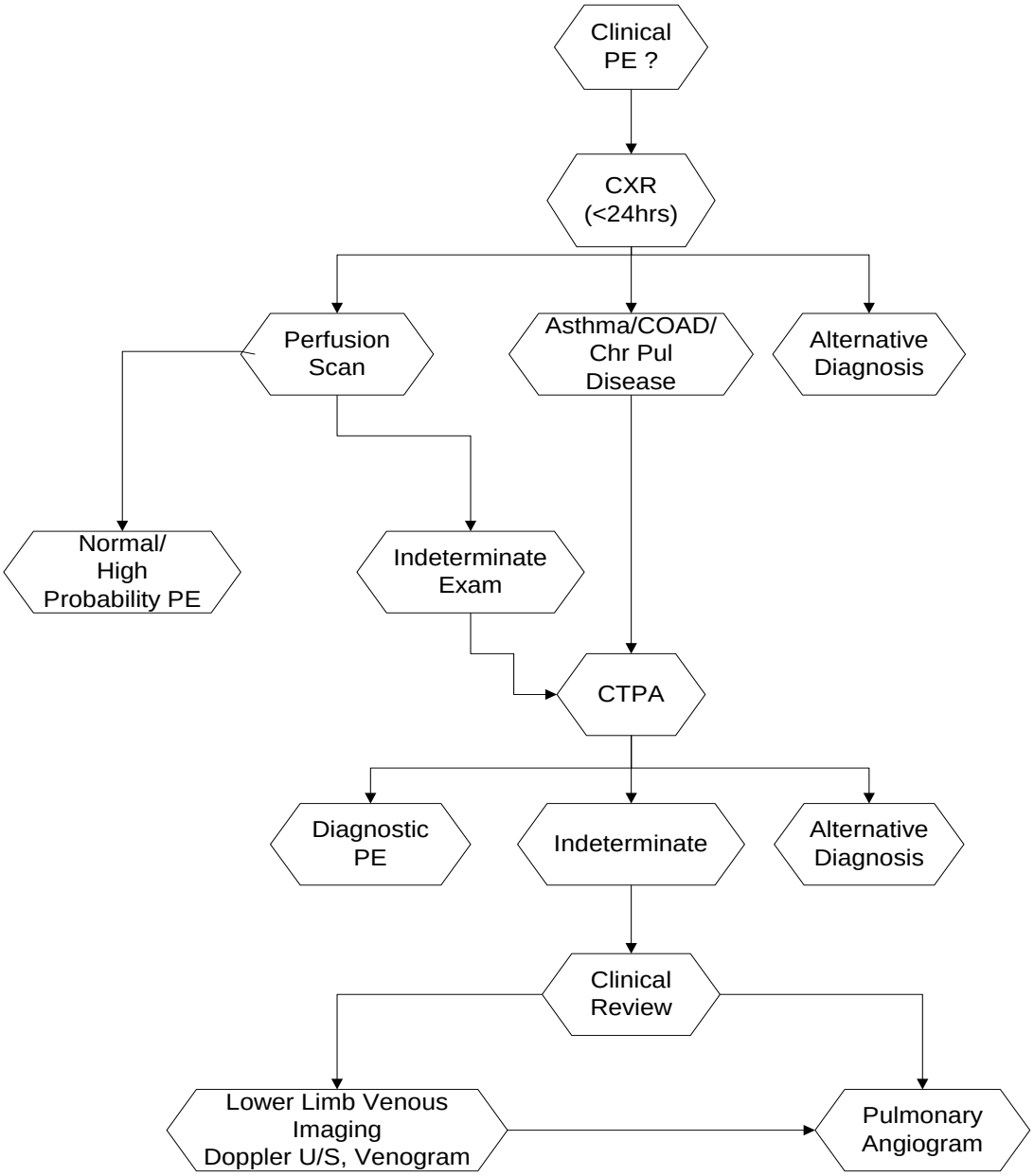

Fig 2-Protocol 2 Radiological investigation of clinically suspected Pulmonary embolism post introduction of CT pulmonary angiography (CTPA). CXR, chest radiograph; U/S, ultrasound

CTPA was performed on a GE HiSpeed Advance CT machine (Milwaukee, WI, USA). 100 MLS non-ionic contrast media (Niopam 300mg/ml) diluted with 40mls of saline was injected via a 16 or 18G needle in the ante-cubital fossa at a rate of 4mls/sec. Images were obtained with a delay of between 10-15 seconds, depending on the patients cardiac status, from diaphragm to aortic arch using a pitch of 1.7, 3mm slice thickness with image reconstruction at 1.5mm intervals. kVp, mA and the number of slices per examination were noted.

Venography and Doppler examinations are well recognized investigations for deep venous thromboembolic disease and were performed using standard protocols. Conventional pulmonary angiography was performed using a femoral approach and 100cm 5F pigtail catheter. Selective right and left main pulmonary artery runs with AP and 30^0 anterior oblique views were performed. Coned segmental runs were acquired when indicated

Patient Dosimetry.

Doses for CT scanning were calculated from the CT dose index measured in air ($CTDI_{air}$) using the matched scanner technique developed by ImPACT [(14)]. Patient organ and effective doses from CT examinations use the NRPB Monte Carlo dose data for CT scanners [(18)]. Doses for the radionuclide studies were derived from activity using ARSAC Notes for Guidance [(15)].

For conventional pulmonary angiography and for venography,, effective dose was calculated from dose-area product (DAP) using conversion factors taken from Hart *et al* [16]. All dose calculations assume that the patients have an average build.

Table 1: Results Protocol 1; %=()

Primary Investigation	V/Q	Secondary ***Investigations*** (Indeterminate Group)	Pul Angio	Venography	Doppler US
Positive	95(18)		4(40)	18(28)	7(41)
Normal	296(56.3)		6(60)	38(59)	10(59)
Indeterminate	135(25.6)		0	8(12.5) result unavailable	0
Total	526		10	64	17

Results

The dose for CTPA was calculated for 16 patients. The average ED was 1.6mSv The standard scanning protocol was used for all patients with the only variant being the scanned length varying from 78mm to 108 mm leading to a relatively small range of ED (1.4-1.9 mSv). V/Q (protocol 1) and Q (protocol 2) imaging were associated with doses of 1.2 mSv and 0.8 mSv, respectively, with no variation since the same activity was used for all patients. Doses for lower limb and pelvic venography were assessed for 12 patients. For these patients the average DAP was 3.1 Gy cm^2 (range 1.7 to 7.2) from which it was estimated that the average ED was 0.3 mSv. Doses for conventional pulmonary angiography were assessed for three patients. The average DAP was 21.3 Gy cm2 from which ED equal to 3.2 mSv was calculated (range 2.3 to 4.1 mSv).

Both years were then reviewed with respect to total investigations and results. In the first year 526 patients were investigated for PE with 617 examinations performed, equivalent to 1.17 per patient. 526 V/Q studies demonstrated a combined positive or normal result in 74.3% with the remaining 25.7% been indeterminate. Additional investigations in the latter group were performed in 63% (Table 1). The average effective dose was 1.30 per patient with 92% of this average being attributed to the V/Q studies. (Table 2).

Table 2: Effective dose (mSv) per Examination Protocol 1

Investigation	ED	Patient No	Total ED
V/Q	1.2	526	631.2
Pul Angio	3.2	10	32
Venography	0.3	64	19.2
Doppler Ultrasound	0.0	17	0.0

Mean ED per patient = 1.30mSv

In the final year of the study 760 patients were investigated for clinically suspected PE, with 805 investigations, equivalent to 1.06 investigations per patient. CTPA was diagnostic in 97.8%, been the primary investigation in 59.3% of patients with Q lung scanning in the remaining 40.7%. The latter examination was diagnostic in 79.3% with 21% indeterminate. Further investigations included CTPA in 48% of the indeterminate group with 26% been positive (Table 3).

Table 3 (a and b) Results Protocol 2, %=()

a) Primary investigation

	CTPA	Q
Positive	136(30.1)	47(15.3)
Normal	304(67.4)	198(64)
Indeterminate	11(2.4)	64(20.7)
Total	451	309

b) Secondary Investigations (Indeterminate Group)

	Pul Angio	Venogram	Doppler	CTPA (Q Indeterminate)	Q (CTPA Indeterminate)
Positive	0	3	4	8(26)	0
Normal	1	4	2	23(74)	1
Indeterminate	0	0	0	0	0
Total	1	7	6	31	1

2.2% of CTPA examinations were indeterminate. In 8.9% of patients in the second protocol further investigations were performed due to discrepancy between the clinical and radiological diagnosis and to assess the presence and extent of peripheral thrombus. The average effective dose was 1.35mSv per patient with 24% and 75% of this being attributed to Q studies and CTPA, respectively (Table 4)

Table 4: Effective dose (mSv) per Examination Protocol 2

Investigation	ED	Patient No	Total ED
Q	0.8	309	247.2
Pul Angio	3.2	1	3.2
Venography	0.3	7	2.1
Doppler Ultrasound	0.0	6	0.0
CTPA (Total)	1.6	482	772.8

Mean ED per patient = 1.35mSv

Discussion

Radiological examinations are required to conform to two principles: justification to ensure that the benefit outweighs the risk, and optimization to ensure that dose is kept as low as reasonably achievable (ALARA) consistent with the clinical imperative for accurate diagnosis. In radiology using ionising radiations, risk is assumed to be proportional to effective dose. In evaluating any new investigation protocol, it is not only necessary to consider the benefits in terms of diagnostic accuracy and patient acceptability, the risks, including the radiation risks, must also be assessed. Radiation risks are assessed in terms of affective dose and for the general population, the fatal cancer risk has been estimated to be 5% per sievert [(17)]. In this study we have considered the radiation risks for two protocols. In protocol 1 all patients for whom PE was not excluded by a preliminary chest X-ray had V/Q scans with an average of 0.16 additional follow up radiology investigations, the average patient dose was 1.3mSv. More recently

(in protocol 2) the chest X-ray has been used to determine whether a perfusion scan or a CT pulmonary angiogram is the most appropriate investigation. For this protocol the number of follow up radiological investigations was reduced (to an average of 0.07 per patient) and the average effective dose per patient (1.35 mSv) was not significantly different. The overall radiological risk for the two protocols is therefore in the range of 6 to 7 fatal cancers per 100 000.

There are significant uncertainties in the estimation of effective dose from the measurable dosimetry quantities, *i.e*. activity, DAP and CTDI. In each case the standard conversion factors from the measured quantity to ED are taken from calculations based on a mathematical phantom representing an average sized person. The inherent uncertainties in the calculation depend on whether it is an internal radiation source, as in radionuclide imaging, or whether it is an external source, CT or conventional angiography. There are additional uncertainties introduced into the CT dose calculation due to the use of the scanner matching method used in the ImPACT dose calculator [(14)]. There are also patient-to-patient dose variations, the effect of which may have influenced the results of the study due to the relatively low proportion of the full patient cohort for whom doses were assessed. However, the effect of these variations was minimized by standardization of the three principle investigations. In protocol 1, 92% of the average patient dose was from the V/Q scan for which a standard activity was administered. In protocol 2, 24% of the dose was from perfusion scans with a standard activity and 75% of the dose from CTPA in which the maximum to minimum dose ratio assessed for 16 patients was 1.36. The much

bigger uncertainties in the dose for the other examinations (venography and conventional angiography) therefore have little significance in the overall conclusions.

The results are for a particular model of a single slice helical scanner used for CTPA in this Hospital at the time of this study. The variation in dose between different models of scanners and between different institutes is known to be very large, *e.g.* by a factor of 8.4 for routine chest CT in an early CT dose survey [19]. It should also be noted that it is increasingly common to use mult-islice scanners for CTPA studies for which the dose might be expected to be higher than reported here due to the use of a lower effective pitch. Notwithstanding these reservations regarding the dose which might be given elsewhere, it has been demonstrated that it is possible to use CTPA in protocol 2 without a significant increase in effective dose and thus in radiation risk.

The new diagnostic protocol that we present has a minimal increase in effective dose. The ED for CTPA is higher than perfusion or V/Q scans and the role and position CTPA in other diagnostic protocols must be carefully examined so the patient receives the optimum benefit while minimizing risk.

In conclusion, our study has reviewed the total effective dose of the diagnostic imaging protocols as outlined above pre and post introduction of CTPA. Although in itself CTPA has a higher ED than the previously used V/Q imaging, the reduction in the number of additional investigations, and performing perfusion only for lung scitigraphy in protocol 2, has limited its impact from an ED viewpoint. With the introduction of CTPA there has

been a significant increase in the total number of patients investigated, which is likely due to a multitude of factors including increased awareness of a disease with the advent of a new diagnostic tool, , a reduction in the numbers of non-diagnostic results and the possibility of identifying alternative diagnosis. This has led to a corresponding increase in the total population radiation dose but only a minimal increase in the ED per patient investigated. This must be balanced against the social, economic and patient benefit due to the reduced number of examinations performed per patient and the significant reduction in the number of non-diagnostic examinations of a potentially fatal medical condition. The study will serve as a valuable baseline for the assessment of multi-slice CT with respect to ED. We hope this paper will serve as a stimulus for the radiology community to examine current protocols in all areas of diagnostic imaging. We stress the importance of assessing new and established imaging investigative protocols to maximize the benefit and reduce any risk to patients.

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Chapter IV

CLINICALLY SUSPECTED ACUTE PULMONARY EMBOLISM (PE): HOW DO OUTCOME AND CLINICO-RADIOLOGICAL FEATURES COMPARE IN PATIENTS WITH AND WITHOUT ACUTE PE?

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ABSTRACT

Background.

Relatively little is known about the prognosis of patients in whom clinically suspected pulmonary embolism (PE) is refuted by diagnostic imaging.

Aim.

This prospective study of suspected PE therefore compared clinico-radiological features and outcome in patients with and without PE.

Methods.

Computed tomographic pulmonary angiography (CTPA) confirmed or refuted PE in consecutive patients. Clinical, laboratory and radiological features were recorded at baseline, and mortality at 1 year determined. Univariate and multivariate analyses identified variables associated with PE.

Results.

PE was diagnosed in 45 patients and refuted in 141. The PE and 'non-PE' groups were similar with regard to extravascular radiology (though consolidation was significantly more common in the PE group [present in 24 (53%) of the PE group and 42 (30%) of the non-PE group, $P<0.01$)], co-morbidities (no significant differences), and baseline characteristics (only serum D-dimer concentrations were independently associated with PE by multivariate analysis, P=0.001). Right ventricular dimensions were significantly

higher in the PE group, [right ventricular to left ventricular ratio was 0.98 (range 0.64-2.48) in the PE group and 0.92 (range 0.66-1.950 in the non-PE group, $P < 0.05$). In the PE group, right ventricular dimensions rose sharply when 10 or more segmental pulmonary arteries were occluded. One year all cause mortality was 6.7% in the PE group and 13.5% in the non-PE group (no significant difference P=0.218).

Conclusion.

Among a cohort of patients presenting with clinically suspected PE, clinical characteristics, co-morbidities and radiological features were similar when comparing groups with CTPA-proven or CTPA refuted PE. However RV dimensions, radiological consolidation on imaging and D-dimer levels were significantly higher in the PE group. Patients with suspected PE have a poor prognosis irrespective of whether PE is confirmed. This appears accentuated in patients without PE, a finding possibly under-recognised in clinical practice.

INTRODUCTION

The annual incidence of PE has been estimated at up to 70 per 100,000 placing a massive strain on health resources [1,2] Acute pulmonary embolism (PE) has been estimated to cause over 50,000 deaths per annum in the United States.'[3]

However the clinical diagnosis of acute PE remains notoriously difficult.[4] Among patients with clinically suspected PE who proceed to diagnostic imaging, objective evidence for thrombus in the pulmonary arteries is typically found in around 20%. Clinical outcomes

after PE have been carefully characterised in previous studies. [5-12] However less is known about the clinical features and outcomes of patients in whom diagnostic imaging refutes PE. By definition these patients present with clinical features mimicking PE. While this heterogeneous subgroup has been studied with respect to the risk of subsequent venous thromboembolism,[13-15] few studies have characterised clinico-radiological features and all-cause mortality in detail.

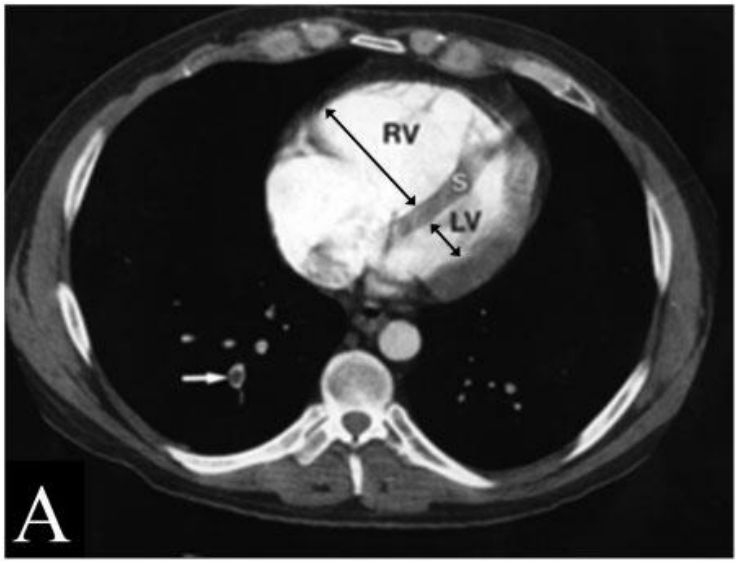

Figure 1. CTPA demonstrates pulmonary embolism and associated right ventricular dilatation. Black arrows demonstrate maximal end-diastolic dimensions of the right ventricle (RV) and left ventricle (LV), showing RV dilatation and septal (S) bowing. The white arrow demonstrates a segmental right lower lobe thrombus.

With this in mind our primary aims were to establish whether patients presenting acutely with suspected PE have a worse outcome if PE is proven, and also whether co-morbidities or radiological changes in the lungs (assessed by CTPA) were differentially distributed in the PE and non-PE groups. CTPA allows detection of pulmonary emboli to the level of

sub-segmental arteries. CTPA also has the advantage of simultaneously assessing the lung parenchyma, the extent of thrombus in the pulmonary arterial tree, and cardiac dimensions.[16-19] Secondary aims of this study were therefore a) to compare right ventricular dimensions in patients with and without PE, and b) to assess the relationship between right ventricular dilatation, thrombus load and outcome within the group of patients with confirmed PE.

METHODS

This was a prospective, observational, non-interventional cohort study performed in a single university teaching hospital over 4.5 months. Eligible patients were those presenting acutely to hospital in whom admitting physicians were sufficiently suspicious of acute PE to request a CTPA, completion of which triggered entry into the study.

The route of entry to the study was designed to be pragmatic and to reflect 'real life', ie CTPA requests were not influenced by the study team and use of pre-test prediction models was entirely at the discretion of the referring physician. Patients who were already in-patients at the time PE was suspected were not included. CTPAs were performed using a multislice CT scanner (Aquilion 16, Toshiba Medical Systems Ltd) and 1mm collimation with images viewed on a Vitrea Workstation (Toshiba Report Direct V500). CTPAs were reported by the hospital's diagnostic service. However all scans were independently reviewed by an experienced pulmonary radiologist (JTM).

Table 1 Univariate analysis of clinical variables in PE and non-PE groups

	PE group		Non-PE group		
	n (%)		*n* (%)		
Sex: Male	30 (66.7)		66 (46.8)		*
Previous PE	3 (6.7)		15 (10.6)		
Previous DVT	7 (15.6)		18 (12.8)		
	Median (range)	*n*	Median (range)	*n*	
Age (years)	63 (23–90)	45	66 (17–96)	141	
D-dimer (ng/ml)	2644 (369–8047)	25	993 (160–5943)	49	**
Prothrombin time (s)	10.0 (8–35)	25	9.75 (3–61)	68	
C reactive protein (mg/l)	74 (7–199)	11	45.5 (2–377)	30	
PaO_2 (kPa)	8.9 (6.5–13.9)	32	9.1 (6.0–14.9)	76	
$PaCO_2$ (kPa)	4.5 (2.7–6.5)	31	4.7 (2.4–9.5)	74	
O_2 saturation (%)	95 (80–100)	39	96 (60–100)	100	
H^+ in arterial blood (nmol/l)	35.5 (26.3–45.7)	32	36.3 (15.2–51.3)	71	
RV:LV ratio	0.98 (0.64–2.48)	45	0.92 (0.66–1.95)	141	*

The first three variables are expressed as *n*(%). The lower nine variables are expressed as medians (ranges),and *n* denotes the number of patients for whom data were available- the study was designed to reflect actual clinical practice (i.e. whether variables were measured/recorded was entirely at the discretion of the attending clinical team), hence *n* is often less than 45 in the PE group and less than 141 in the non-PE group. Values from the arterial blood samples (PaO_2 and $PaCO_2$ and H^+) and O_2 saturation were only included in analysis if the sample or reading were taken with the patient breathing room air.
In the right hand column *P<0.05,**P<0.001 when comparing the PE and non-PE groups. Absence of symbols denotes no statistically significant difference.

The study design stipulated that discrepancies in opinion between the study radiologist and the diagnostic service would be discussed and the final diagnosis reached by consensus. The study design also stipulated that CTPAs deemed to be indeterminate for technical reasons were excluded from analysis. The study radiologist assessed cardiac

dimensions in all patients, and quantified the degree of pulmonary arterial occlusion in patients with PE. Cardiac dimensions were assessed using axial images to determine the maximum diastolic dimension of the right and left ventricular (RV and LV) chambers, expressed as a ratio (RV:LV ratio) (Figure 1). Thrombus load was quantified according to criteria described by Miller, adjusted for CTPA by Bankier et al.[16,17]This generates a modified Miller score (MMS) of 0-16, whereby the segmental pulmonary arteries (nine on the right, seven on the left) are observed and a score of 1 is attributed to each artery occluded by thrombus. Any more proximal occlusion scores the number of segmental branches distal to the occlusion.

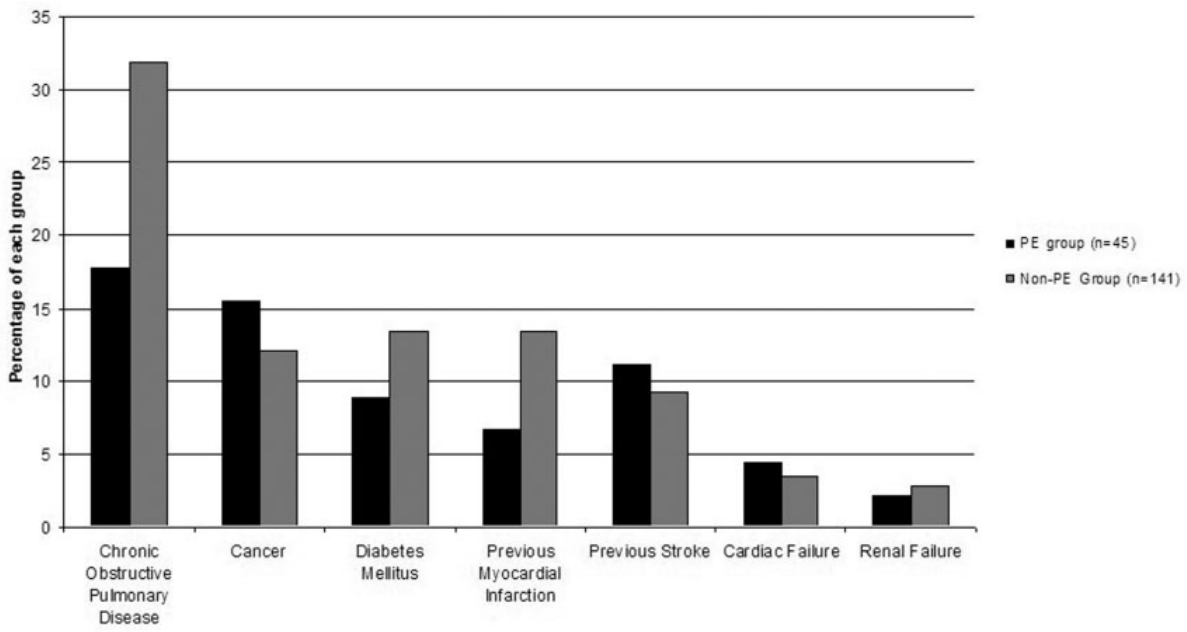

Figure 2. Co-morbidities described in the PE and 'non-PE' groups. No statistically significant differences were observed when comparing the two groups.

Evidence of other cardiopulmonary diseases detectable at CTPA (eg consolidation, pleural effusions, emphysema etc) was also systematically recorded. Co-morbidities and results of investigations performed at presentation (before CTPA) were recorded. All patients provided a short history covering co-morbidities and potential risk factors for PE.

Dates of discharge from hospital or death in hospital were recorded. Mortality data relating to the period after hospital discharge were obtained from the National Registry Office for Scotland. Patients' details were matched to the national registry of deaths occurring in Scotland by name, date of birth, sex and post code. Matching was considered to be adequate if at least three of these characteristics concurred with a death recorded in the registry, and under these circumstances the patient's death was considered to be confirmed.

Patients were excluded if case records were unavailable throughout hospital admission or if the presence or absence of acute PE could not be confidently diagnosed at CTPA. If more than one CTPA was performed during the study period, only data from the first scan were included. Patients were excluded if they had a CTPA in the three months prior to the study period and had a follow-up CTPA during the study period that did not relate to a new presentation.

The study was approved by the ethical review process for medical student projects in our institution.

Statistical analysis

The distribution of gender, previous PE and previous deep vein thrombosis (DVT) in the PE and the non-PE groups were compared using the chi-squared test. Comparisons of numerical variable in the PE and non-PE groups was performed using the Mann-Whitney U-test. A significance level of 0.05 was used.

To obtain an estimate of the relationship between RV:LV ratio and MMS, the RV:LV ratio data for the PE group were tested for outliers. Three extreme outliers more than 87% higher than the median were eliminated. To minimise roughness caused by measurement uncertainty a smoothing procedure - the LOcally-WEighted Scatter plot Smoother, LOWESS - was then applied to a plot of RV:LV ratios versus MMS. Using polynomial regression analysis, a quadratic curve was fitted to the smoothed data using the statistical software package Minitab 14. The resultant polynomial curve fitted to the smoothed data was tested using an F-ratio test with a significance level of 0.05. Using a bivariate model with two outcomes - occurrence or non-occurrence of PE - a binary logistic regression analysis was performed to test for factors differentiating PE and non-PE patients at presentation, adjusting for confounding effects. Variables adjusted for in the binary logistic regression included age, previous PE, previous DVT, PaO_2, $PACO_2$. SaO_2, hydrogen ion concentration in arterial blood, serum D-dimer, prothrombin time, serum C reactive protein, RV:LV ratio. Logistic regression analysis was performed using the statistical package SPSS 12.0.

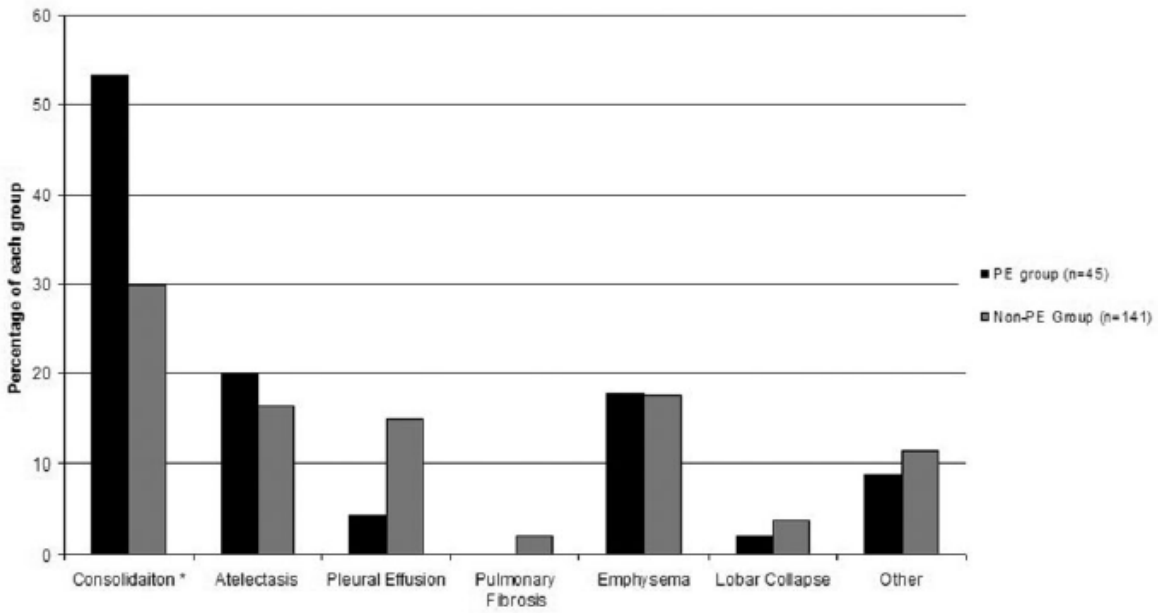

Figure 3 Extravascular radiological features detected at CTPA. *P<0.01 when comparing the two groups.

RESULTS

One hundred and ninety-four patients were admitted to hospital with suspected acute PE and had CTPA. Eight patients were excluded (two scans were indeterminate, two patients were transferred to another hospital before being seen by study investigators, and four were lost to follow up after transfer to other hospitals). Therefore data analysis was performed on 186 patients followed through to discharge from hospital or death in hospital.

Forty-five patients (24.2%) had a diagnosis of acute PE at CTPA. With regard to whether PE was present or absent, no discrepancies were found in observations made by the study radiologist and the diagnostic service for any of the 186 scans.

Table 2 Final working diagnoses among the 141 patients in whom PE was excluded at CTPA

Pneumonia (38 patients)
Exacerbation of COPD (15)
Ischaemic heart disease (9)
Musculoskeletal chest pain (7)
Pleural effusion (6)
Lung cancer (5)
Left ventricular failure (5)
Arrhythmia (3)
Pleurisy of unknown cause (3)
Exacerbation of pulmonary fibrosis (2)
Gastro-oesophageal reflux disease (2)
Sepsis (2)
Trauma (2)
Psychological chest pain/anxiety (2)
Upper respiratory tract infection (1)
Lobar/segmental collapse (1)
Exacerbation of asthma (1)
Exacerbation of bronchiectasis (1)
Pneumothorax (1)
Methotrexate pneumonitis (1)
Primary pulmonary hypertension (1)
Dilated cardiomyopathy (1)
Acute pancreatitis (1)
Splenic rupture (1)
Vertebral metastases (1)
Unknown cause (34)

Numbers exceed 141 because some patients were given more than one simultaneous working diagnosis to explain presentation.

Baseline characteristics for the PE and 'non-PE' groups are shown in table 1. Patients with PE were significantly more likely to be male (P=0.020), to have higher circulating D-dimer (P<0.0005), and to have increased RV:LV ratio (P=0.037). However, when these factors were entered into binary logistic regression analysis and adjustments made for mutual confounding factors, only elevated serum D-dimer level remained significantly associated with PE (adjusted odds ratio 1.12, 90% confidence intervals 1.06-1.08).

Significant co-morbidities were evenly distributed in patients with and without PE (Figure 2). Chronic Obstructive Pulmonary Disease (COPD) was more common in the non-PE group but this finding did not reach statistical significance (P=0.101). Working diagnosis for the 141 patients with no evidence of acute PE is shown in table 2.

No significant differences were found when comparing major pulmonary and pleural radiological abnormalities in patients with and without PE, with the exception of consolidation which was more common among patients with PE .

There were seven deaths in hospital, all in the non-PE group (no significant difference between the groups). None of these seven patients had a post-mortem examination. In each case bronchopneumonia was listed as a cause of death, though three patients had another significant pathology (idiopathic pulmonary fibrosis, left ventricular failure and cancer). At 1 year all-cause mortality in the PE group was 3/45 (6.7%) as compared with 19/141 (13.5%) in the non-PE group (no significant difference). None of the deaths were attributed to PE.

Among patients with PE the median MMS was six (range 1-16) and there was a significant positive correlation between MMS (reflecting thrombus load) and RV:LV ratio. Following LOWESS smoothing, a highly significant quadratic relationship (R^2= 0.99, $p < 0.0005$) was observed between MMS and RV:LV ratio (Figure 4). The fitted curve demonstrates convergence towards an approximate linear relationship for MMS scores of 10 or more. In patients with PE neither MMS nor RV:LV ratio were significantly correlated with length of hospital stay.

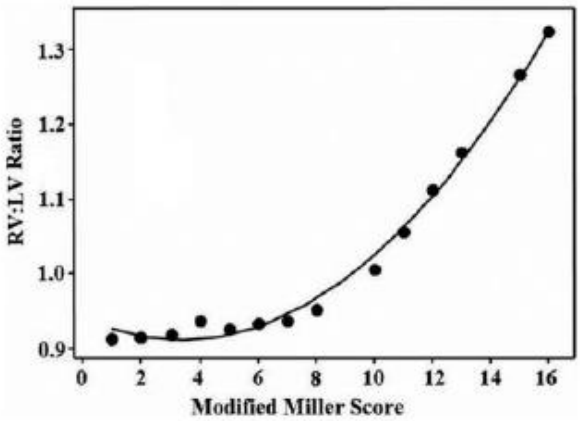

Figure 4 Plot of quadratic fit to smoothed RV:LV data. RV:LV =0.003 MMS^2 - 0.018 MMS +0.941. R^2 = 0.99. Data apply only to patients with PE.

DISCUSSION

Our data suggest that patients with and without PE were strikingly similar with regard to comorbidities, clinical features at presentation and outcome. A retrospective study by Poulsen et al[20], which relied on scintigraphy for the diagnosis of PE, found similar trends. The clinical implication is that patients presenting with clinical features compatible with acute PE have a relatively poor prognosis irrespective of whether PE is detected.

Considering the group without PE specifically, our data suggest an all-cause mortality rate of 13% at 1 year with a trend towards this group having a worse prognosis than patients with PE. This can be compared with an all-cause 1 year mortality in 65-year olds in Scotland of 2.5% (personal communication, Ms. Marie Climson, General Register Office for Scotland). This trend supports data from a separate retrospective study

performed by our group which showed that patients with an indeterminate lung scintigraphy scan had significantly worse prognosis than patients with a high probability scan over 5 years of follow-up[21]. The mortality figures presented here are broadly in keeping with the small number of studies that have quantified mortality in patients with diagnostic imaging that refuted PE, the emerging picture suggesting a 1 year mortality of around 15% but with venous thromboembolism responsible for only a small fraction of those deaths.[22-26] Indeed, subsequent presentation with venous thromboembolism is well studied in this group of patients and reported rates are consistently low.[13-15] The poor prognosis in patients without PE therefore seems likely to arise from the multiple co-morbidities represented in this group, with an additional short-term contribution made by in-patient mortality caused by pneumonia. We believe that the clinically heterogeneous group of patients in whom suspected acute PE is refuted deserves further prospective study given the consistently poor overall prognosis emerging in the literature. Whether health professionals are aware of the poor prognosis of this cohort remains to be determined, but our anecdotal impression is that this is under-recognised.

One interpretation of our findings is that treated PE itself makes little impression on the prognosis of patients presenting with 'clinically suspected PE.' An extension of this argument holds that if patients survive the haemodynamic insult of the acute embolic event to reach hospital and receive appropriate treatment, their prognosis is largely determined by their comorbidities rather than by effects of PE. This contention is supported by observations elsewhere.[5-7] Interestingly, mortality rates among patients with

PE were comparatively low in our study. The reasons for this remain unclear but may partly reflect the use of CTPA which can pick up smaller PEs with greater specificity than scintigraphy (used in several previous studies). Our data emphasise the usefulness of CTPA not only for diagnosis of PE, but for additional information that can be derived with regard to extravascular pathology.[17] We found a high rate of consolidation at CTPA, this being significantly more common in patients with PE. Secondary consolidation has been recognised as a frequent accompaniment to PE before.[27-29]

The similar clinical and radiological features of patients with and without PE confirm and emphasise the notorious difficulties in making the clinical diagnosis. In recent years pre-test prediction models have made significant advances in identifying patients who are at very low risk of PE, do not require invasive imaging, and have a relatively good prognosis.[15, 30-33] Identification of positive clinical predictors of acute PE would also be helpful. However, we only found elevated D-dimer concentrations to be significantly associated with PE. While these data must be interpreted with caution given the small number of patients for whom data were available, D-dimer concentrations have been found clinical utility as a negative predictor for PE[30.33.34] and high concentrations have been associated with larger thrombi.[35]

The PE group in our study was also found to have a higher RV:LV ratio , which is a well recognised consequence of acute pulmonary arterial obstruction The ratio correlated closely with thrombus load, the relationship appearing to be particularly strong above a MMS of 10. This observation is in keeping with the concept that there is a break point

below which the right ventricle copes with increased pulmonary vascular resistance, but above which acute dilatation proceeds. Right ventricular dilatation, increasing thrombus load and interventricular-septal bowing have been identified as adverse prognostic factors in acute PE.[36-38] Measurements of RV diastolic dimensions on axial multi-slice CT scan have been found to correlate with outcome,[39] and CT dimensions have been shown to correlate with findings using transthoracic echocardiography. [40.41]

We acknowledge several limitations of our study. In particular the study is relatively small. Other limitations relate to the decision to make the study design entirely observational and 'non-interventional', i.e. investigators were not permitted to influence investigations or management in the expectation that the study would reflect 'real life' clinical practice (thereby having greater general applicability). In addition, data were not complete for each variable studied, as the decision whether to perform an investigation (e.g. D-dimer) was entirely dependent on attending physicians. Furthermore, we cannot determine how many patients considered initially to be at high clinical risk of PE were not submitted for CTPA on the grounds of a low probability clinical prediction score. Therefore our data should only be interpreted in the setting of patients in whom clinical suspicion was sufficient to warrant a CTPA. Similarly, detection of mortality out of hospital was reliant on hospital-recorded demographics matching those held by the Registrar General for Scotland (responsible for collating all deaths in Scotland). The main confounding factor for this system would arise if a patient died outside Scotland (e.g. a visitor to Scotland who died on returning home, or a Scottish resident who died whilst

visiting another country). We have no data to suggest either eventuality arose. While we believe it is unlikely that mortality rates were biased by these factors, we acknowledge that cause of death as determined by death certificates are notoriously inaccurate. Whilst recognising the relevance of all these limitations we have no reason to believe that biases should be specifically over-represented in either group of patients studied.

In summary, patients with clinically suspected PE have a poor prognosis regardless of whether PE is confirmed on definitive imaging and comprise a group deserving of further study and careful medical follow up.

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ABBREVIATIONS

COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
CTPA	Computed tomographic pulmonary arteriography
CXR	Chest x-ray
LV	Left ventricle/ventricular
MMS	Modified Miller score
$PaCO_2$	Partial pressure of carbon dioxide in arterial blood
PaO_2	Partial pressure of oxygen in arterial blood
PE	Pulmonary embolism
RV	Right ventricle/ventricular
RV:LV ratio	Ratio of the dimensions of the right ventricular and left ventricular cavities
SaO_2	Oxygen saturation

Chapter V

USE OF SIMPLIRED D-DIMER ASSAY AND COMPUTERISED TOMOGRAPHY IN THE DIAGNOSIS OF ACUTE PULMONARY EMBOLISM

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ABSTRACT

Background:

The utility of D-dimer in the diagnostic workup of pulmonary embolism has been established. Several D-dimer tests are available with different sensitivities and specificities. SimpliRED D-dimer is a rapid qualitative whole blood D-dimer assay suitable for bedside use.

Objective:

To assess the value of SimpliRED D-dimer test in patients with suspected acute pulmonary embolism investigated with CTPA in the absence of formal 'risk scoring'

Design:

A prospective study measuring SimpliRED D-dimer in unselected patients undergoing computed tomographic pulmonary angiography (CTPA) examination for suspected acute pulmonary embolism.

Main outcome measures:

D-dimer and CTPA results were compared. Sensitivity, specificity, and positive and negative predictive values of SimpliRED D-dimer were calculated for the unselected patient group.

Results:

Forty-seven patients had valid D-dimer and CTPA. SimpliRED D-dimer was positive in 23 and negative in 24 patients. D-dimer was positive in only 6 (50%) of the 12 patients with positive CTPA, only 6 had positive. Of the 35 with negative CTPA, 17 had positive D-dimer. Sensitivity of SimpliRED D-dimer was 50.0% and specificity 51.4%. The positive predictive value of the D-dimer was 26.1 % and the negative predictive value 75.0%.

Conclusion:

SimpliRED D-dimer should not be used in the diagnosis of pulmonary embolism in the absence of risk scoring.

Introduction

The diagnosis of pulmonary embolism (PE) can be difficult. The incidence of clinically suspected PE is estimated at 2-3 per 1000 per year in the western world[1,2] and only a third of these clinically suspected cases actually have a PE.[3-5] Diagnostic imaging is required to confirm or refute the diagnosis. Computed tomographic pulmonary angiography (CTPA) is a sensitive and specific imaging test for diagnosis of pulmonary embolism. As the diagnosis is confirmed in only about 25% of suspected cases,[5,7-8] clinical algorithms have been developed[6] to reduce the need for diagnostic imaging.

D-dimer, a degradation product of cross-linked fibrin, is raised in several conditions including DVT and PE.[9 -11] A combination of negative D-dimer results combined with a low clinical probability of PE can safely the presence of pulmonary embolism without the need for further imaging tests.[12] D-dimer testing has been included in the diagnostic algorithm in the British Thoracic Society (BTS) guidelines for the management of suspected acute pulmonary embolism.[6]

The SimpliRED assay (Agen Biomedical Ltd., Brisbane, Australia) is a rapid qualitative whole blood D-dimer assay suitable for bedside use. The overall specificity of this test to be 68.4% with an overall negative predictive value of 85%.[13]Furthermore this assay was used in the original validation study for the Wells Score,[12] which is now widely used in the calculation of pre-test probability of the diagnosis.

Objectives

To determine whether SimpliRED D-dimer could be used as a means of reducing CTPA testing in unselected patients referred to the radiology department for imaging to exclude PE.

Methods

A prospective study was performed on 48 patients who had been referred to the radiology department for CTPA for investigation of suspected acute pulmonary embolism. None of

these patients had undergone formal assessment of pre-test clinical probability. The SimpliRED D-dimer test was performed on venous blood in the radiology department when the patient attended for the CTPA. The Radiologist, who was blinded to the results of the D-dimer assay, reported the CTPA as positive or negative for pulmonary embolism. The results of D-dimer and CTPA were later compared.

Results

Forty-eight patients underwent D-dimer and CTPA, males 19 (39.6%) and females 29 (60.4%). D-dimer was deemed invalid for technical reasons in one male patient and was taken out of analysis.

SimpliRED D-dimer was positive in 23 and negative in 24 patients. CTPA was positive in 12 and negative in 35 patients. Out of the 12 patients with positive CTPA, 6 had positive D-dimer. Of the 35 patients with negative CTPA, 17 had positive D-dimer and the rest had negative D-dimer. (table 1)

The prevalence of pulmonary embolism in the study population was 25.5%. The sensitivity of SimpliRED D-dimer was 50.0% and the specificity 51.4% with the test accuracy of 51.1%. The positive predictive value of the D-dimer was 26.1 % and the negative predictive value 75.0%.

Table 1. **Results of SimpliRED D-dimer test and CTPA**

	CTPA			
SimpliRED D-dimer		**Positive**	**Negative**	**Total**
	Positive	6	17	23
	Negative	6	18	24
	Total	12	35	

Discussion

The results of this study re-enforce the dangers of interpreting D-dimer results in the absence of formal risk scoring. Current guidelines recommend the use of blood D-dimer assay only following assessment of clinical probability, and not performed in patients with high clinical probability.[6] A negative D-dimer test is valuable in excluding pulmonary embolism in the patients with a low clinical probability for pulmonary embolism' .[15]

In our study, the specificity as well as the negative predictive value of SimpliRED D-dimer test was much lower compared to the previous studies[13]. The test was done independent of clinical probability and as such the test did not prove to be useful in excluding pulmonary embolism in this study population. This is however still seen in clinical practice with D-dimer tests often ordered at point of entry to care without clinical

probability being fully assessed and at times compounded by radiology departments wishing to know the result prior to proceeding to imaging.

The practice of indiscriminate D-dimer testing without an assessment of clinical probability is not useful or acceptable. This study suggests that SimpliRED D-dimer in the absence of a clinical probability score has no greater predictive value for PE than the toss of a coin. However the test has previously shown a negative predictive value of 99%[13] when used in a subgroup of patients with low clinical probability. This highlights the fact that, when used properly and in conjunction with clinical probability scores, the test remains useful.

There are several different assays available to measure D-dimer levels. The SimpliRED is a rapid qualitative red cell agglutination test with low specificity and sensitivity as explained above. Rapid quantitative ELISA (Vidas) has been useful even in patients with intermediate clinical probability but has a low specificity.[6] MDA D-dimer has a better specificity and can also be used in both low and intermediate clinical probability groups.[16]

Conclusion

A negative SimpliRED D-dimer assay in isolation does not safely exclude the diagnosis of a pulmonary embolism. It is imperative that the test result is always interpreted in the context of clinical probability scoring.

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Chapter VI

PROSPECTIVE EVALUATION OF UNSUSPECTED PULMONARY EMBOLISM ON CONTRAST ENHANCED MULTIDETECTOR CT (MDCT)

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ABSTRACT

Aim To quantify the incidence of unsuspected pulmonary emboli (PE) in an unselected in-patient population undergoing contrast enhanced multi-detector CT (MDCT) thorax and to assess aetiological factors in their development.

Materials and Methods All in-patients undergoing MDCT thorax over a ten month period were prospectively identified. Patients with previous or suspected current PE were excluded. CT scans were reviewed and the degree of contrast enhancement and presence of PE recorded. Where PE was found the level of most proximal thrombus was identified. Patient age, length of admission, slice scan thickness and clinical indication was noted.

Results 547 in-patients having undergone MDCT were identified. Following exclusions 487 remained. 5.7% (28/487) demonstrated PE. Unsuspected PE was more common with increasing age ($p<0.001$), identified in 9.2% (20/218) of all patients over 70 years and 16.7% (11/66) of over 80 year olds. 64.3% were at segmental or sub-segmental level. No other aetiological factor was identified which significantly increased the incidence of unsuspected PE. No significant difference was noted between 4- and 16-slice MDCT. 32.1% of incidental PE were not identified by the original reporting radiologists.

Conclusion PE is an unsuspected finding on contrast enhanced MDCT thorax in 5.7% of all in-patients. This includes an incidence of 9.2% in patients > 70 years rising to 16.7% in over 80 years old. Most are peripheral and >30% are missed on initial review.

PE should be routinely sought in all contrast enhanced MDCT of the chest irrespective of the indication for the scan.

INTRODUCTION

Pulmonary embolism (PE) is a common disease estimated to be a contributory factor in approximately 200,000 deaths per year in the United States, occurring in 5-10% of hospital deaths.[1] PE is a difficult disease to positively diagnose clinically, presenting with varied and sometimes minimal symptoms that mimic a myriad of other pathologies. The actual annual incidence of PE is therefore difficult to determine but has been estimated at around 60-70 per 100,000 people.[2]

In the past PE was only ever firmly diagnosed after the diagnosis had been first considered by a clinician then proven by radiological study; either an isotope perfusion lung scan, a conventional pulmonary angiogram or in recent years a CT pulmonary angiogram (CTPA). With the advent of multidetector CT (MDCT), which allows assessment of the chest with thin section collimation using rapid acquisition, it is now possible to visualise the pulmonary arterial tree down to sub-segmental level on most contrast enhanced scans allowing unsuspected PE to be detected on routine MDCT of the chest.

METHODS

Patient Inclusion

Over a period of 10 months from 1st January 2004 to 13th October 2004, consecutive in-patients undergoing contrast enhanced MDCT chest for an indication other than suspected

PE, were identified at a large teaching hospital. In-patients were selected for the patient study group as this was the population thought to be most at risk and in whom it was considered most likely that unsuspected PE might be detected. Patients were scanned either using either a 4 or 16 slice scanner (both Toshiba Aquilion series, Toshiba Medical Systems, Tokyo, Japan).

Patient details were recorded for the purpose of identification of the computer images and for accessing demographic information from the hospital database. From the request card, logbooks and hospital database, record was made of age, referring speciality, date of admission (to calculate length of hospital stay prior to scanning), scan slice thickness and brief clinical information or reason for referral. Recruited patients were hospital in-patients, from the wards, Admissions unit, Day Case Unit or Accident and Emergency (excluding trauma cases). Patients were excluded if they were suspected or known to have had a PE. CTPA studies were not included.

Protocol	kV	Contrast and Concentration (mg/ml)	Contrast Volume (ml)	Table Feed (mm/rotation)	Pitch
Chest (16 slice)	120	Niopam 300	90	23	23
Aorta (16 slice)	120	Iomeron 400	100	23	23
Chest (4 slice)	120	Niopam 300	90	11	5.5
Aorta (4 slice)	120	Iomeron 400	100	11	5.5

Table 1: Scan Parameters

Scan Parameters

Scan protocol varied depending on the indication for study. In most studies 100mls iodinated contrast was injected at between 3 and 4 mls per second with the scan commencing at around 20 seconds post start of the contrast injection. Scan parameters are outlined in Table 1.

Tube current (mA) is not given as this is controlled by in-built dose modulation software (Real EC, Toshiba Medical Systems, Tokyo, Japan).

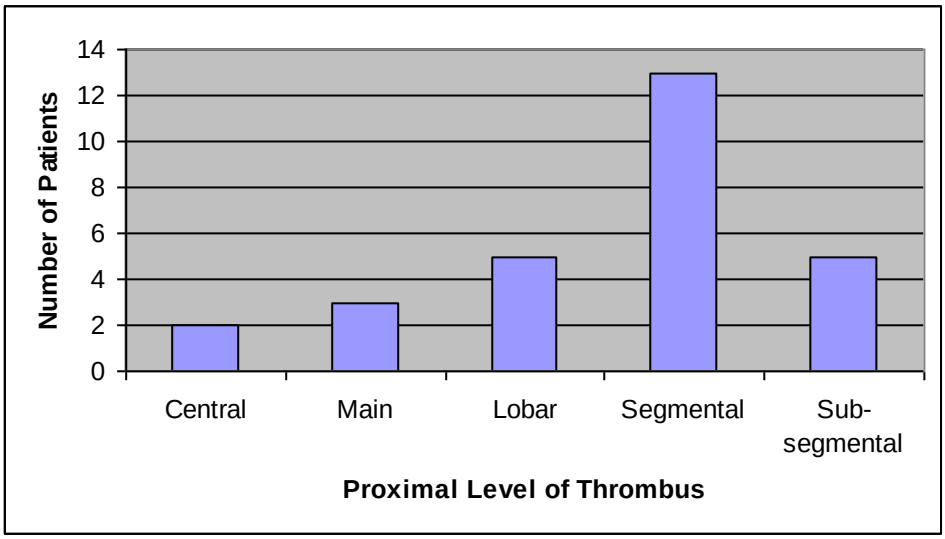

Figure 1. Proximal extend of thrombus in the study population

Image Interpretation

All studies were initially reported as per routine practice in our institution. Subsequently, a single Consultant Thoracic Radiologist who was blinded to the initial report reviewed the studies. All images were assessed using a workstation allowing multi-planar reformatting. For each patient the degree of contrast enhancement and presence or absence of PE was noted.

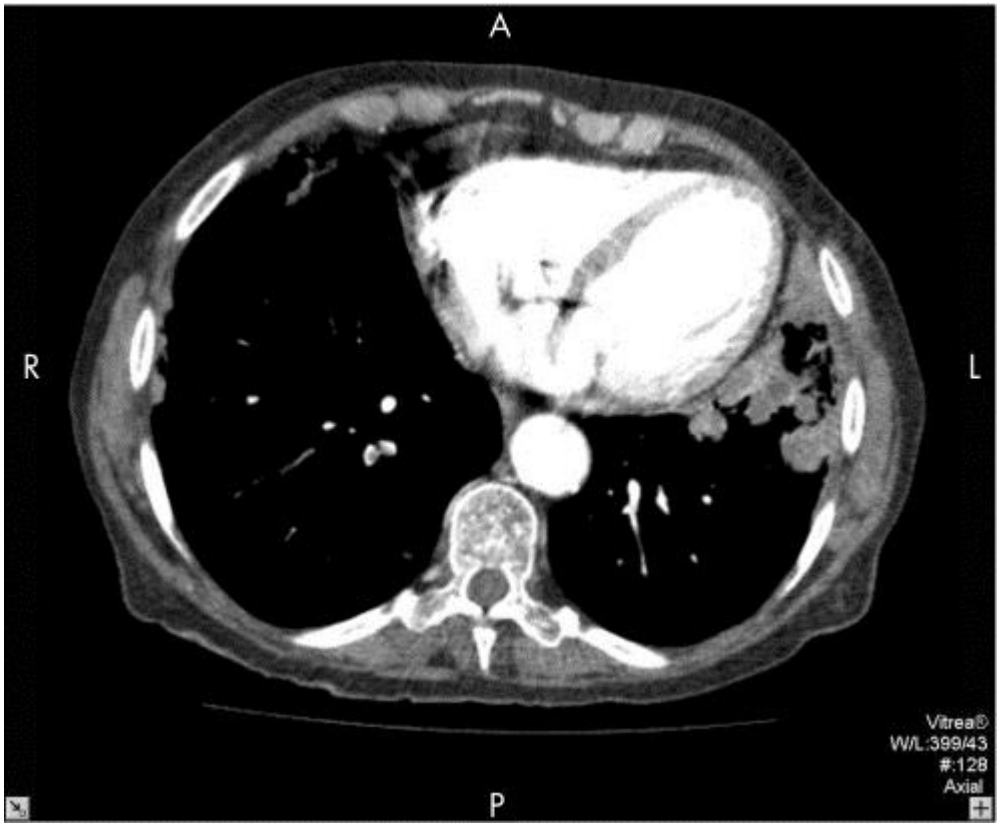

Figure 2 Sub-segmental thrombus in the right lower lobe

If the scan was positive the level of thrombus was recorded as central, lobar, segmental or sub-segmental. Contrast enhancement was classified as good (good enhancement of segmental and sub-segmental arteries), moderate (good enhancement of segmental but not of sub-segmental branches) or poor (inadequate enhancement of entire pulmonary arterial tree). Patients were excluded from the study at this stage if there was poor or absent contrast enhancement, if the lungs were only partially imaged or the images were not retrievable on the workstation (technical difficulties).

If scans were found to demonstrate pulmonary emboli which had not previously been reported, the appropriate clinical team were informed.

Age	**Number**	**Number Positive**	% Positive
<50 yrs	47	0	0
50-59	75	3	4
60-69	147	5	3.4
70-79	152	9	5.9
>80	66	11	16.7

Table 2: Age Distribution of Studies

RESULTS

During the study period 547 consecutive in-patients undergoing MDCT thorax were identified from the scanner logbooks. 16 patients were excluded due to absence of

intravenous contrast, 25 due to incomplete lung imaging and 19 were excluded due to poor contrast enhancement.

Following exclusions a population of 487 study patients remained. These subjects were the in-patients with good or moderate contrast enhancement of the pulmonary arteries and no suspected or prior history of PE. Study group included 200 female (41%) and 287 male patients (59%). Median age 69 years (range 15-93 years). 28/487 scans demonstrated pulmonary emboli, an incidence of 5.7% in the total study population. 20/218 patients over 70 years old had unsuspected PE, an incidence of 9.2% in this cumulative grouping. This rises in the over 80 year age group to an incidence of 16.7% (11/66).

Median age of all patients with positive scan was 77 years, range 52-88 years. There was a statistically significant association between age group and the rate of unsuspected PE (χ^2=13.28, p=<0.001) with a significant difference in rate of PE with increasing age. The distribution of PE by age is recorded in table II although for the purposes of analysis the <50 and 50-59 age groups have been combined.

Of the positive scans, 27/28 (96.4%) showed good contrast enhancement, the one scan which showed only moderate enhancement had thrombus at a segmental level.

402/487 (82.5%) of the study patients were scanned on a 16-slice scanner, and images reconstructed at 1mm thickness, the incidence of PE among this subgroup was 24/402 (6.0%). 85/487 (17.5%) patients were scanned on a 4-slice scanner with slice

reconstructions at either 2mm or 3mm. A total of 4/85 scans were positive for PE, an incidence of 4.7%. Of these, 3 were scanned with 3mm slice thickness. No statistically significant difference was noted between 4 and 16 slice scanners in their ability to identify unsuspected PE (p=0.80 using Fishers exact test).

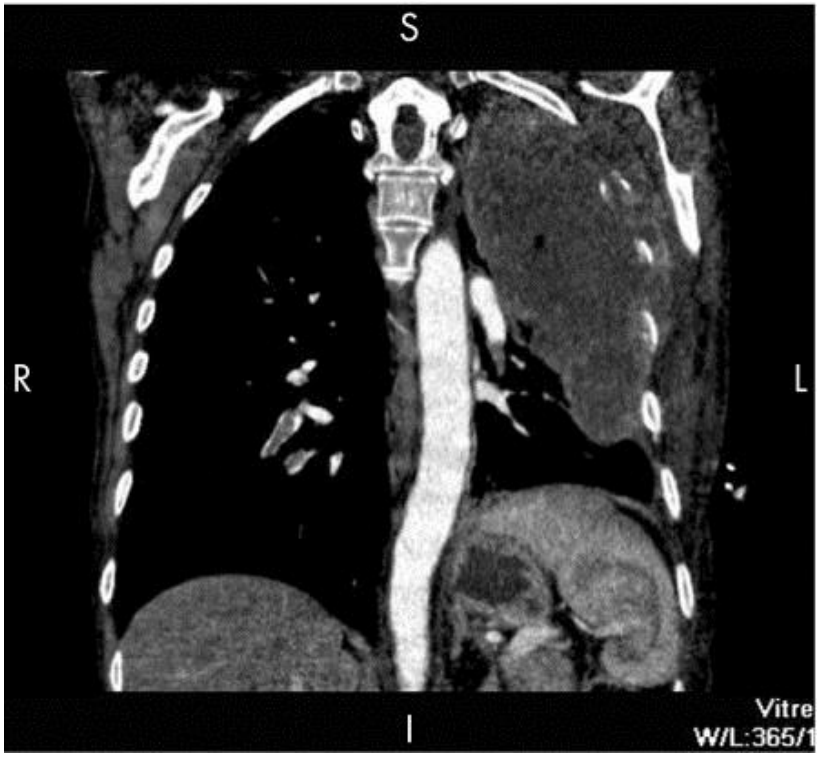

Figure 3 Segmental level thrombus

Distribution of proximal thrombus in the entire population is shown in Figure 1. Image 1 is an example of sub-segmental thrombus in the right lower lobe, Image 2 demonstrates segmental level thrombus and Image 3 shows more proximal PE in the main pulmonary arteries bilaterally, all were unsuspected.

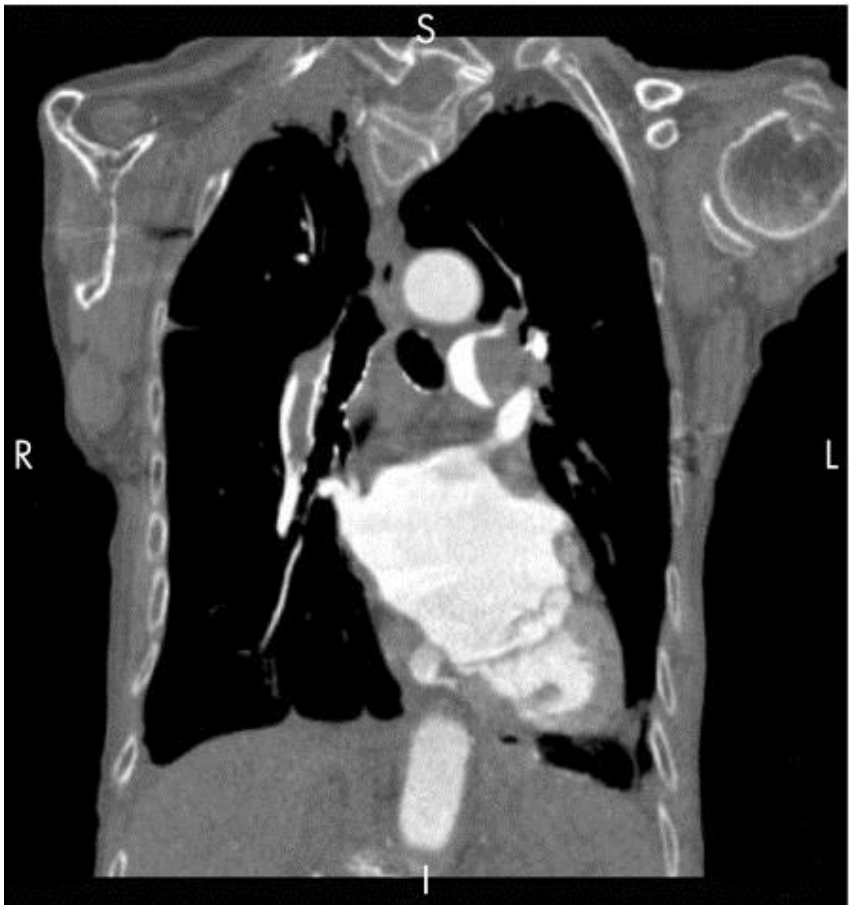

Figure 4 Thrombus in the main pulmonary artery

19/28 (67.9%) of pulmonary emboli were positively identified on initial report. Of the 9 positive studies not identified at initial review, thrombus was segmental in 6 cases and sub-segmental in 3 cases. Distribution of involved lobes is summarised in figure 5.

Referral speciality and clinical information given on the request card was used to determine any prior risk. The presumptive diagnosis of all patients at referral is illustrated in figure 6. Most referrals, accounting for just over a third, were from the respiratory physicians (166/487), the general surgeons and general medical

teams accounted for just over 10% of referrals each, with fewer referrals from GI medicine, the Transplant unit, geriatrics and ITU.

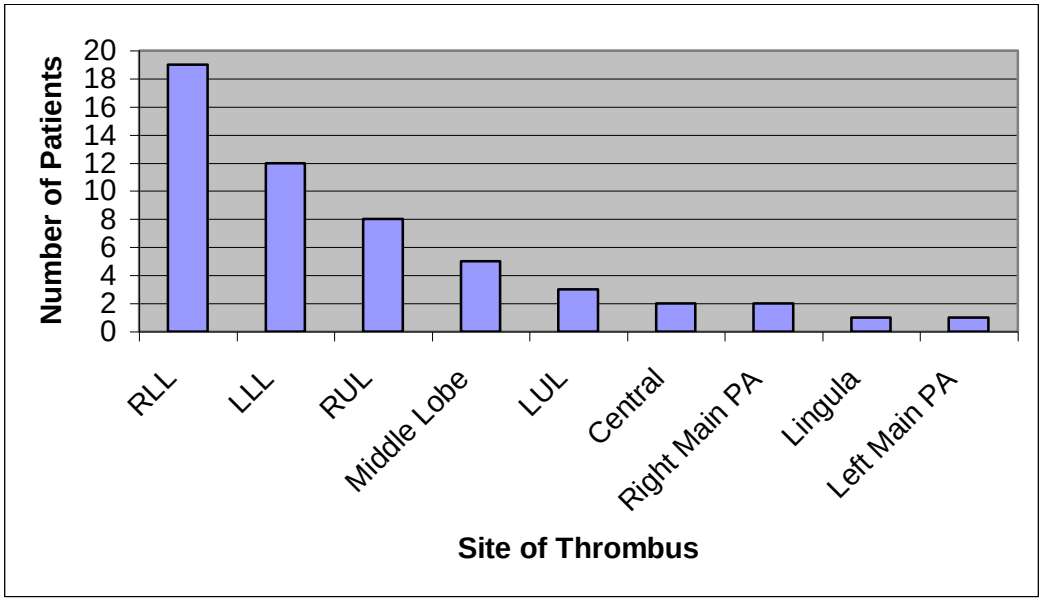

Figure 5: Site of Thrombus in study population

Cancer refers to any patient with known or suspected cancer, mediastinal or pulmonary mass. Collection covers patients being imaged to evaluate pleural or pericardial collections. Infection includes patients with slow to resolve pneumonia or sepsis. Transplant identifies a group of patients being assessed for hepatic and renal transplantation. Aneurysm covers patients with thoracic aneurysm as well as patients suspected of having acute aortic syndrome. Miscellaneous describes a heterogeneous group with diverse presumptive diagnoses including pulmonary fibrosis, emphysema, collapse, hoarseness and dysphagia .Studies were performed as determined by clinical urgency, based largely on information provided on patient request card.

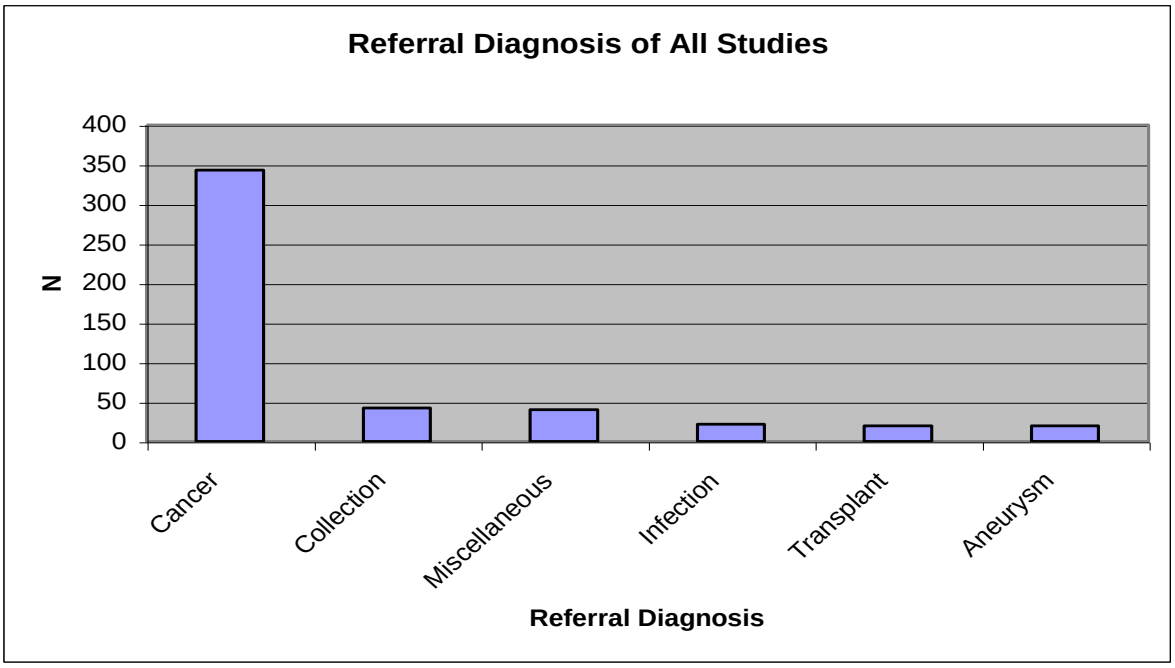

Figure 6: Presumptive Diagnosis at Referral

At our institution the vast majority of in-patient CT scans are performed within 3 days of request. Of the positive studies 18/28 (64.3%) were carried out for confirmed or presumed malignancy. Of the total study population, 343 studies (70.4%) were carried out for confirmed or presumed malignancy. There was no evidence of a statistically significant difference in the proportion of PE cases in those with suspected malignancy (18/343, 5.2%) compared to the proportion of PE in non-malignancy (10/144, 6.9%). Difference in proportions is -1.7% with a 95% CI for difference (-6.47%, 3.08%), p=0.486 (binomial test for proportions).

Median duration of in-patient admission prior to scan was 3 days, (range 0-255 days).

Distribution of hospital stay for positive scans is recorded in Figure 7.

Looking at grouped hospital stays (0-1, 2-3, 4-6 and 7+ days) there was no statistically significant relationship between length of hospital stay and likelihood of finding unsuspected PE (χ^2=2.169, p=0.538)

DISCUSSION

Terminology and Significance of Unsuspected PE

Previous studies[3,4] have described the finding of pulmonary embolism, in situations where this is not suspected, as *incidental* PE. In this study we have chosen to use the term *unsuspected* PE, previously also used by Gosselin *et al.*[5] The term incidental to some suggests clinical insignificance. We feel there is little evidence to support the implication that these emboli are necessarily of less clinical significance just because they are identified as an incidental finding.

Recent meta-analysis of necropsy studies has demonstrated that pulmonary embolism remains a common condition where there is discrepancy between clinically suspected and

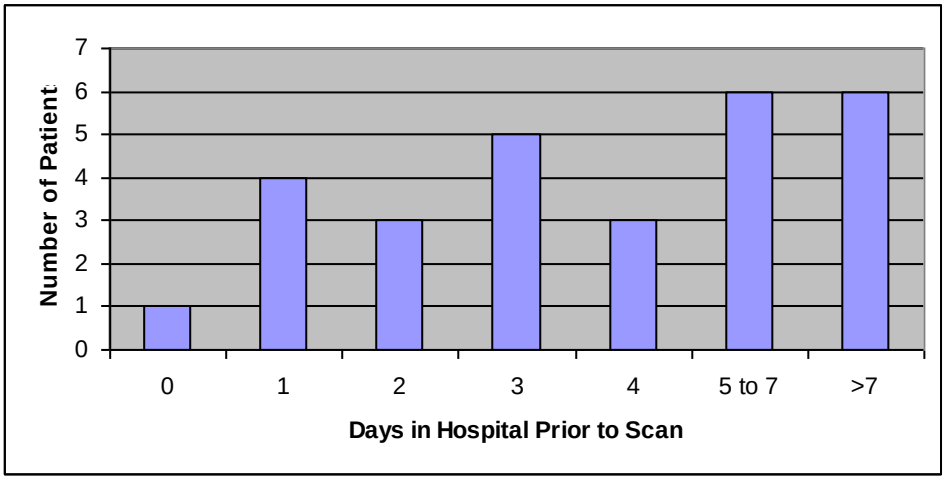

Figure 7. Days in hospital prior to diagnosis of PE

necropsy proven cause of death.[6] The significance of small pulmonary emboli has been called in to question. While discussion as to the importance of small emboli is beyond the scope of this article, a comprehensive summary of the evidence regarding small pulmonary emboli is contained in a recent editorial by Goodman.[7] It is of note that of the emboli identified in this study, 18/28 were at segmental or sub-segmental level and might be classified as small.

Identification and Estimates of Prevalence of PE

Contrast enhanced CT, specifically CTPA, has become the first line investigation in many centres in the diagnosis of pulmonary embolism due to a high inter-observer agreement,[8] identification of unsuspected pathologies[9] and because it is a cost effective method of imaging PE.[10]

Unsuspected PE has previously been demonstrated in patients undergoing contrast enhanced CT of the chest for reasons other than suspected PE. Using older technologies in a study of 1879 patients undergoing contrast enhanced helical CT thorax, Winston *et al*[4] identified 18 patients with unsuspected PE, estimating the prevalence at 1%. A similar study by Gosselin *et al*[5] demonstrated an overall rate of 1.5%, with up to 5% of in-patients demonstrating PE. More recently, with a 4 slice MDCT, Storto *et al*[3] found incidental PE in 4% of 474 in-patients. No previous studies have reported rates of unsuspected PE using 16-slice MDCT.

Our study has shown an overall rate of unsuspected PE of 5.7%. We identified only those in-patients in whom PE was an unexpected finding. Due to the exclusion of CTPA examinations and patients with a known PE, this figure must be an underestimation of the actual prevalence of PE in the hospital population. The fact that we are now identifying these unsuspected PE on a regular basis implies that PE is much more common than previously appreciated. Many of the unsuspected PE, were in the smaller segmental and sub-segmental arteries. Whilst large central PE may seem more likely to be clinically apparent, peripheral emboli are also important because of the tendency to cause pulmonary infarction, pleuritic chest symptoms and as a possible prelude to larger potentially life threatening emboli. Until the natural history of these smaller PE is better understood it remains the responsibility of the radiologist to report them and of the clinician to define the therapy. We cannot conclude from this study whether or not patients with unsuspected PE should be anti-coagulated or not. We would expect that the larger emboli at least require treatment. Evidence is uncertain as to optimal management so far as the smaller asymptomatic emboli are concerned. In our institution clinicians certainly still consider all detected PE as significant and treat as such. The question which

our study does raise is whether PE, and in particular small PE, are more common than previously recognised. If this is the case then these small PE may be of lesser clinical significance than larger clinically evident PE and may merit a different management strategy. A possible strategy, which would need to be fully evaluated, would be to do leg U/S in patients with unsuspected or asymptomatic emboli, to look for possible DVT and avoid anticoagulation if negative.

Spatial Resolution and Identification of PE

The higher incidence of PE demonstrated in our study compared to previous studies may be due to improved spatial resolution. Previous work has indicated that MDCT increases conspicuity of small, peripheral arteries.[11,12] Several studies have also demonstrated increased sensitivity for detection of pulmonary embolism in sub-segmental vessels using MDCT.[13-15] Patel *et al*[16] have previously demonstrated that MDCT scanning demonstrates more PE and in smaller vessels than single slice scanning. In addition, the same study demonstrated that using MDCT decreasing slice thickness from 2.5mm to 1.25 mm improved visualisation of segmental and sub-segmental vessels and PE.

If spatial resolution is the principal determining factor in identification of peripheral emboli, it is perhaps not surprising that our data demonstrates more incidental PE in patients scanned using a 16 slice scanner with 1mm slice thickness than in a 4 slice scanner with a 2 or 3mm slice thickness. The difference in this study between 4 and 16-slice scanning was not statistically significant. This likely reflects the small number of positive studies identified.

In this study, only 67.9% of the positive scans were initially reported as showing PE. In all 9 cases (32.1%) where PE was not identified, thrombus was at segmental level or more distally. These data suggests that smaller clots are more easily overlooked and highlights the need to include a thorough assessment of pulmonary arteries in all contrast enhanced thoracic CT scans.

Aetiological Factors in Unsuspected PE

Age:

Older patients are significantly more likely to develop symptomatic thrombo-embolic disease.[2,17,18] This study demonstrates that older people are also more likely to develop unsuspected PE. Most dramatically illustrated, in the over 80 age group who were found to have PE in 16.7% of cases (Table II). We recognise that age may be a surrogate for other risk factors known to be associated with an increased risk of PE such as malignancy, immobility or heart failure.

Malignancy:

The suggestion that rates of incidental PE are higher in patients with confirmed or presumed malignancy is not new. In a sub-group assessment following the PIOPED study, 14 of 20 patients proven to have unsuspected pulmonary embolism as the principal cause of death at autopsy had advanced associated diseases, with malignancy in 4 patients.[19] The link between thrombo-embolic disease and malignancy is further suggested by the finding of an increased risk of the diagnosis of malignancy in the 2 years following diagnosis of venous thrombo-embolism in a large retrospective study.[20] In a recent

paper regarding incidental PE, Storto *et al* have noted that 70% of patients with incidental PE had malignancy.[3]

No statistically significant correlation between malignancy and incidence of PE was noted in this study. The reasons for this are uncertain but may reflect in part the small number of positive cases and the fact that the great majority of patients having a contrast enhanced CT of thorax fell into this category and that many of the scans were for presumed, rather than confirmed malignancy.

Hospital Admission:

No significant association is seen in this study between length of hospital admission and presence of PE. Hospital in-patient stays are now relatively short. The average stay for all patients scanned in this study was only three days and 17 of the 28 positive cases were identified within five day of admission. We would suggest that at least some of these emboli had been present prior to admission. We would also suggest that for patients with longer admissions, the use of low molecular weight heparin (LMWH) as prophylaxis might have a protective effect, this information however was not easily available during this study.

The rate of unsuspected in-patient PE will not reflect the general out-patient incidence. This population theoretically should have fewer risk factors for PE and therefore presumably a lower incidence.[3]

A small number of outpatient scans were inadvertently assessed before exclusion from our study. Of 43 such studies, 4 patients (9.3%) showed incidental PE. This is at odds with the suggestion that prolonged hospital admission increases the rate of PE, but is felt likely to

be spuriously high due to small patient numbers involved and a larger study is needed in this out-patient group.

CONCLUSIONS

Unsuspected PE is present in 5.7% of in-patients having contrast enhanced MDCT thorax. The detection of these thrombi suggests that the actual prevalence of PE in the hospital population is greater than previously appreciated. The incidence increases significantly with age with 9.2% of the over 70 year old, and 16.7% of the over 80 year old population affected. We showed no statistical correlation with the length of admission or associated malignancy.

In this study >30% of emboli are missed on initial review, all of these were found in segmental or sub-segmental vessels, but the clinical significance of these smaller thrombi remains uncertain. Routine assessment of the pulmonary arteries should be considered standard practice when reporting any contrast enhanced MDCT thorax.

ETHICS APPROVAL Institutional approval was obtained for the study.

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Chapter VII

UNSUSPECTED PULMONARY EMBOLISM IDENTIFIED ON MULTI-DETECTOR COMPUTED TOMOGRAPHY (MDCT) IN HOSPITAL OUTPATIENTS

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Abstract

Aim

To evaluate the incidence of unsuspected pulmonary embolism (PE) in an unselected population of outpatients undergoing contrast-enhanced multi-detector computed tomography (MDCT) for indications other than the investigation of PE.

Materials and methods

Outpatients undergoing CT of the chest over a 6-month period were retrospectively identified and images reviewed. Inpatients and patients undergoing unenhanced CT of the chest were excluded. Data, including referring specialty, patient age and sex, reasons for examination, level of embolism, image quality, and section thickness were recorded. Radiology reports were reviewed with respect to whether or not the embolism was noted at the time of initial reporting.

Results

Following exclusions 440 patients were reviewed (195 women and 245 men). PE was identified in 10 of the 440 patients, an incidence of 2.23%. One pulmonary embolus was in the main pulmonary artery, three were in lobar arteries, three in segmental arteries, and three in sub-segmental arteries. Patients over the age of 60 years were more likely to have an embolism (9/300, 2.9%) compared with those under 60 years (1/140, 0.7%). Seven of the 10 positive examinations were carried out in patients who were known or later shown to have malignancy. Seven of the 10 emboli were reported at the time of initial reporting.

Conclusion

The outpatient population has a significant incidence of unsuspected PE. PE should be actively sought when reporting examinations performed for alternative indications, particularly where cancer is a known or suspected diagnosis.

Introduction

Pulmonary embolism (PE) is a common condition with a documented annual incidence of 500 000 cases in the United States, [1] and is responsible for considerable morbidity and mortality. The advent of thin-slice multi-detector CT (MDCT) has led to the diagnosis of unsuspected pulmonary emboli being made in contrast enhanced CT examinations of the thorax where there was no clinical suspicion of pulmonary emboli. It is therefore important that radiologists are aware of the capability of their modality in diagnosing unexpected pulmonary emboli and actively seek to exclude the diagnosis on all contrast enhanced CT chest scans whatever the indication.

Previous studies have highlighted an incidence of unsuspected PEs of up to 5.7% in high risk populations such as cancer patients and inpatients. [2,3,4,5] Silent PEs are also well described in patients with deep vein thrombosis [6,7,8].The aim of this study is to investigate the incidence of unsuspected pulmonary emboli in outpatients undergoing routine contrast enhanced MDCT of the chest. We also aim to evaluate the aetiological factors relating to PE in outpatients and to compare the enhancement and diagnostic utility of the 4 and 16 slice scanners.

Materials and Methods

Outpatients undergoing CT of the chest for indications other than suspected pulmonary emboli over a 6 month period were retrospectively identified and analysed within one week of the scan being performed. Data including the referring specialty, age of the patient, indication for scan, most proximal level of the embolism, quality of the scan and scan slice thickness were documented. The radiology reports were reviewed with respect to whether or not the embolism had been noted at the time of initial reporting. Patients were scanned using either a 16-slice or a 4-slice scanner, (Toshiba Aquillion Series, Toshiba Medical Systems, Tokyo). Patients who had been referred for outpatient investigation by a range of medical and surgical specialties were included. Inpatients and non contrast scans were excluded, as were patients with a past history of venous thromboembolism.

Institutional approval was obtained for the study.

Imaging Protocols

The parameters used for the scan depended on the indication for the study. Most studies were performed using a standard protocol with 100mls of iodinated contrast medium injected at a rate of 3-4mls/second with scanning performed in a single breath hold 20 seconds after the start of contrast injection. 1mm thick images were reconstructed using the 16 slice scanner and 2-3mm slice thickness for the 4 slice scanner. Scan protocols employed are outlined in table 1.

Image evaluation

All images were routinely reported at the time the study was performed. Images were re-examined for this study using a 3-D workstation within a week of the examination being performed by one of 2 radiology registrars under supervision of a consultant cardiothoracic radiologist who reviewed all the positive and equivocal scans. The radiologists were blinded to the initial report. CT scans were assessed for the presence of pulmonary embolism and the location of the most proximal thrombus in the central,lobar, segmental or sub-segmental pulmonary arteries, recorded. The radiologist reviewing the scan also noted whether the contrast opacification of the pulmonary

Protocol	kV	Contrast and concentration (mg/ml)	Contrast volume (ml)	Table feed (mm/rotation)	Pitch	No of patients
Chest (16-section)	120	Niopam 300	90	23	23	358
Aorta (16-section)	120	Iomeron 400	100	23	23	6
Chest (4-section)	120	Niopam 300	90	11	5.5	76
Aorta (4-section)	120	Iomeron 400	100	11	5.5	0

aTube current (mA) is controlled by software

Table 1 Imaging parameters

arteries was good (good enhancement of segmental and sub-segmental pulmonary arteries), moderate (good enhancement of segmental but not sub-segmental pulmonary arteries) or poor (poor enhancement of the entire pulmonary arterial tree). Patients who had poor contrast enhancement were excluded from the study.

Results

Among the 449 scans evaluated 440 (97.8%) were considered to have good (n=395) or moderate (n=45) pulmonary artery opacification. 9 scans showed poor contrast enhancement and these were excluded from further study. Of the 440 patients remaining 195 (44.3%) were female and 245 (55.7%) male. The age range of patients was 19 to 94, median age 67.

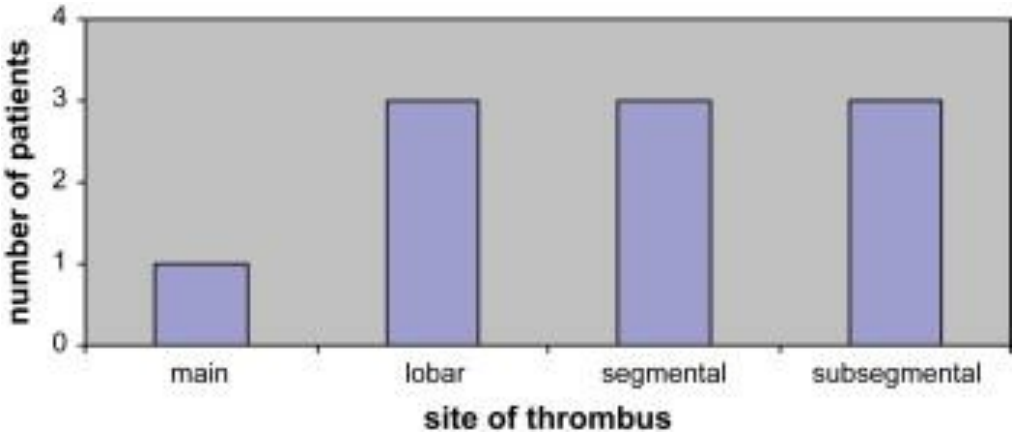

Figure 1. Proximal extent of thrombus.

PE was discovered using CT in ten of the 440 patients, an overall incidence of 2.23%. The proximal extent of thrombus is shown in figure 1. One pulmonary embolus was in the main pulmonary artery, 3 were in lobar arteries, 3 in segmental arteries and 3 in sub-segmental arteries. 7 of the 10 pulmonary emboli were identified at the initial time of reporting. The emboli which were not identified were all sub-segmental and the clinical teams were informed within a week of the scan being performed.

Age (years)	*n*	No. positive	Percent positive
<50	58	0	0
50–59	80	1	1.3
60–69	113	6	5.3
70–79	135	2	1.5
>80	54	1	1.9

Table 2. Age distribution of patients.

The age distribution for all patients is shown in table 2. Patients over the age of 60 were more likely to have an unsuspected pulmonary embolus (9/300, 3%) compared to those aged under 60 (1/140, 0.7%) but this was not a statistically significant finding (Fisher's exact test, p=0.1853).

The majority of patients who underwent outpatient CT of the thorax were referred by chest physicians (227/440) or by general surgeons (154/440). Of the 10 patients who had pulmonary emboli, 5 were referred by the chest physicians, 4 by general surgeons and 1 by orthopaedics The indication for the majority (77.7%) of the scans was investigation of known or suspected cancer (342/440). 7 of the 10 positive scans were carried out in patients who had known malignancy or where later proved to have malignancy. There was a similar proportion of positive scans in patients with malignancy (6/342, 1.7%) and in those being investigated for other conditions (1/98, 1.0%, p=1.0) although numbers of positive cases were small.

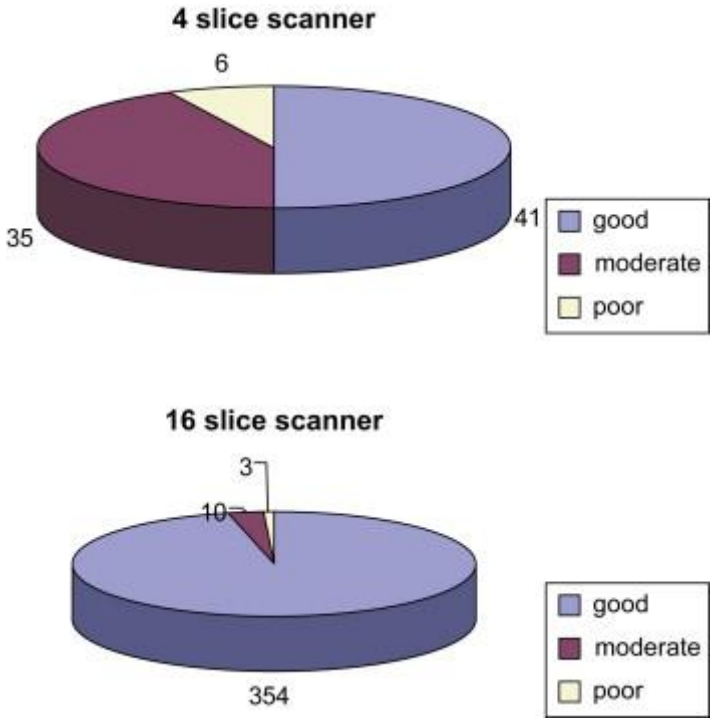

Figure 2
Enhancement of the pulmonary arteries using the four and 16-section machines.

The four-section machine was far more likely to show poor or moderate enhancement of the pulmonary arteries when compared with the 16 section machine. Of the 367 patients scanned on the 16 slice scanner only 10 (2.7%) showed moderate enhancement of the pulmonary arteries and 3 (0.8%) showed poor enhancement while 354 (96.5%) showed good enhancement. Of the 82 patients scanned on the 4 slice scanner 35 (42.7%) showed moderate enhancement, 6 (7.3%) showed poor enhancement of the pulmonary arteries and 41 (50%) showed good enhancement. Contrast enhancement is illustrated in figure 2. These numbers include the scans which showed poor enhancement of the pulmonary arteries, which were excluded from the remainder of the analysis above.

Three hundred and sixty-four of the patients included in the study were scanned on the 16-slice scanner and 76 patients on the 4 slice scanner. Two of the scans which were positive for PE were performed on the 4 slice scanner. One of these showed a PE in a lobar artery

and one in a segmental artery. There was no difference in the proportion of scans positive for PEs using the 4 slice (2/76, 2.6%) or the 16 slice (8/364, 2.2%) scanner provided the contrast enhancement of the pulmonary arteries was adequate (p=0.69), however all the unsuspected sub-segmental PE's were detected using the 16 slice scanner.

Discussion

Of the outpatient population undergoing CT thorax in the present study, 2.2% had unsuspected PEs. The incidence of PEs is higher than in previously published studies that used thicker collimation, but lower than in the inpatient population for the same institution. The findings of the present study raise the likelihood that PE may be a more frequent event in the hospital outpatient population than was previously recognized.

Our institution does not manage the bulk of the oncology work for our region (with the exception of upper gastrointestinal, hepato-biliary, and some chest oncology). Allowing for this, there are still a very high proportion of patients being investigated for malignancy (77.7%). The number of positive examinations in this study was too small to permit detailed analysis of this group. A larger study with greater numbers of positives would be necessary to draw more significant conclusions regarding the characteristics of the patients with unsuspected PEs. It has been shown that the older population is more likely to develop thromboembolic disease[2 9,10,11] and although more PEs were found in the over 60 years age group, this only represents a suggestion of an age effect and is not supported by statistical analysis. The lack of a statistically significant effect of age may be related to the relatively small number of patients and small number of positive results. There was no relationship between PE and referral specialty.

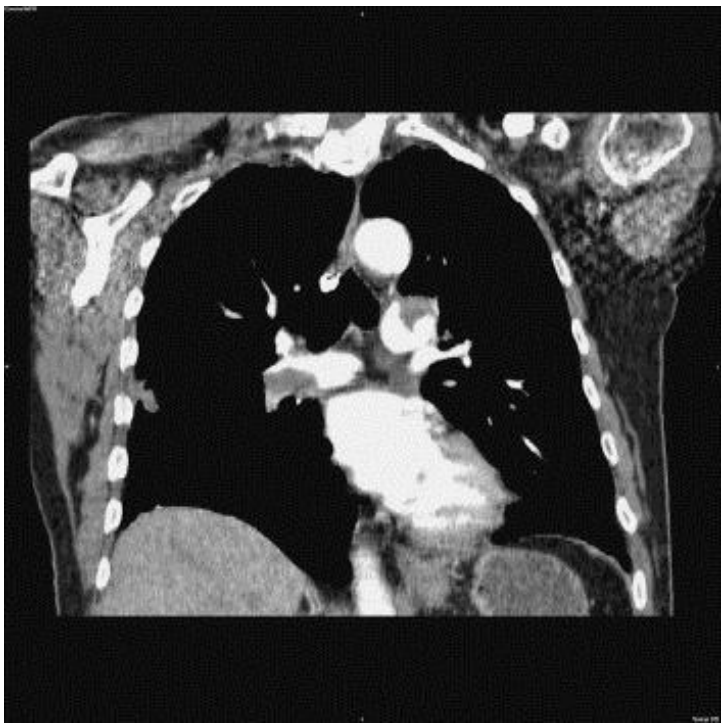

Figure 3 74 year old with unsuspected right main pulmonary artery embolus.

The clinical significance of these unsuspected PE remains unclear. One of the patients had a lobar embolus (Fig. 3), and there was no reason to suppose that unsuspected large central or lobar emboli are of any less importance than those that present with clinical symptoms. The majority of the unsuspected PEs in the present study were small, occurring at the segmental or sub-segmental level (Figure 4, Figure 5) and the clinical significance of these smaller PEs is less certain. In one study of patients without previous cardiovascular disease, the arm of patients randomized to receive no anticoagulation following silent PE did not show any adverse outcome compared with those who were treated.[8] One of the physiological functions of the lung is to act as a filter for embolic particles to prevent their passage into the systemic circulation.[12] However, there is a belief that small PEs occurring without symptoms may be a precursor of larger events with more serious clinical consequences.[13]

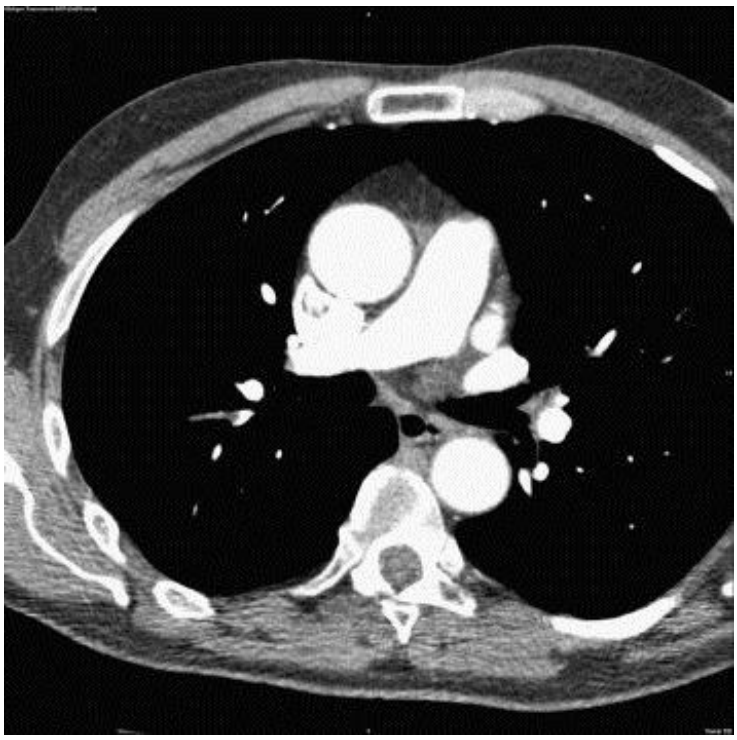

Figure 4. A 66year-old man with a subsegmental pulmonary embolus. Thisd was not seen at the intial time of reporting. The clinical team were informed of the finding 1-week later.

These small events may also play a role in later development of thromboembolic pulmonary hypertension. At our institution all unsuspected emboli are currently managed with anticoagulation in the same manner as any embolus that is diagnosed following investigation to look specifically for PE. It remains to be seen whether in the future clinical practice may change in the management of these smaller unsuspected emboli.

A recent study at our institution showed an inpatient rate of unsuspected PE of 5.7%.[2] This rate almost certainly underestimated the true prevalence of PE in the inpatient population as patients being investigated for PE were not included. The present study has found the rate of unsuspected PE in the hospital outpatient population to be 2.2%. Patients

with known or suspected thromboembolic disease were also excluded from this study, so this may also be an underestimation.

It can probably be assumed that the outpatient hospital population has more risk factors for PE than the general population and indeed 77.7% of the present study population were under investigation for known or suspected malignancy, which is a widely accepted risk factor. Although not unwell enough to warrant admission to hospital, outpatients have co-morbidities and are likely to be less mobile than the general population.

The first studies to describe the frequency of "incidental" PE detected on CT tended to show lower rates of PE than more recent studies. Winston et al.[13] found an incidence of unsuspected PE of 0.4% in 1996 in an outpatient population of 1320 patients. Gosselin et al.[14] examined a population of 625 outpatients in 1998 and found an incidental rate of

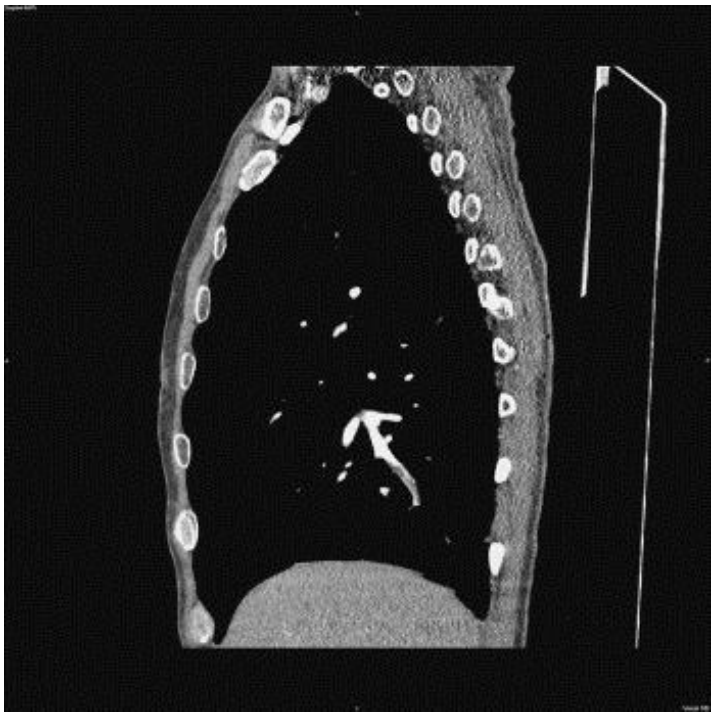

Figure 5 Segmental embolus in a patient known to have lung cancer.

PE of 0.6%. Both these studies were performed using single-detector systems with relatively large collimation (5–10 mm). More recently in 2005, Storto et al.[3] reported an incidence of 0.9% unsuspected PEs in 107 outpatient examinations using a four-section system. The present study found a higher incidence at 2.2% in an unselected outpatient group of 440 and similarly, a study performed recently at our institution by Ritchie et al.[2] reported an incidence of 5.7% of unsuspected PEs in inpatients. Both these recent studies used mostly 16-section MDCT, and a high proportion of the unexpected emboli were at the segmental or sub-segemental level. The higher rate of detection of PE in recent studies is likely to reflect the improvements in resolution of small pulmonary arteries using 16-section MDCT[15],[16] and the ability to identify small peripheral emboli that were not previously seen using single-section systems.[17-21,]

In the present study, the majority of PEs were positively identified at the time of the initial report, but three of the 10 positives were initially missed, which is a similar finding to the previous study.[2] It is possible that suboptimal window settings could have contributed to failure to identify these emboli. In a study of 581 patients, Storto et al.[3] concluded that the use of wide window settings improved the detection of PEs. It is also possible that the size of the emboli resulted in their being overlooked (all were sub-segmental).

In conclusion, an unsuspected PE was found in 2.2% of the unselected outpatient population undergoing MDCT examinations of the thorax. This is a higher proportion than has previously been described presumably owing to the use of a 16-section machine. Statistical analysis was hampered by small numbers of positive results. There was no statistically significant relationship between age and PE. There was also no pattern regarding the anatomical distribution of the emboli, although again the numbers of

positive examinations were small. These findings suggest that the incidence of PE in the outpatient population is higher than previously suspected and unless specifically sought, a significant proportion will be overlooked on the initial report.

This study reaffirms the need for radiologists to be vigilant in the reporting of contrast-enhanced CT chest and to pay close attention to the pulmonary arteries, even if the examination has not been optimally timed for their examination. This study also poses questions regarding the management of patients with small asymptomatic peripheral PEs.

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CHAPTER VIII

A PROFILE OF LOWER-LIMB DEEP-VEIN THROMBOSIS: THE HIDDEN MENACE OF BELOW-KNEE DVT

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Abstract

Aims

To describe the anatomical site and laterality of deep-vein thrombosis (DVT) in symptomatic patients using contrast venography (CV), and to assess age, sex distribution, and accuracy of pre-test clinical suspicion of DVT.

Methods

One thousand, five hundred and seventy two patients undergoing CV because of clinical suspicion of DVT at a large teaching hospital from October 1995 to March 2003 were prospectively studied.

Results

Thrombi were demonstrated in 511 (32.5%) of all CV studies. Isolated, below-knee thrombi were identified in 29.4% of positive studies. There was a left-sided predominance of DVT (ratio 1.24: 1) that was most evident in the elderly and in more proximal veins.

Conclusion

Almost a third of positive cases were shown to be isolated, below knee thrombi. These are thrombi that are more difficult to detect by non-invasive means. A left sided predominance of DVT is evident.

Introduction

Venous ultrasound (US) has replaced contrast venography (CV) as the primary diagnostic tool in the investigation of suspected deep venous thrombosis (DVT) in most hospitals. Venography is still accorded the status of 'gold standard' for imaging DVT,[1,2] and is more sensitive than US in detecting below knee DVT and asymptomatic DVT.

The main benefits for the use of venous US are its non-invasive nature and lack of exposure to ionising radiation.[3,4] Published data suggests that US studies may miss a variable proportion of below knee thrombus with sensitivity for US relative to venography

in detecting lower extremity DVT lying between 63% and 100% .[5-8] The clinical importance of below knee DVT is a source of great debate. The main concerns with below knee DVT are the short term risk of above knee propagation and the longer term risk of post-phlebitic syndrome. Both have associated significant morbidity. With the widespread adoption of US, it seems appropriate to define the anatomical distribution of symptomatic DVT, with particular reference to the percentage of isolated below knee thrombi relative to above knee DVT. The principal aim of the study was to examine the anatomical distribution and laterality of thrombi according to age and gender in a large cohort of patients who underwent CV for suspected DVT, thus defining demographic characteristics of the cohort. A secondary aim was to evaluate accuracy of a simple clinical assessment of the likelihood of DVT.

Methods

Between 10th October 1995 and 14th March 2003, 1572 symptomatic patients who underwent CV for suspected DVT had clinical and imaging details entered on a venous thromboembolism database. Venography was the principal imaging technique in our institution until 2003 when the switch to ultrasound was implemented – virtually no venograms are now undertaken. Currently, around 1100 Doppler venograms are performed per year. We serve a population of about 786000.

Data Collection

Doctors requesting imaging for suspected venous thromboembolism (VTE) were requested to complete a short data sheet recording clinical and demographic information. Level of pre-test clinical suspicion was also noted. Once radiological investigation had been performed, results were recorded by a radiologist and the information collated. Data collected included the nature of the study performed, the site investigated and the location of any detected thrombus. Studies were usually carried out by a Specialist Registrar using a standard protocol which included screening of the calf veins to ensure all were visualised with the films reviewed by a consultant radiologist. Data collection required the cooperation of a large number of individuals in different departments and, as is the nature with such studies, was incomplete. We have no reason to believe that has biased the study in any way.

Ethical approval was granted via the Medical School's ethics guidelines for medical student projects.

Statistical Analysis

Statistical analyses were carried out using the Mann-Whitney U-test, the binomial test and chi-square test of association. A 5% significance level was assumed for all tests and 95% confidence intervals were calculated using the Wilson[8] score method.

Results

Demographics

The 1572 patients investigated comprised 676 males (43.0%) and 896 females (57.0%). The age range varied between 16 and 99, with a median age at investigation of 65 years. The 511 patients (32.5%) who had a positive result consisted of 265 males (51.9% of positive cases) and 246 females (48.1% of positive cases). Males were almost twice as likely as females to have a positive result (odds ratio = 1.70, 95% CI: (1.38, 2.11)).

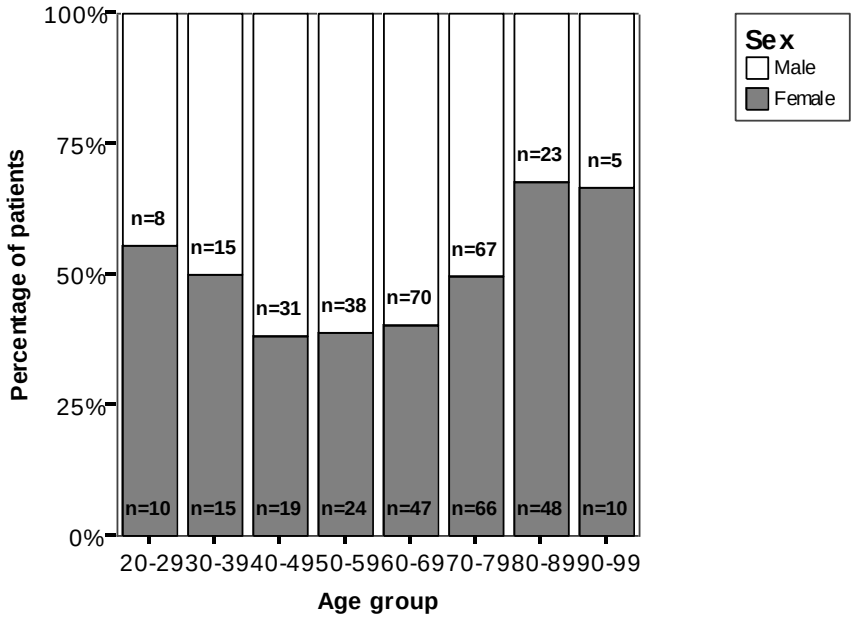

Figure 1 – Age demographics in positive contrast venograms

Distribution of thrombi according to age, sex and laterality

Of the 511 positive cases 15 cases (eight males, seven females) had no data on age recorded and were excluded from the analysis of age distribution. The age at presentation

for females (median = 67 years) was significantly higher (p=0.004) than for males (median = 62 years).

In 1396 cases (88.8%) data were available indicating which leg venography was performed on. The number of cases for which venography was performed on the left leg only, the right leg only and both legs were 694 (49.7%), 565 (40.5%) and 137 (9.8%), respectively. A positive CV result for investigation of the left leg only, the right leg only and both legs was obtained for 221 (15.8%), 178 (12.8%) and 63 (4.5%). In cases where both legs were examined the laterality of thrombus, whether right, left or indeed both, was not recorded.

Table 1 – Distribution of Thrombi in Positive Contrast Venograms

	Males				*Females*			
	Left Leg Investigated	Right Leg Investigated	Both Legs Investigated (laterality not recorded)	Data Missing on Leg(s) Investigated	Left Leg Investigated	Right Leg Investigated	Both Legs Investigated (laterality not recorded)	Data Missing on Leg(s) Investigated
Isolated below knee thrombus	27	33	12	8	26	32	8	4
Above knee DVT thrombus not extending to pelvis or IVC	72	51	15	20	71	49	15	10
Above knee thrombus extending to pelvis or IVC	10	7	5	3	8	5	8	3
Isolated pelvic or IVC thrombus	2	0	0	0	5	1	1	0

The proportion of males and females who had examinations of the left leg only, right leg only or both legs proved to be similar (no significant difference, data not shown). thrombi

were identified in 29.4% (150/511) of positive cases and in 9.5% (150/1572) of all patients undergoing CV.

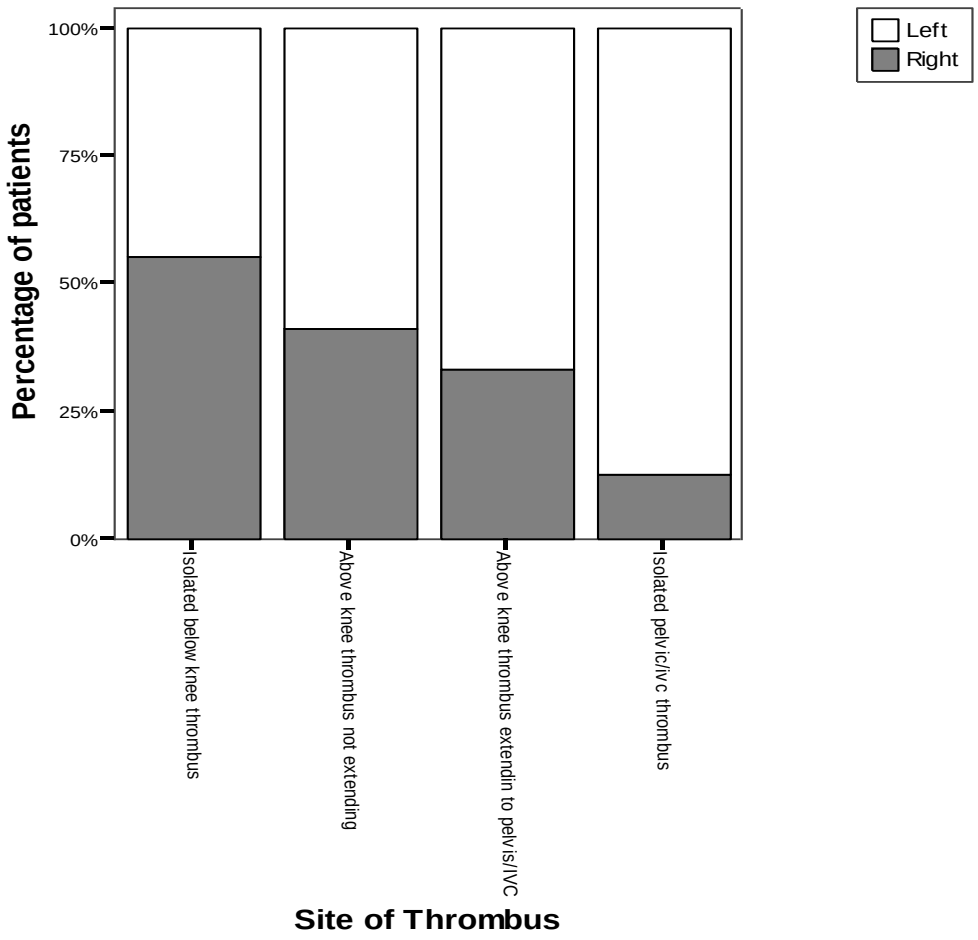

Figure 2 – Laterality with increasing proximity of thrombus

Table 1 demonstrates the anatomical distribution of thrombi. Isolated below knee left sided thrombi were more common than right sided thrombi, with a left-to-right ratio of 1.24:1. (This analysis excluded the 63 patients where both legs were investigated). The left-to right-sided ratios for the location categories 'isolated below knee thrombus',

'above knee thrombus not extending to pelvis or IVC', 'above knee thrombus extending to pelvis or IVC' and 'isolated pelvic or IVC thrombus' were 0.82:1, 1.43:1, 1.5:1 and 7:1 respectively (Figure 2). This suggests the detected left sided predominance is evident above the knee and becomes more pronounced in more proximal veins. The odds ratios for males versus females of thrombi falling into a particular location category are 1.09 (95% CI: 0.74, 1.59), 1.16 (95% CI: (0.89, 1.43)), 0.96 (95% CI: (0.39, 1.52)) and 0.26 (95% CI: (0.05, 1.26)) respectively.

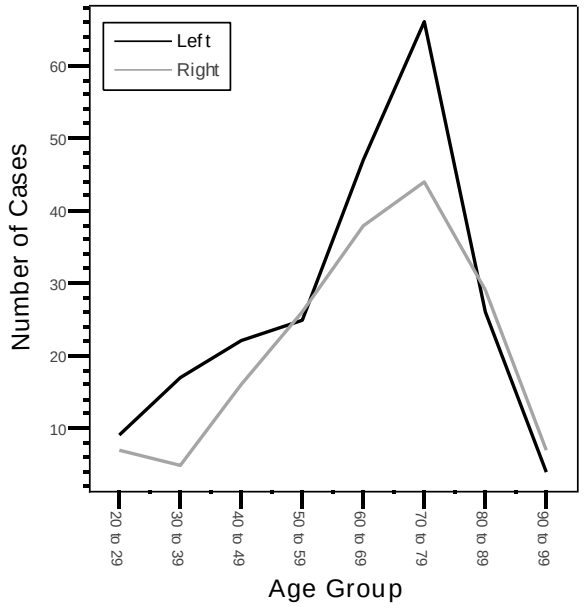

Figure 3 – Leg Distribution by age in positive contrast venograms

Figure 3 demonstrates that the left sided preponderance is most apparent between 70 and 79 with a general trend for the effect to be accentuated with increasing age. However left sided predominance can also be demonstrated in the 30 to 39 age range. Neither of these differences are statistically significant.

Association between clinical suspicion and result

Table 2 compares the level of clinical suspicion with the CV results for DVT for the 1410 patients for whom data on clinical suspicion were recorded. The sensitivity and positive predictive values of clinical suspicions were calculated with 'moderate' and 'high' groups combined to create a 'DVT suspected' group. Under these circumstances, the sensitivity and positive predictive value of clinical suspicion were calculated as 92.1% (95% CI: (89.3%, 94.3%)) and 35.5% (95% CI: (32.8%, 38.3%)) respectively.

Table 2 – Clinical Suspicion

	Result of Scan	
Clinical Suspicion	*Positive*	*Negative*
Low	36	185
Moderate	131	376
High	291	391
Moderate and High Combined	422	767

Discussion

Venous ultrasonography has superseded contrast venography as the primary test in the diagnosis of DVT in the vast majority of centres,[10,11] although venography is still considered the 'gold standard' and continues to have a role in DVT imaging, particularly in the presence of high clinical suspicion but a negative non-invasive test.[12,13] Advantages of US include rapidity, safety, availability and non-invasiveness. US has previously been associated with a low sensitivity and specificity in detection of below knee thrombosis. However, it has been shown that in expert hands ultrasound can have a sensitivity and specificity relative to CV 85% to 100% and 85%

to 100% respectively.[5-8] It is expected that, whilst US is user-dependant, in centres where detection rate is nearing 100% then the proportion of below knee DVT detected would be approaching the figures that we have reported. It is also acknowledged that contrast venography also suffers from a degree of operator dependence and as its use declines that its accuracy is also likely to decline. It must be emphasized that this study was not designed to test the accuracy of either technique but was aimed at mapping the site and extent of lower limb deep venous thrombosis anatomically in a large symptomatic cohort. This is of particular relevance when considering isolated below knee DVT, which may remain undetected by US. Previous work has demonstrated the fact that below knee DVT is almost never confined to the anterior tibial veins and has highlighted importance of imaging the posterior tibial and peroneal veins.[14, 15] The actual veins involved when below knee DVT was present were not recorded in our study.

Debate continues to surround the clinical importance of detecting below knee DVT but there is no doubt that undetected calf thrombi may unpredictably propagate above the knee to give clinically relevant thromboembolism. Reported rates of propagation of below knee DVT vary between 6% and 32%.[16-19] Detection of below knee DVT may also be significant because of its recognized association with post-phlebitic syndrome in the long term.[20,21]

The threshold for investigation of suspected DVT generally drops following the replacement of CV with US as the principle screening tool. With such a change it might be expected that there would be more negative studies but also that the proportion of patients imaged with isolated below knee DVTs would if anything increase as a less symptomatic population associated with a lower investigation threshold would tend to have smaller more distal thrombi. A population of patients undergoing Doppler US

assessment might be expected to have a roughly similar or possibly slightly higher proportion of isolated below knee DVT compared with above knee DVT to that described here. Ultrasound is recognized as being particularly user-dependent with detection rates of below knee DVT varying considerably between operators and departments. Using these CV figures as a 'gold standard' departments and individuals will be able to extrapolate roughly how many, if any, below knee DVTs they are missing. These are particularly likely to be missed if the simple 3 point compression test is used.[22]

In the present study, although more venograms were carried out on females, our finding of roughly equal overall numbers of positive examinations in both sexes corresponds with other studies.[23] It may be that the possibility and thus investigation of DVT is more readily considered in women, perhaps due to greater awareness of risk factors such as the oral contraceptive pill, pregnancy or hormone replacement therapy[24], or they may be more prone to leg swelling for other reasons.

Increasing prevalence of DVT with increasing age (as illustrated in Figure 1) is well recognised[25-27]. This can be accounted for by the accumulation of known risk factors with increasing age for VTE, such as immobility and malignancy. [28-30] Longer female life expectancy is likely to explain the predominance of positive female cases above the age of 70 and also the significant difference in the median age of presentation.

Sex did not significantly influence the regional distribution of thrombi, though there was a trend for males to have more thrombus below the inguinal region and for females to have greater rates of thrombus confined to the pelvis or IVC. The number of isolated pelvic and IVC DVT in our series was very small (<3%), but these thrombi can also be missed by US.

The increased incidence of DVT in the left as opposed to right leg has been recognised[31]. However, there are two additional features of this left-sided predominance highlighted here; its tendency to be particularly marked in more proximal regions and its apparent augmentation in elderly patients (Figure 3). The difference between legs in more elderly groups may be partially attributed to the May-Thurner effect, where left iliac vein external compression is associated with a higher rate of venous thrombosis in left sided veins.[32,33] We postulate that the increase in left-sided DVT in elderly patients above the age of 60 may be due to augmentation of the May-Thurner effect caused by atheromatous dilatation, tortuosity and reduced compliance of the iliac arteries.

The May-Thurner effect may also be responsible for the increased ratio of thrombi in the left side veins proximally. Thrombi usually originate from the calf in the venous sinuses or the valve cusp pockets, and some of these propagate above the knee.[34-36] It may be the rate of development of calf DVT distally is similar in both legs but because of the May-Thurner effect and the venous stasis associated with it, after development of a thrombus it is more likely to propagate on the left with that tendency increasing the more proximally the thrombus extends.

It is reassuring to see that the increasing clinical suspicion of DVT was associated with greater rates of radiologically proven DVT. However, even among patients with a high clinical suspicion of DVT, 57.3% of investigations were negative. This supports the adoption of a standardised scoring system for grading the suspected severity of DVT in order to improve the pre-test predictive value.[37]

In conclusion, in this large prospective series of patients undergoing CV for suspected VTE, 29.4% of positive patients had isolated below knee DVT,with the high proportion of

isolated below knee DVT demonstrated providing a useful baseline for US-based studies of DVT distribution. A left- sided predominance was evident between 30 and 39 and 70 and 79 and more pronounced with more proximal DVT, whilst a moderate or even high clinical suspicion of DVT is a poor positive predictor for thrombi, reinforcing the requirement for more robust methods for establishing the likelihood of DVT.

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Chapter IX

EXCESS RISK OF CANCER IN PATIENTS WITH PRIMARY VENOUS THROMBOEMBOLISM: A NATIONAL, POPULATION-BASED COHORT STUDY

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Abstract

We conducted a nationwide, retrospective cohort study assessing the risk of cancer in VTE patients diagnosed in Scotland 1982-2000.

Significantly elevated risks of cancer were sustained for two years after VTE diagnosis; most notably for ovarian tumours and lymphomas. Younger patients were at an increased relative risk from this association.

Introduction

Trousseau (1872) observed the association between thrombotic phenomena and cancer as far back in 1865. Since then numerous studies have documented the increased risk of cancer patients developing DVT and PE. More recently association has been made between initial presentation with venous thromboembolism (VTE) and subsequent increased risk of cancer. This association has been investigated in several studies but conclusions vary widely from no excess risk (Griffin et al, 1987: O'Connor et al 1984) , to a definite increased risk (Golgberg et al 1987: Prandoni et al 1992: Sorensen et al 1998: Baron et al 1998) . Results of the time span of increased risk after DVT/PE diagnosis also vary, as do the types of cancer involved and the age groups that are at highest risk. This study was designed to determine 1) if there is an increased incidence of cancer in a large population-based cohort of Scottish patients with a new diagnosis of VTE, 2) to investigate any excess risk in relation to time since, and age at diagnosis of VTE and 3) to identify which cancers, in a Scottish population, are particularly associated with previous VTE.

Materials and Methods

Patients.

The Information and Statistics Division (ISD) of the National Health Service (NHS) in Scotland has linked (at time of analysis), using probability matching, information on all Scottish hospital inpatient discharges (1981-July 2002), death records (1981-2002), and cancer registry records (1981-2000). For this study all records for patients diagnosed with a DVT (ICD 9 451.1 and ICD10 I26, I80.1, I80.2), or PE (ICD9 415.1 and ICD 10 I26) between 1982 and 2000 were selected from the linked database giving a population based database covering 19 years. Individuals presumed to be visitors who did not have a Scottish postcode and for whom follow-up data would not be available were excluded. To reduce the number of patients with secondary VTE, patients who had undergone surgery in the 6 weeks prior to VTE were excluded, as were pregnant females. Due to the difficulties in coding we were unable to exclude those with haemostatic defects (thrombophilia). Follow-up for the occurrence of cancer was from the initial diagnosis of DVT/PE until the end of 2000 because the cancer records were not complete beyond this point. Hospital inpatient discharge data was available from 1981 onwards; however, the starting date was restricted to 1982 to reduce the erroneous inclusion of cases that had recurrent VTE.

Cancer diagnosis following DVT/PE was included if it was a first diagnosis of malignant cancer. Patients with a previous primary malignant cancer were excluded from the study. Only first cancers were included to avoid cancer itself being a confounding factor for a subsequent cancer, through genetic susceptibility, shared risk factors, or the

effects of therapy. Data for non-melanoma skin cancer was excluded, as data is less likely to be complete for this common and usually non-fatal condition that often does not require hospital admission. Patients with cancer diagnosed within 1 month of VTE diagnosis were excluded.

Statistical Analysis

The expected number of cases of cancer in the cohort of VTE patients was calculated on the basis of Scottish national incidence rates of first malignant cancer according to age (5 year age bands to 85+), sex and period of diagnosis (1982-86, 1987-91, 1992-96, 1997-2000). Multiplying the number of person years of observation accumulated by the cohort (calculated from the date of diagnosis of VTE to the date of cancer diagnosis, date of death, or 31/12/2000, whichever came first) by the national incidence rates (by age, sex and time period) yielded the expected number of cancers of the VTE cohort if they were exposed to the same risk as the general population, calculating person-years for each subgroup (age at VTE diagnosis and time since VTE diagnosis) separately. The ratio of observed to expected cases gives the standardised incidence ratio (SIR) or relative risk, and confidence intervals were estimated assuming the observed number of cases follows a Poisson distribution.

Results

In total 77,572 patients were identified with DVT/PE or both diagnosed between 1981 and 2000. After applying the exclusion criteria our cohort contained 59,534 patients, of whom 55% were female and 45% male. In all 11.1% were ≤39, 21.2% were 40-59, 22.4% 60-69, 26.7% 60-79 and 18.7% 80+. The median duration of follow-up was 32 months.

Overall Risk of Developing Cancer

Over the 19 -year period 4,441 (7.5%) patients were diagnosed with a first primary cancer after (at least 1 month after) their VTE diagnosis. The standardised incidence rate (SIR) for all cancers was 1.28 (CI 1.25-1.33) compared to that expected based on the incidence of first malignancies in Scotland.

Table 1: Observed and Standardised Incidence Ratios (SIR) of First Cancers Diagnosed among Patients with previous DVT/PE, in Scotland 1982-2000.

Cancer group	ICD10 code	1 month to 1 year after VTE diagnosis		1st to 2nd year after VTE diagnosis		3rd to the 5th year after VTE diagnosis	
Oesophagus	C15	21	1.4 (0.87 2.18)	28	2.1 (1.36 2.97)	29	1.0 (0.63 1.36)
Stomach	C16	77	3.2 (2.50 4.01)	25	1.1 (0.73 1.69)	45	0.9 (0.67 1.24)
Colon	C18	127	2.9 (2.43 3.48)	49	1.2 (0.90 1.62)	104	1.2 (0.94 1.40)
Rectum and anus	C19 C21	28	1.3 (0.84 1.84)	18	0.9 (0.53 1.41)	42	0.9 (0.67 1.25)
Liver	C22	17	3.9 (2.26 6.23)	2	0.5 (0.04 1.82)	12	1.3 (0.67 2.32)
Gallbladder and biliary tree	C24	5	2.6 (0.80 6.03)	3	1.7 (0.30 4.96)	4	1.0 (0.26 2.57)
Pancreas	C25	55	4.1 (3.07 5.32)	16	1.3 (0.74 2.12)	23	0.8 (0.53 1.27)
Lung	C33 C34	305	3.0 (2.71 3.39)	125	1.4 (1.13 1.62)	183	0.9 (0.77 1.03)
Breast	C50	70	1.6 (1.20 1.96)	54	1.3 (0.98 1.71)	98	1.1 (0.87 1.30)
Corpus	C54	15	2.7 (1.46 4.38)	3	0.6 (0.10 1.72)	10	0.9 (0.42 1.63)
Cervix	C53	15	3.6 (2.01 6.02)	5	1.3 (0.41 3.13)	12	1.5 (0.74 2.54)
Ovary	C56	64	7.1 (5.48 9.03)	11	1.3 (0.66 2.40)	22	1.2 (0.76 1.84)
Prostate	C61	112	3.0 (2.42 3.54)	41	1.1 (0.81 1.54)	111	1.3 (1.08 1.58)
Bladder	C67	50	2.0 (1.51 2.67)	16	0.7 (0.40 1.15)	59	1.2 (0.88 1.49)
Kidney and urothelium	C64, C68	37	4.3 (3.00 5.86)	9	1.1 (0.51 2.14)	22	1.2 (0.76 1.85)
Meninges and brain	C70 C72	12	2.5 (1.28 4.40)	5	1.1 (0.35 2.66)	9	0.9 (0.41 1.75)
Non-Hodgkins lymphoma	C82 C85	64	5.1 (3.95 6.51)	19	1.6 (0.98 2.56)	24	0.9 (0.58 1.37)
Hodgkins disease	C81	7	6.0 (2.34 12.4)	2	1.9 (0.17 6.83)	2	0.9 (0.08 3.17)
Multiple myeloma	C88, C90	24	3.8 (2.42 5.72)	10	1.7 (0.82 3.19)	15	1.2 (0.63 1.90)
Leukaemia	C91 C96	20	1.9 (1.14 2.93)	10	1.0 (0.48 1.90)	20	0.9 (0.55 1.41)
Other cancers*		220	3.2 (2.82 3.70)	74	1.2 (0.92 1.48)	174	1.2 (1.04 1.42)
All cancers*	C00 C96	1345	2.9 (2.74 3.06)	525	1.2 (1.12 1.33)	1020	1.1 (0.99 1.13)

*Excluding nonmelanoma skin cancer (ICD10: C44).

Risk of cancer in relation to time since, and age at diagnosis of VTE

For all malignancies combined there was a high excess risk of being diagnosed with cancer (SIR 4.2, CI 3.9-4.5) within 1 to 6 months after diagnosis of VTE; with a slowly declining but still significant excess risks for each six-month follow-up period up to two

years. The risk was significantly raised for all individual malignancies calculated, but of particular note with SIRS greater than 5.0 were cancers of the ovaries, and Hodgkins

	Age at VTE diagnosis				
Time since VTE diagnosis	20–39	40–59	60–79	80+	All ages
1 6 months	5.8 (2.7 11)	7.5 (6.4 8.8)	4.2 (3.8 4.5)	3.0 (2.6 3.5)	4.2 (3.9 4.5)
6 12 months	2.3 (0.6 5.8)	2.3 (1.8 3.0)	1.7 (1.5 1.9)	1.5 (1.2 1.9)	1.7 (1.5 1.9)
12 18 months	1.0 (0.1 3.7)	1.5 (1.0 2.1)	1.3 (1.1 1.5)	1.0 (0.8 1.3)	1.2 (1.1 1.4)
18 24 months	2.2 (0.6 5.6)	1.6 (1.1 2.2)	1.1 (0.9 1.3)	1.4 (1.1 1.8)	1.2 (1.1 1.4)
24 30 months	1.5 (0.3 4.5)	1.1 (0.7 1.6)	1.0 (0.8 1.2)	1.1 (0.8 1.4)	1.0 (0.9 1.2)
30 36 months	0.5 (0.0 3.1)	0.8 (0.5 1.3)	1.1 (1.0 1.4)	1.0 (0.7 1.5)	1.1 (0.9 1.3)
36 48 months	1.1 (0.3 2.7)	1.2 (0.9 1.5)	1.1 (1.0 1.3)	1.1 (0.8 1.4)	1.1 (1.0 1.2)
48 60 months	1.6 (0.6 3.5)	1.2 (0.9 1.5)	1.0 (0.9 1.2)	1.0 (0.7 1.3)	1.1 (0.9 1.2)
5 10 years	1.2 (0.7 1.8)	1.1 (1.0 1.3)	1.0 (0.9 1.1)	0.9 (0.8 1.2)	1.0 (1.0 1.1)

Table 2 Standardised Incidence Ratios (SIR) with 95% confidence intervals of First Cancers Diagnosed among Patients with previous VTE assessed according to age band and time interval after diagnosis of VTE.

and Non-Hodgkins lymphoma (Table 1). The risk after 2 years was very similar to that expected in the general population. This excess risk within the first two years was seen in all age groups but declined as age increased (table 2) with excess risk approximately twice as large in patients aged under 60 at VTE diagnosis compared to those aged 60 or over (table 2) .

Discussion

We evaluated the association between VTE and subsequent diagnosis of cancer in a large cohort and demonstrated a definite increased risk of being diagnosed with malignancy after a primary episode of VTE. The risk is particularly marked within 1 to 12 months after VTE diagnosis. Some studies have suggested that a small increase in risk persists many years after the diagnosis of VTE (Golgberg et al 1987: Prandoni et al 1992).

Our overall figures show an excess risk sustained for the first 2 years after VTE diagnosis, and thereafter, the risk returns to that expected based on background rates. In our cohort the excess risk of cancer was highest in patients aged under 60 at VTE diagnosis, however, as malignancy has an increased prevalence with increasing age, older patients have a greater absolute risk of malignancy after a first episode of VTE with one in twenty-five 60-75 year olds developing cancer within one year (fig1). The results of this study can only be generalised to patients admitted to hospital, and relies on accurate discharge coding, cancer registration and linkage. As almost all acute illnesses are treated in NHS hospitals in Scotland and as over the period of the study the practice was to admit acute VTE to hospital for stabilisation of anticoagulation it is likely that most diagnosed cases have been included. There may however be other undiagnosed cases that we are unaware of as VTE is a diagnosis which is difficult to make clinically and which is often overlooked. The accuracy of discharge coding data in Scotland is estimated at around 90% (Harley et al 1996) and the quality of cancer registry data is also high (Brewster et al 1994: Brewster et al 1997). Mismatched records in the Scottish record linkage system occur in less than 2% of cases (Kenrick and Clarke 1993). Any bias introduced by mis-coding or mismatched records is likely to underestimate risk. Bias occurring due to loss of subjects through migration is likely to be small and would also lead to an underestimation of risk.

Although our analysis had the strength of being a large population-based study, our data lacked clinical detail, in particular about risk factors for thromboembolism and the stage of the cancer at diagnosis.

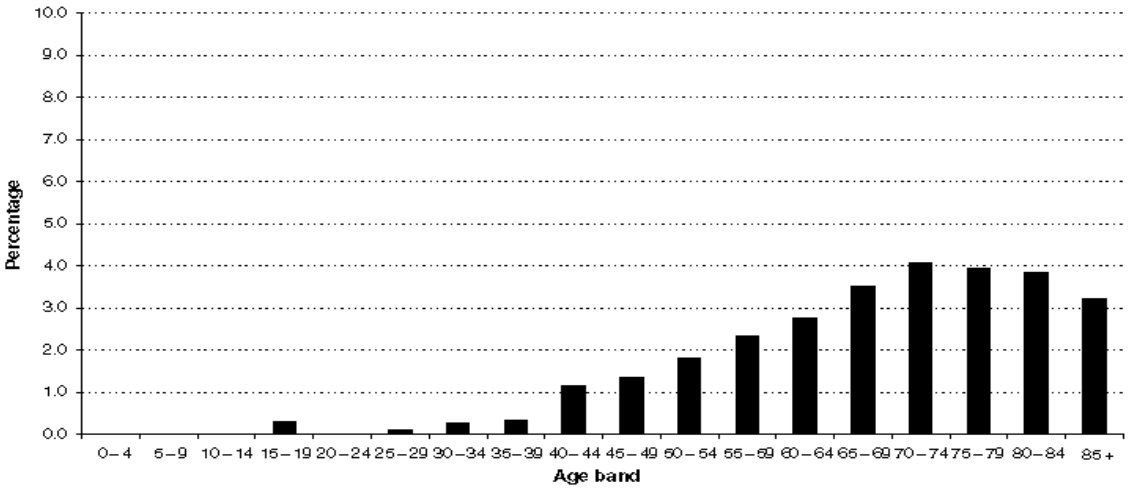

Figure 1 Percentage of patients who developed cancer within 1–12 months after the first episode of VTE in relation to the total number of VTE patients, by age at VTE diagnosis.

This study provides further evidence for the increased risk of developing cancer after an episode of primary VTE and shows this persists for a 2 year period, however, it does not provide an answer to the question whether such patients should be screened for occult malignancy. It is reported that in cases where cancer is diagnosed after an episode of VTE the cancer is often advanced and the outcome is very poor with a one-year survival of only 12% (Sorenson et al 2000). It is also uncertain whether earlier diagnosis changes outcome, and any perceived benefits of earlier diagnosis must be weighed against the psychological and physical morbidity and discomfort associated with extensive investigations (Nordstrom et al 1994: Prins et al 1994). Simple clinical and diagnostic methods of screening, in patients with idiopathic DVT/PE seem sensible and are recommended in other studies (Monreal et al 1991: Sorensen et al 2000: Piccioli et al 1996).

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Table 1: Observed and Standardised Incidence Ratios (SIR) of First Cancers Diagnosed among Patients with previous DVT/PE, in Scotland 1982-2000.

Chapter X

THE INFLUENCE OF METEOROLOGICAL VARIABLES ON THE DEVELOPMENT OF DEEP VEIN THROMBOSIS

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SUMMARY

The influence of weather on deep venous thrombosis (DVT) incidence remains controversial. We aimed to characterise the temporal association between DVT and meteorological variables including atmospheric pressure. Data relating to hospital admissions with DVT in Scotland were collected retrospectively for a 20 year period for which corresponding meteorological recordings were available. Weather variables were calculated as weighed daily averages to adjust for variations in population density. Seasonal variation in DVT and short-term effects of weather variables on the relative risk of developing DVT were assessed using Poisson regression modelling. The model allowed for the identification of lag periods between variation in the weather and DVT presentation. A total of 37.336 cases of DVT were recorded. There was significant seasonal variation in DVT with winter peak. Seasonal variation in wind speed and temperature were significantly associated with seasonal variation in DVT. When studying more immediate meteorological influences, low atmospheric pressure, high wind speed and high rainfall were significantly associated with an increased risk of DVT approximately 9-11 days later. The effect was most strikingly demonstrated with atmospheric pressure, every 10 millibars decrease in pressure being associated with a 2.1% increase in relative risk of DVT. DVT is particularly associated with reduction in atmospheric pressure giving weight to the hypothesis that reduced cabin pressure in long haul flights contributes to DVT. These findings have implications for our understanding of the pathogenesis of DVT.

INTRODUCTION

In the US venous thromboembolism (VTE) has an estimated incidence exceeding 1 per 1000 of the population, contributing to over 50,000 deaths per annum.[1] While a number of well defined risk factors for the development of VTE are recognised (such as immobility, recent surgery, recent fracture, pregnancy, malignancy and oestrogen therapy) the influence of meteorological variables remains controversial.

Pulmonary embolism (PE) has been associated with low atmospheric pressure, low temperature, high rainfall, high relative humidity and high vapour pressure.[2-6] The effects of meteorological variables on deep vein thrombosis (DVT) are less well characterized. Overall, the emergence of a consistent effect of weather on VTE has been hampered by the requirement for large datasets to detect relatively small influences on the risk of VTE, and a tendency for previous, smaller studies to yield conflicting conclusions.

Scotland is a comparatively small country both geographically and demographically (population approximately 5.1 million), with a relatively stable population, well-established meteorological records and a centralized diagnostic coding system for hospital admissions. This combination presented us with the opportunity to make a detailed assessment of the associations between DVT and variations in weather. The aim of this study was therefore to investigate the temporal association between DVT and meteorological variables, with particular emphasis on atmospheric pressure.

METHODS

Data on all discharges from Scottish hospitals, covering the country's entire population, are compiled at the Information Services Division (ISD), National Health Service (NHS) Scotland. Diagnoses are recorded on each patient's hospital discharge summary using standard International Classification of Disease (ICD) codes. All acute presentations to hospital with a diagnosis of DVT over the period 1st January 1981 to 31st May 2001 were included in the study. Patients were considered to have had DVT if the principal diagnosis recorded was ICD9 (4511 or 4151) or ICD10 (I80). The index date for each patient was taken to be the date of admission to hospital.

Data from weather stations in each of the fifteen NHS Trusts in Scotland were recorded each day during the corresponding period and provided by the National Meteorological Office. Measured variables included atmospheric pressure, temperature (minimum and maximum), hours of sunshine, rainfall, snowfall and wind speed. Atmospheric pressure and wind speed were calculated as the average of four 6 hourly readings taken each day. Average daily weather statistics for the whole of Scotland were calculated as weighted daily averages of the values recorded at the 15 weather stations, with weights taken as the population sizes of the NHS Trusts. This ensured that weather statistics most closely matched the population covered.

To test for seasonal variation in the rate of DVT, the number of DVTs per calendar month was calculated, and a Poisson regression model was used to determine whether the months differed significantly.

On the assumption that weather may affect the incidence of DVTs through seasonal effects and/or short-term changes, models were constructed to incorporate these influences. To assess the seasonal influence, average weather statistics and numbers of DVTs were calculated for each week of the year (ie 1,2,3,…,52) and Spearman rank correlation coefficients calculated to assess the correlations between them. To assess the short term effects of weather, daily meteorological statistics and numbers of DVTs were analysed using Poisson regression models. These models adjusted for day of the week, seasonal trend (by fitting week of the year), time trend (to allow for the increasing incidence of DVT observed throughout the study period) and change in diagnosis rates following the switch from ICD9 to ICD10 coding in April 1997. On the assumption that there would be a delay between any biological influence of meteorological variables and clinical presentation with DVT, models included lag periods for the effect of weather varying from 0 to 21 days prior to presentation.

RESULTS

A total of 37336 cases of DVT were recorded in the study period. The mean age of the patients was 60.8 (SD 17.6) years and 48.0% were male. There was a significant seasonal variation in the incidence of DVT, with the highest average incidence in January and the lowest in August ($p<0.0001$; Figure 1). Meteorological data for the study period are described in Table 1 and all measured weather variables had a highly significant seasonal variation ($p<0.0001$). The seasonal variation in DVT was significantly associated with the

seasonal variation in wind speed (p=0.006), minimum and maximum temperature (p=0.0009 and 0.001 respectively), and snowfall (p=0.01), but not with atmospheric pressure, rainfall or hours of sunshine.

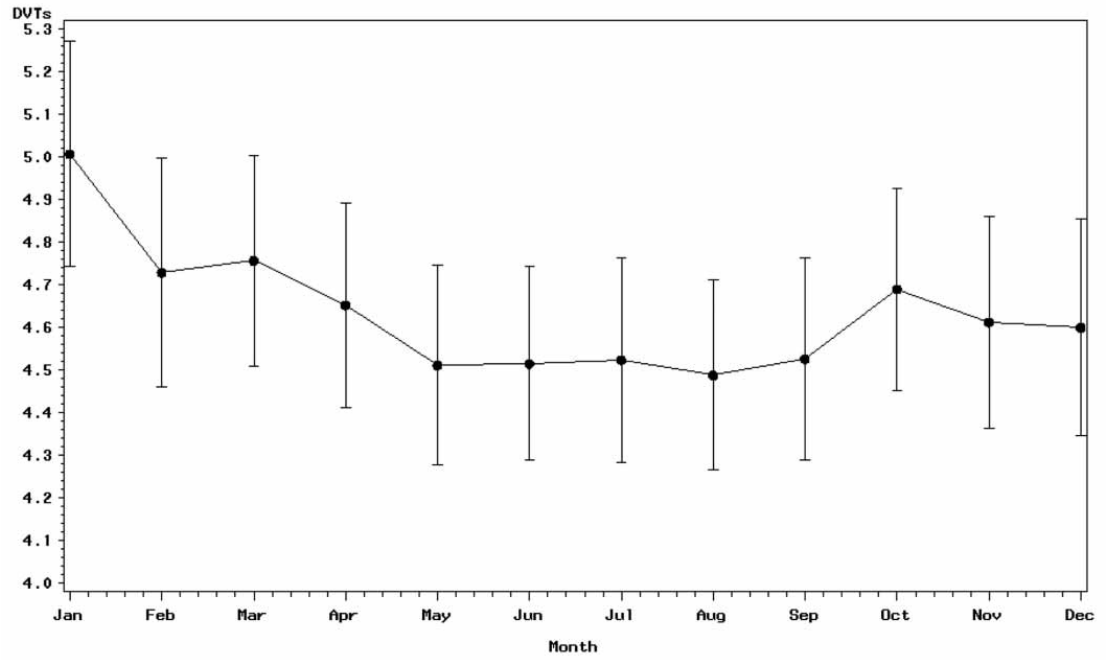

Figure 1: Seasonal variation in DVT rate. Result represents the mean daily rate (%) of DVT in each calendar month (error bars represent 95% confidence intervals.)

When considering short-term influences of weather, low atmospheric pressure, high wind speed and high rainfall were associated with significantly increased rates of DVT (Table 2). The association was most striking for atmospheric pressure (Figure 2). For each variable the association was characterized by a lag period, typically of the order of 9-10 days. The data suggest that a relative decrease in atmospheric pressure results in an increased risk of presenting with DVT some 6 to 12 days later. The risk was greatest for a lag period of 9 days with the relative rate of DVT increased by 2.06% (95% CI 1.14-2.99%) per 10 millibars decrease in pressure. Similarly an increased wind speed was

associated with a significantly increased rate of presenting with DVT 9 to 12 days later, the greatest increase being identified for a lag period of 10 days. An increase in rainfall is associated with a significantly increased rate of presenting with DVT 2, 10,11 and 13 days later, the relative rate being greatest for a lag period of 10 days. High snowfall on the date of admission was associated with a reduction in the rate of presenting with DVT. No clear association was found between the incidence of DVT and the short term effect of temperature or hours of sunshine.

Table 1: Mean daily values for measured meteorological variables by calendar month

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Ave. within month SE
Pressure (millibars)	1009.7	1011.7	1009.9	1012.7	1015.2	1014.8	1014.3	1013.3	1011.6	1008.9	1009.3	1008.6	0.5
Wind speed (knots)	9.55	9.91	9.72	8.29	7.66	7.37	7.07	7.04	7.65	8.28	8.17	8.46	0.14
Minimum tempera-ture (°C)	0.82	0.97	1.83	2.98	5.18	7.70	9.68	9.60	7.91	5.37	2.96	1.28	0.09
Maximum tempera-ture (°C)	5.94	6.35	7.91	10.02	13.07	14.95	16.94	16.80	14.48	11.33	8.37	6.50	0.09
Rainfall (mm)	3.35	2.89	2.87	1.92	1.78	2.01	2.03	2.31	3.18	3.61	3.36	3.49	0.13
Daily sunshine (hours)	1.39	2.39	3.23	4.54	6.00	5.39	5.12	4.86	3.91	2.80	1.85	1.09	0.10
Snow (prob-ability)	0.196	0.160	0.088	0.017	0.004	0.002	0.004	0.003	0.002	0.001	0.037	0.124	0.004

DISCUSSION

The study benefits from the large number of patients accumulated using a consistent national system for recording health outcome data throughout Scotland over a 20 year period. As a small country (approximately 79000 km^2) with a temperate climate influenced largely by the Atlantic Gulf Stream, widely ranging extremes of weather in different locations on the same day are relatively unlikely.

It is recognised by physicians and radiologists involved in the diagnosis and management of venous thrombo-embolism that, although a common disease, the numbers of patients presenting with the disease varies greatly from week to week and month to month.

Table 2:Short-term effects of weather on incidence of DVT's, adjusted for seasonality. Results are expressed as percentage relative rate. *Statistically significant alterations in rate at the p<0.01 level. Thus, for example, for every 10 millibars fall in pressure on a given day, the relative rate of DVT 9 days later is increased 2.06%, the relative rate 10 days later is increased by 1.85% etc.

Days prior to admission	Atmospheric Pressure (per 10 millibar decrease)	Windspeed (per 1 knot decrease)	Daily rainfall (per mm increase)	Snow (if any)	Maximum Temp (per 1°C decrease)	Minimum Temp (per 1°C decrease)	Daily sunshine (per hour decrease)
0	0.19	0.28	0.10	–13.04*	–0.45	–0.53	0.35
1	0.54	0.32	–0.13	–8.86	–0.29	0.03	0.16
2	0.19	–0.05	0.56*	–1.14	–0.09	0.34	0.33
3	0.33	0.20	0.18	3.16	0.41	0.21	–0.24
4	0.85	0.26	–0.12	–1.23	0.34	0.23	0.16
5	1.18	0.22	0.15	–3.04	0.36	0.42	0.15
6	1.30*	0.24	0.36	–3.34	0.53	0.25	0.13
7	1.46*	0.31	0.27	–4.85	0.67	0.60	0.44
8	1.82*	0.20	0.40	–3.23	0.48	0.38	0.25
9	2.06*	0.52*	0.30	–1.76	0.51	0.17	0.26
10	1.85*	0.59*	0.80*	–2.45	0.24	–0.04	0.30
11	1.27*	0.49*	0.59*	–1.26	0.25	–0.09	0.18
12	1.26*	0.54*	0.29	–2.39	0.01	–0.24	0.23
13	0.94	0.34	0.46*	–3.55	–0.26	–0.35	0.55
14	0.93	0.32	0.15	–2.94	–0.09	–0.06	0.26
15	1.01	0.25	–0.11	–2.19	–0.10	0.07	–0.04
16	0.61	0.09	0.19	–0.09	–0.04	0.08	0.15
17	0.76	0.28	0.18	–3.77	–0.26	–0.12	–0.01
18	0.46	0.04	0.37	–5.11	–0.38	–0.10	0.01
19	0.42	0.22	0.36	–1.20	–0.19	–0.29	0.04
20	0.45	0.36	0.08	–3.21	–0.05	–0.35	0.00
21	0.05	0.17	0.36	–3.30	–0.36	–0.40	0.40

Our findings suggest that meteorological factors may contribute to this variability describing a seasonal variation in the incidence of DVT, with winter predominance. They

also suggest that low atmospheric pressure, high rainfall and high wind speed are associated with a small but significantly increased rate of DVT with a distinct lag period (typically 9-12 days) characterizing the relationship between these variables and subsequent presentation with DVT. Small calf DVT are often initially asymptomatic and it is recognised that is often a lag time between insult the initial insult where DVT first develops and the time of clinical presentation and diagnosis at hospital. The finding of a significant correlation between a drop in atmospheric pressure and presentation with DVT puts that delay at maximum between days 6 and 12. High rainfall 2 days prior to presentation was also statistically significant in predicting DVT, however the biological significance is unclear as high rainfall for lag periods of 1 and 3 days was not significant.

Various studies have addressed the question of seasonal variation in VTE. A large retrospective study involving 65000 cases of DVT and over 60000 cases of PE in France found clear evidence for seasonal variation,[7] broadly in keeping with smaller studies from Europe and Australia.[3,8-12] This effect appears to extend beyond idiopathic DVT, having also been described for post-operative DVT.[13] Importantly, in studies reporting a seasonal variation the trend for a winter and autumn predominance has been relatively consistent. It must be emphasized that seasonal variation has not been observed by all investigators,[14-17] however it may be relevant that the two largest studies to date (our own study and that by Boulay et al,[7]) found a trend towards winter predominance.

Many biological variables could potentially contribute to the seasonal influence on VTE. For example a procoagulant profile is known to develop in venous blood during colder months.[18] In addition respiratory infections are commoner in winter months and are

themselves associated with an increase in VTE.[19] Furthermore, it may be plausible to argue that populations are more sedentary during the winter.

Our finding that low atmospheric pressure is associated with DVT is broadly in keeping with previous observations in VTE. In particular Esquenet et al[20] found an association between DVT and low atmospheric pressure which was more pronounced as pressure gradients widened. In an earlier study Scott et al[4] found that PE was associated with a decrease in atmospheric pressure. Importantly, they also found a lag effect but this was of the order of 3 days as opposed to the longer interval described here. A Turkish study found that PE was more common in spring, which in turn was associated with relatively low atmospheric pressure.[6]

In contrast, studies by Becker et al[2] and Clauss et al[5] failed to demonstrate an association between atmospheric pressure (or temperature) and PE. Interestingly however these studies, both of which were smaller than the present study, identified a relationship between PE and high rainfall in keeping with our own observations.

The emerging picture for VTE finds some parallels in studies of arterial thrombosis. [21] For example myocardial infarction has variously been associated with increased incidence in the winter months, low temperature, and low/falling atmospheric pressure.[22-24]

Our analyses of short term weather effects (Table 2) were adjusted for seasonality and therefore the association found between meteorological variables and DVT is not an epiphenomenon based on seasonality. This in turn begs the question of how influential atmospheric pressure, rainfall and wind speed are in the development of DVT. Our data

suggest that the influence is small but statistically significant. To place this in context a relative decrease in atmospheric pressure of 10 millibars predicts for a 2% increase in the rate of DVT nine days later (Table 2).

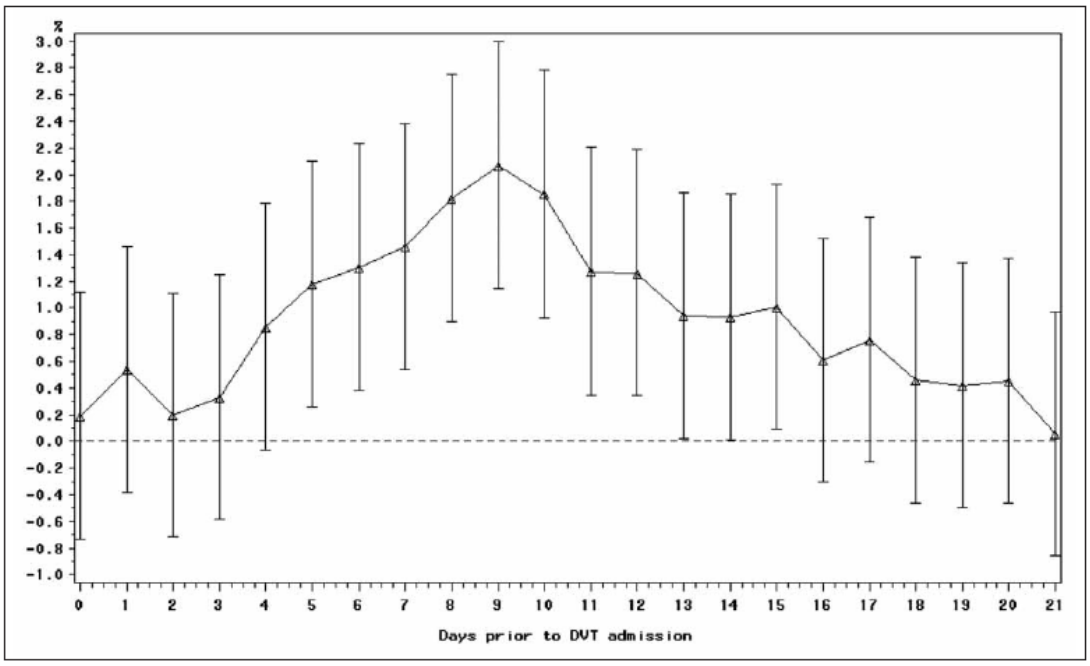

Figure 2: Short-term effects of atmospheric pressure on the rate of presentation with DVT. Results are expressed as percentage relative rate for every drop in atmospheric pressure of 10 millibars. (error bars represent 95% confidence intervals.) Any point above the broken horizontal line represents an increased rate (and any point below the broken line represents a decreased rate) of DVT. Wherever both confidence limits fall above (or below) the line, the difference is statistically significant at the $p<0.05$ level.

The mean daily variation (SD) in atmospheric pressure in Scotland during the study period was 12.8 millibars. Thus on average pressure is predicted to cause DVT incidence to rise or fall by 2.6 % each day. Similarly, for every increase in rainfall of 1 mm or for every 1 knot increase in wind speed, the rate of DVT 10 days later was increased 0.8% and 0.6% respectively, while mean daily variability (SD) in rainfall and wind speed in Scotland were 3.4 mm and 3.8 knots respectively. Weather statistics are inter-related, for example low pressure often accompanies a period of heavy rainfall. Therefore the effects of pressure, wind speed and rainfall on the incidence of DVTs cannot be considered

additive. Although statistical models can demonstrate which of the measurements is the most predictive statistically, they cannot provide evidence for a causal relationship to DVT. However it is tempting to speculate on biological plausibility linking these factors to DVT. In this regard it has been shown that hypobaric hypoxia, but not normobaric hypoxia, is associated with hypercoagulability in humans,[25-27] while hypobaric conditions favour DVT formation in postoperative rabbits.[28] Toff et al[29] did not show a statistical increase in hypercoagulability in relation to hypobaric oxygen in a group of patients without known thrombophilia. However their exploratory analysis did show greater dispersion with more outliers in the distribution of changes in coagulation activation in the hyperbaric than in the normobaric limbs of their study. They accepted that some individuals may respond differently and were unable to say whether this finding was due to chance or to a genuine biological difference. Our hypothesis is that some, but not all, individuals are susceptible to the effects of reduced pressure and that those who are susceptible are more likely to be those with a pre-existing thrombotic tendency. In the background, a vigorous debate continues to surround the effect of flying on VTE.[30-35] The cabins of commercial aircraft are generally pressurised to a level equivalent to 8000 feet above sea level (700 millibars), and have relatively low humidity. Evidence for a small increase in the rate of DVT on particularly long flights seems to be emerging and it could be speculated that our data broadly support reduced air pressure as a plausible contributing factor towards the development of DVT in long haul flights in susceptible individuals.

The effects of rainfall and wind speed on DVT have not received much scientific attention. It has been postulated that pro-thrombotic pollutants could be carried as

condensation nuclei in water droplets.[5] This contention could be extended to encompass increased dispersal of atmospheric pollutants and/or organic/infective particles by increased wind speeds. However this remains entirely conjectural and has not been scientifically tested. Alternatively the relationship with rainfall and wind speed may have arisen purely as a consequence of their association with atmospheric pressure.

Several potential limitations of this study should be acknowledged, particularly the retrospective design. This raises concerns especially over accuracy of diagnosis of DVT, and the potential for missed cases. Available evidence suggests that over the duration of the study hospital-based diagnosis of DVT in Scotland was increasingly based on objective investigations rather than clinical assessment alone[36,37] and diagnostic confirmation is therefore likely to have been high. It is also reassuring that the incidence of DVT over the 20 year study period (approximately 30 per 100,000 per annum) is broadly in line with other incidence estimations.[1] However, any inconsistencies in diagnosis are unlikely to alter the seasonal and short term associations demonstrated. Also, multiple tests of significance have been carried out to assess the different weather statistics and lag periods and caution is needed when interpreting significance levels. However, the overall pattern of results across the lag periods helps to confirm the presence of a genuine effect.[38] For example, the effect of atmospheric pressure is negligible on the day of presentation, significant during days 6-12 reaching a peak at 9 days and then negligible again by 21 days.

In summary low atmospheric pressure, high rainfall and high wind speed are associated with a small but significant increase in the rate of DVT. The mechanisms and interactions involved deserve further scientific attention.

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Chapter XI

IDIOPATHIC VENOUS THROMBOEMBOLIC DISEASE IS ASSOCIATED WITH A POORER PROGNOSIS FROM SUBSEQUENT MALIGNANCY

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ABSTRACT

Methods

We carried out a retrospective study of prognosis in Scottish patients diagnosed with cancer within five years following a venous thromboembolism (VTE).

Results and Conclusions

Prognosis was significantly poorer if a VTE occurred up to two years before cancer diagnosis, most notably if cancer was diagnosed in the six months after a VTE.

INTRODUCTION

Trousseau first described an association between malignancy and venous thromboembolism (VTE) more than a hundred years ago (Trousseau 1872), since which time it has become clear that malignancy is a risk factor for VTE. More recently, several large retrospective population studies have shown an increased risk of cancer after a diagnosis of idiopathic VTE with standardised incidence ratios of 3 - 4.2 within the first six months.[1-3] The length of time for which increased risk can be shown varies and we have previously shown a persistent, albeit declining, risk up to two years from VTE diagnosis.[3] Those with secondary VTE do not seem to be at similar risk of future malignancy.[4-5] In view of this increased risk, there has been an interest in screening patients with idiopathic VTE for occult malignancy. Initial retrospective studies in patients with idiopathic deep vein thrombosis (DVT) suggested that most occult

malignancy could be detected at presentation by routine evaluation.[1,6] However, more recent prospective studies advocate a more intensive investigative approach[7-8] .

Relatively little is known about the impact that a preceding VTE has on the prognosis of subsequent malignancy and this may well inform the screening debate. A Danish registry study compared survival in patients with cancer and a preceding history of idiopathic VTE with that of a matched control group of cancer patients without preceding VTE. Those diagnosed with cancer during their admission for VTE had a one year survival of 12% compared to 36% in the control group. One year survival rates were also poorer in those diagnosed with cancer in the year following a VTE. [9]

Following on from previous work, we conducted a retrospective study examining the prognosis of Scottish patients in whom malignancy was diagnosed at the time of, or in the five years following, a VTE.

METHODS

The Information Services Division (ISD) of the National Health Service in Scotland has linked anonymised information (using probability matching) on all Scottish hospital inpatient discharges, death records and cancer registry records from 1981 to 2005. For this study, all records with a diagnosis of DVT or pulmonary embolism (PE) between 1982 and 2000 were selected from the linked, non-identifiable database, giving a population-based database covering 19 years.

To reduce the number of patients with secondary VTE, those who had undergone surgery in the preceding six weeks were excluded, as were pregnant females. Due to difficulties

in coding, we were unable to exclude those with thrombophilias. Records without a Scottish postcode were excluded

Cancers were classified as occurring following a VTE if they represented a first diagnosis of malignancy, excluding non-melanomatous skin cancers, in the five years following a VTE.

Table 1: Numbers available for analysis according to cancer site and time period from diagnosis of VTE to diagnosis of malignancy.

	Number of patients according to time period from diagnosis of VTE to diagnosis of malignancy				
Site of malignancy	**0-6 months**	**6-12 months**	**1-2 years**	**2-5 years**	**No VTE in 0-5 years**
Oesophagus	42	21	27	8	8,697
Stomach	143	20	38	20	13,247
Colon	307	43	81	29	25,801
Rectum	69	6	37	8	12,776
Pancreas	186	15	18	7	7,284
Lung	538	107	155	72	56,779
Breast	92	39	80	24	39,262
Cervix uteri	29	4	11	2	5,305
Corpus uteri	29	2	8	5	4,479
Ovary	177	10	19	11	7,115
Prostate	163	35	92	33	19,750
Kidney	72	6	21	8	5,453
Bladder	78	16	56	9	15,275
NHL	121	12	21	12	9,117
Lymphoid leukaemia	35	10	13	4	3,532
All malignancies [&]	2,710	425	871	316	299,714

ICD= International Classification of Disease; VTE = venous thromboembolism. .. [&]All malignancies within the range ICD 10 C00-C96 excluding non-melanomatous skin cancer

Patients with a previous diagnosis of malignancy were excluded to avoid cancer itself being a confounding factor for subsequent malignancy. Cancer registrations derived

solely from death certificates were excluded due to lack of survival information. Follow-up for the occurrence of cancer was from the initial diagnosis of VTE until the end of 2000, allowing five year survival analysis of all cancer patients following diagnosis up to the end of 2005.

Kaplan-Meier survival analysis was used to obtain estimates of crude survival at one and five years following cancer diagnosis, by cancer site and timing of VTE. Multivariate Cox's proportional hazard models[10] were used to assess the impact of VTE on survival for each cancer site separately. Adjustment was made for age (<50, 50-59, 60-69, 70-79, 80+ years), sex, period of diagnosis (1986-90, 1991-95, 1996-2000) and deprivation decile[11]. Patients without a VTE in the five year prior to malignancy served as the reference group for the multivariate analyses. The endpoint was death from any cause.

RESULTS

We identified 4322 patients diagnosed with VTE who were then diagnosed with a first malignancy in the subsequent five years. The 299 714 patients diagnosed with malignancy in the same time period, but who had not been diagnosed with a VTE in the preceding five years served as the reference group. The breakdown of these figures by cancer site and timing of cancer diagnosis is given in Table 1. Amongst those with VTE and malignancy, the commonest cancer sites were lung, colon, prostate and breast reflecting the most common cancer sites overall. Patients with a VTE up to two years before a diagnosis of malignancy was made had a poorer prognosis than those without a preceding VTE as detailed in Table 2. Across all the cancer sites examined and in the group as a whole, the prognosis was particularly poor if the VTE occurred at the time of,

or in the six months prior to, diagnosis of malignancy with a hazard ratio (HR) of 2.48 ($p<0.001$) for all cancers combined. Within this group, malignancies of the cervix, uterus, pancreas, rectum and breast had the poorest prognosis comparatively with hazard ratios greater than 2.5. For all cancers combined, the hazard ratios remained elevated at 1.21 ($p= 0.002$) and 1.26 ($p<0.001$) respectively for those with a VTE 6-12 months and 1-2 years prior to cancer diagnosis.

DISCUSSION

This study examined the survival of over 4000 patients diagnosed with cancer at the same time as, or in the five years after a diagnosis of VTE and compared it to cancer patients who did not have VTE at presentation or in the preceding five years. Those diagnosed with cancer 0-6 months after a diagnosis of VTE have a significantly poorer prognosis, and this remains so for patients diagnosed with VTE up to two years before cancer diagnosis. The crude one-year survival for all cancers combined was 19% for those diagnosed at the time of, or in the six months following, a Cancers were classified as occurring following a VTE if they represented a first diagnosis of malignancy, excluding non-melanomatous skin cancers, in the five years following a VTE. This compares to a 54% one-year survival for all cancers in the reference group (data not shown). Our findings are in keeping with those of earlier work showing a mortality ratio of 2.46 at one year if VTE and cancer were diagnosed concurrently [9]

A limitation of our study is the lack of staging data which. ISD only began collecting staging data for a limited number if cancers in 1997 and which were insufficient for analysis.

Table 2 Multivariate hazard ratios according to time period for each cancer site.

	Multivariate hazard ratio according to time period from diagnosis of VTE to diagnosis of malignancy				
Cancer site	Control group	0-6 months	6-12 months	1-2 years	2-5 years
Oesophagus	1.00	2.45 (1.78-3.38)†	2.50 (1.25-5.01)*	0.73 (0.44-1.21)	0.84 (0.54-1.31)
Stomach	1.00	2.35 (1.98-2.79)†	1.61 (1.02-2.52)*	1.61 (1.04-2.50)*	0.87 (0.61-1.23)
Colon	1.00	1.95 (1.73-2.21)†	1.23 (0.83-1.84)	1.41 (1.01-1.98)*	1.16 (0.91-1.47)
Rectum	1.00	2.72 (2.12-3.49)†	1.62 (0.73-3.62)	2.60 (1.17-5.80)*	1.08 (0.74-1.58)
Pancreas	1.00	3.23 (2.77-3.77)†	0.97 (0.46-2.04)	0.70 (0.41-1.19)	1.36 (0.85-2.20)
Lung	1.00	1.93 (1.77-2.12)†	1.05 (0.82-1.35)	1.08 (0.88-1.32)	0.88 (0.75-1.04)
Breast	1.00	2.61 (2.09-3.27)†	0.86 (0.50-1.49)	1.14 (0.78-1.68)	1.18 (0.90-1.55)
Cervix uteri	1.00	4.84 (3.22-7.29)†	4.03 (1.0-16.22)*	1.45 (0.54-3.89)	1.44 (0.75-2.77)
Corpus uteri	1.00	3.87 (2.62-5.72)†	1.38 (0.44-4.33)	0.43 (0.06-3.06)	2.51 (0.94-6.73)
Ovary	1.00	2.34 (1.99-2.75)†	1.30 (0.72-2.36)	1.22 (0.55-2.72)	1.17 (0.70-1.95)
Prostate	1.00	2.07 (1.75-2.45)†	1.14 (0.78-1.66)	0.71 (0.45-1.09)	1.46 (1.17-1.83)†
Kidney	1.00	2.00 (1.55-2.57)†	0.94 (0.47-1.89)	1.13 (0.42-3.03)	2.07 (1.32-3.26)†
Bladder	1.00	2.24 (1.74-2.88)†	1.40 (0.67-2.93)	1.39 (0.81-2.40)	1.12 (0.82-1.52)
NHL	1.00	2.09 (1.72-2.54)†	1.36 (0.70-2.61)	1.24 (0.62-2.48)	1.07 (0.65-1.75)
Lymphoid leukaemia	1.00	1.61 (1.12-2.29)*	1.20 (0.45-3.20)	1.04 (0.54-2.01)	0.89 (0.49-1.62)
All malignancies[&]	**1.00**	**2.48 (2.38-2.58) p < 0.001**	**1.21 (1.07-1.37) p= 0.002**	**1.26 (1.13-1.40) p < 0.001**	**1.07 (0.99-1.15) p= 0.079**

ICD= International Classification of Disease; VTE = venous thromboembolism. . Results quoted are hazard ratios with 95% lower and upper confidence intervals in brackets. †Indicates a P-value of < 0.001. *Indicates a P value of <,0.05. [&]All malignancies within the range ICD 10 C00-C96 excluding non-melanomatous skin cancer.

Therefore, we cannot comment on the prevalence of metastatic disease at presentation, and the poor prognosis seen in those with VTE at presentation or in the preceding six months, may reflect a later stage at diagnosis. Sorensen *et al* did not match for stage, but did have staging data. They found a prevalence ratio of 1.26 for metastases in those diagnosed with VTE and malignancy concurrently as compared with controls.[12] It is therefore likely that the extent of cancer spread at presentation, as measured by traditional staging methods, does not fully explain the poorer prognosis of these patients.

Morbidity and mortality directly arising from the VTE itself are unlikely to be solely responsible, particularly as the prognosis remains poor for malignancies diagnosed up to

two years after the thromboembolic event. A complex interaction between coagulation cascades and tumour cell biology exists and there is a growing understanding of the potential role of coagulation pathways in modulating tumour growth.[13-15]

However it is not clear whether hypercoagulability itself predisposes to a more aggressive cancer or whether hypercoagulability is simply an early manifestation of such a disease. The former possibility suggests a potential for modulating tumour growth using agents acting upon the coagulation cascade.

This is a retrospective study and as such relies on the accuracy of the databases. The accuracy of discharge coding in Scotland is estimated at around 90%.[16] The quality of cancer registry data is also high[17] (with mismatches in the linkage system occurring in less that 2% of cases.[18]

This study provides evidence that, for all cancers combined, a diagnosis of VTE in the two years before cancer diagnosis is associated with a poorer prognosis, particularly if VTE is diagnosed concurrently or in the six months before cancer diagnosis. In view of the poor prognosis experienced by these patients, extensive investigation for underlying malignancy may not yield a survival benefit and additional studies are needed to clarify this. Further work is required into the mechanisms behind this association and the possibility for treatment targeted at the coagulation process.

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Chapter XII

THROMBUS LOAD AND ACUTE RIGHT VENTRICULAR FAILURE : CORRELATION AND DEMONSTRATION OF A 'TIPPING POINT' ON CT PULMONARY ANGIOGRAPHY

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Abstract

Objectives:

To determine the correlation between increasing pulmonary embolism thrombus load and right ventricular dilatation as demonstrated by CTPA and to assess the thrombus load threshold which indicates impending right ventricular decompensation.

Methods:

2425 consecutive CTPAs were retrospectively analysed. Thrombus load using a modified Miller score (MMS), RV: LV ratio, presence of septal shift, pulmonary artery and aortic size were analysed in 504 positive CTPA scans and a representative cohort of 100 negative scans. Results were correlated using non-parametric analysis (two-tailed or chi-squared test) and Pearsons rank correlation.

Results:

Increasing thrombus load correlated with higher RV: LV ratio with statistically significant difference in RV: LV ratios between the negative and positive PE cohorts. Larger thrombus loads (MMS $\geq$ 12 vs. <12) were strongly correlated with right ventricular strain (mean RV: LV ratio 1.323 vs. 0.930, $p < 0.0001$). Smaller thrombus loads had no significant influence on RV strain. Septal shift was also more likely with a MMS $\geq$12, as was an increase in pulmonary artery diameter (Pearson rank coefficient $r=0.221$, $p<0.001$).

Conclusion:

With increasing thrombus load in PE, there is CTPA evidence of right ventricular decompensation with a MMS threshold of 12. This suggest a 'tipping point' beyond which right ventricular decompensation is more likely to occur.

Advances in knowledge:

This is the first study to describe this 'tipping point' between thrombus load above MMS 12 and an increase in RV: LV ratio. This finding may help improve risk stratification in patients with acute pulmonary embolism diagnosed by CTPA.

Introduction:

Acute pulmonary embolism (PE) remains a diagnostic challenge for physicians and accounts for significant morbidity and mortality in hospitalised patients. In the UK, the incidence of proven PE is 60-70 per 100,000 population and mortality rates range from 6-15%. Clinical manifestations vary widely from asymptomatic patients with small peripheral emboli to patients who present with circulatory collapse who have large thromboembolic loads who may warrant thrombolysis. Between these extremes, there is a significant group who present with PE in whom there is apparent clinical haemodynamic stability but there are radiological findings (e.g. echocardiography, CT pulmonary angiography) or biomarkers (such as BNP or troponin) of right heart strain in whom the prognosis may be poorer and for whom the role of thrombolysis has not been established [1-4]. Studies to date have demonstrated that right heart strain is associated with higher mortality than those with no right heart strain [5,6] and CT assessment of the right heart strain correlates with echocardiographic findings [7].

CT pulmonary angiography (CTPA) has been established as the imaging modality of choice for the initial diagnosis of pulmonary thromboembolism [8, 9] and also confers the ability to assess right ventricular afterload [10, 11]. It also readily allows quantification of thrombus load for which a variety of methods are available. These include the modified Miller Score (MMS), a catheter pulmonary angiography score [12] adapted for CTPA by Bankier et al. [13] or more complex systems such as the Qanadli and Mastora scores [14, 15].

The aim of this study was to determine if there was a correlation between increasing thrombus load using MMS and right ventricular dilatation as a predictor of right ventricular failure according to CTPA findings.

Methods

The reports of 2425 consecutive CTPA scans undertaken over a 40 month period from 2001 to 2004 at the Royal Infirmary of Edinburgh (RIE), Scotland, UK were retrospectively reviewed. All CTPA scans reported positive for the presence of PE were included in the study and the Modified Miller Score and right and left ventricular dimensions were calculated.

To act as a comparison group we included scans in 100 consecutive patients in whom PE was suspected but subsequently refuted by CTPA imaging. A 100 matched controls was calculated to be sufficiently powered, based on the mean RV: LV ratio of 1.087 in this PE cohort (SD 0.412), to achieve a true reduction in mean RV: LV ratio of 0.117, using power of 80% and a two-sided 0.05 significance level.

Imaging Protocol

The CTPAs were performed using a multislice CT scanner without cardiac gating on a GE Hi-speed Advantage CT scanner, (IG, Milwaukee, WI) using a slice thickness of 3mm and a pitch of 1.7:1 with 1.5mm reconstruction from the thoracic inlet to the inferior extent of the diaphragm. Approximately 100mLs of intravenous contrast material (200mgI/ml) was injected at a rate of 3ml/s. CTPAs were initially reported by the hospital's diagnostic service. All study scans were independently reviewed by a senior radiology specialist registrar with 5 years of CTPA experience and every scan where there was discordance in the diagnosis or extent of thrombus was also reviewed by an experienced pulmonary radiologist with 16 years of experience of CTPA reporting.

Calculation of Modified Miller Score and Ventricular Dimensions

The modified Miller Score (MMS) is a score of thrombus load proposed by Miller et al [12] for conventional angiography and adapted for CTPA scan by Bankier et al [13]. Each segmental pulmonary artery (nine on the right, seven on the left) that is fully or partly occluded by thrombus is given a score of 1. Any more proximal involved vessels scores the number of segmental branches distal to that vessel thereby giving a MMS of 0 (no thrombus) to 16 (thrombus in all segmental arteries or saddle embolism). The modified Miller Score was evaluated in consensus between observers.

The right ventricular to left ventricular ratio was calculated using the minor axes of the RV and LV chambers in the axial plane at the widest points between the inner surface of the free wall and the surface of the interventricular septum. The maximum dimensions of

the right ventricle and left ventricles may be found at different axial scan levels. This is illustrated in Figure 1.

The presence of septal shift, maximum pulmonary artery and ascending aortic diameter were also recorded. Finally, the presence or absence of consolidation, atelectasis or an effusion was recorded.

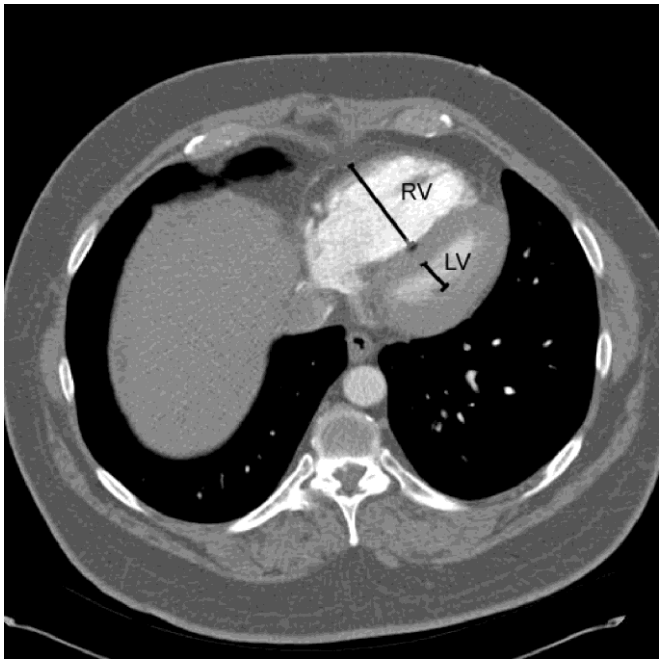

Figure 1: Illustration of measurement of maximum minor axis dimensions in a patient with right ventricular strain and septal shift. RV = right ventricle measurement. LV= left ventricular measurement

Statistical methods

All data were analysed using SPSS V.13 for windows (SPSS INC., Chicago, IL). Data are presented as mean (standard deviation) unless otherwise stated. Non-parametric analysis was undertaken using Independent samples two-tailed test or chi-squared. Correlations were calculated using Pearson rank correlation. A significance value of $p \leq 0.05$ was applied. Inter-observer reproducibility between the two observers for the RV: LV ratio was assessed on 25 scans using Bland-Altman analysis [16].

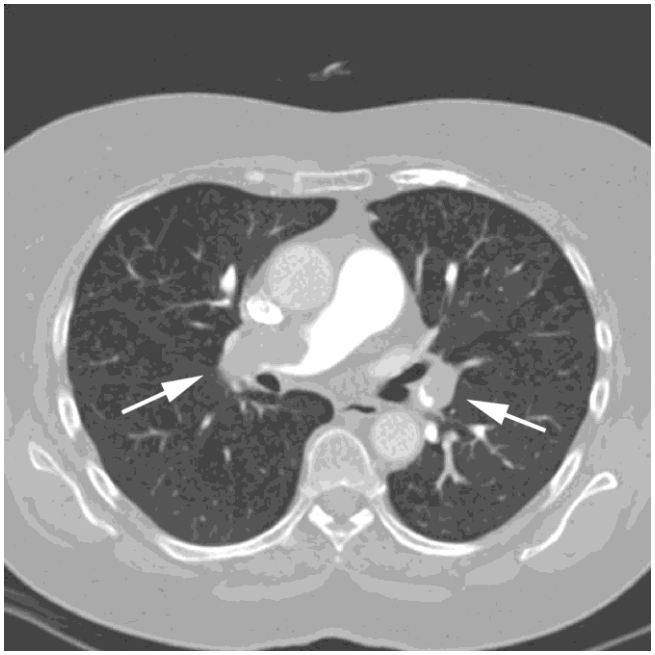

Figure 2 a

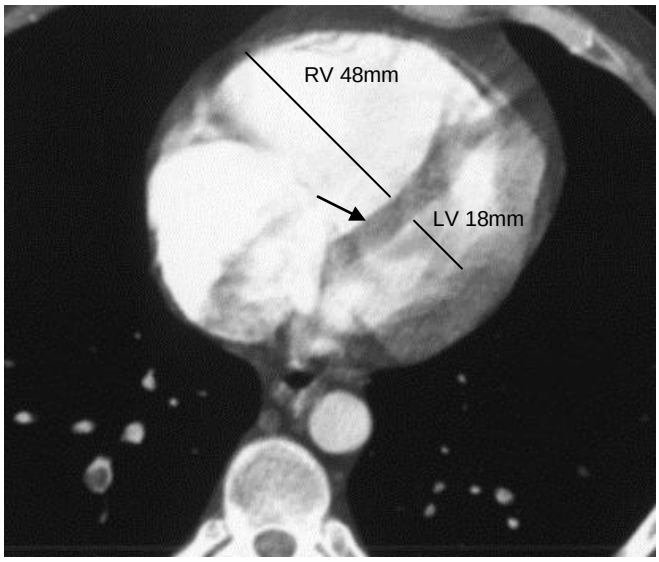

Figure 2b

(a) Large central embolus *(arrows)* with Modified Miller Score (MMS) 16. (b) RV dilatation, septal straightening *(arrow)* and increase in RV: LV ratio indicating right ventricular strain.

Results

During the 40 month period 559 CTPA scans were reported as positive for pulmonary embolism (PE); of these 55 were excluded for reasons including change in diagnosis on review or technically suboptimal scans for the accurate calculation of MMS. A final total of 504 scans where included in the study. For the negative PE group, the results of 100 consecutive scans within an equivalent cohort during the study period were included.

For the patients with PE, the MMS ranged from 1-16, with a mean MMS of 7.86. The mean RV: LV ratio was 1.087 (SD 0.412) and median 0.9794 (range 0.52-3.29). This along with the presence of consolidation, atelectasis and pleural effusion is demonstrated in Table 1. In the entire cohort, increasing MMS was shown to correlate with a higher RV: LV ratio (Pearson rank co-efficient $r=0.390$, $p<0.001$) and with pulmonary artery diameter (Pearson rank co-efficient $r=0.221$, $p<0.001$). Positive CTPA scan with increased RV: LV ratio is illustrated in Figure 2 (a and b).

The mean RV: LV ratio remained unchanged until a thrombus load of MMS of ≥ 12 was reached. For patients with lower thrombus loads (MMS ≤ 12, n=338,) there was no significant differences for RV: LV ratio when comparing to the no PE cohort (mean RV: LV ratio 0.971 (SD 0.242) Vs 0.930 (SD 0.133), $p=0.108$) but there was a significant difference in mean ratio for higher thrombus loads (MMS ≥ 12, n=166) when compared to the no-PE cohort (mean RV: LV ratio 1.323 (SD 0.561) Vs 0.930 (SD 0.133), $p<0.0001$). Multiple analyses were carried out comparing each MMS from 1 - 12 and demonstrated there was no statistical significance between any two mean MMS scores in this cohort

(independent samples t-test, all p>0.05 for all comparison). The correlation coefficients were calculated for MMS 1-12, which demonstrated no significant correlation (Pearson rank correlation = 0.0526, p=0.315). For larger thrombus loads of MMS ≥ 12, however, there was a significant correlation between MMS and RV: LV ratio (Pearson rank co-efficient r=0.232, p=0.003). This association did not hold true for either pulmonary artery diameter or aortic diameter (non-significant for MMS <12 and MMS ≥ 12 groups). This is demonstrated in Table 2 and in graphical form in Figure 3.

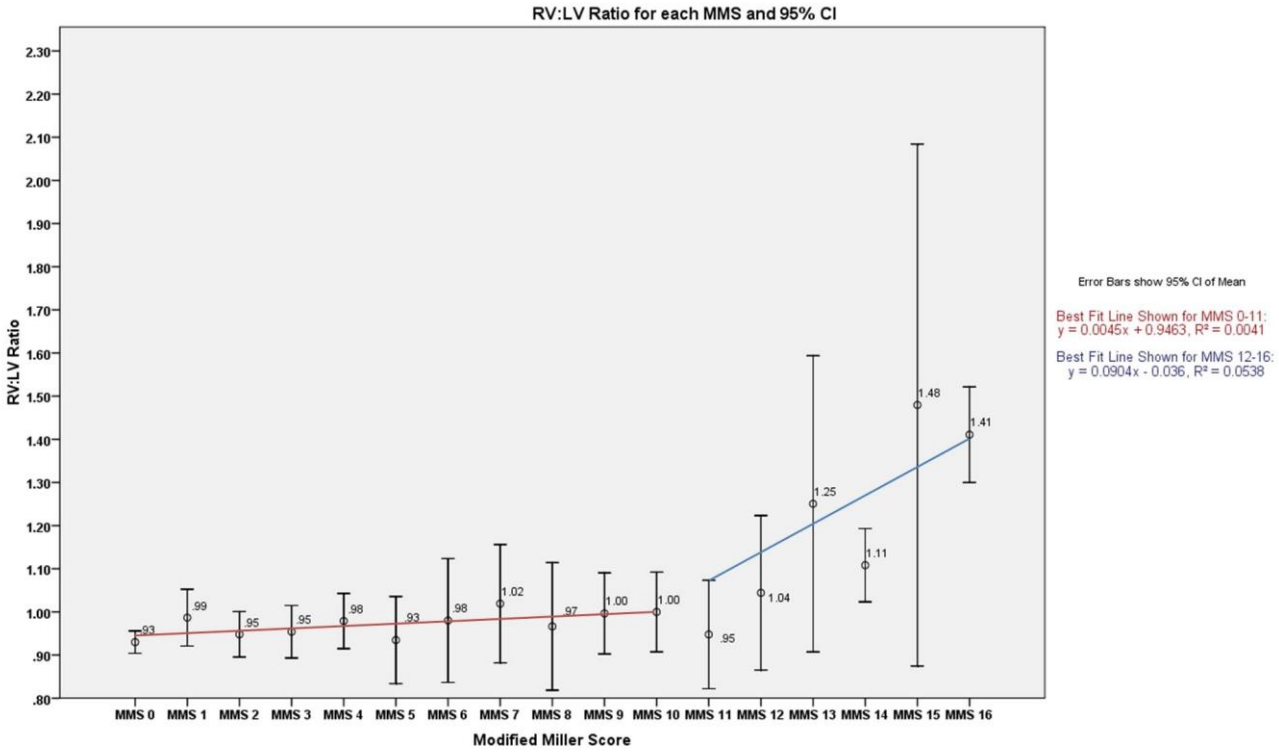

Figure 3: Graph of data showing the relationship of mean RV: LV ratio with Modified Miller Score with the RV: LV ratio remaining stable until MMS ≥ 12 with statistically significant higher mean ratio for higher thrombus loads (MMS ≥12) compared with non-PE cohort (p <0.0001).

Septal changes (defined as septal straightening or septal bulge into the left ventricle) were also more likely with MMS of ≥ 12 than MMS ≤ 12 (63.8% Vs 18.6% P<0.001).

In terms of interobserver agreement, on Bland-Altman analysis of the RV: LV ratio measurements, the means and SDs between the two observers were 0.04 and 0.22 respectively. The Bland-Altman plot is shown in Figure 4.

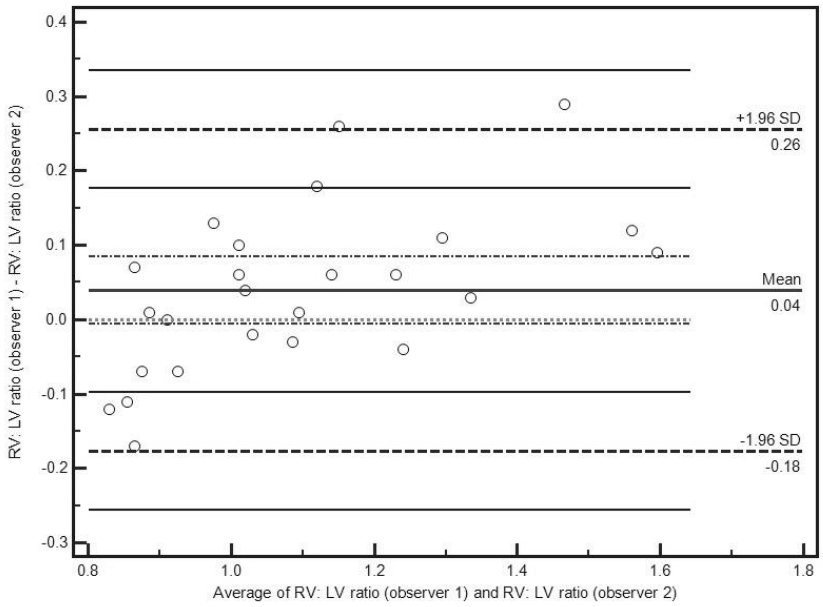

Figure 4: Bland-Altman plot of the RV: LV ratio as measured by the two study observers in 25 patients

Discussion

We believe this to be the first study to describe the relationship between thrombus load and RV: LV ratio on CTPA examinations. The RV: LV ratio remains relatively unchanged until MMS score ≥ 12. Above this thrombus load, the right ventricle begins to dilate in keeping with decompensation indicating a 'tipping point'. 'Tipping point' is a concept used in physics and sociology and is defined as the critical point in an evolving situation that leads to a new and potentially irreversible development [17].

Our results show that not all patients with a high thrombus load have evidence of RV decompensation. This implies that some patients with high thrombus loads are able to compensate while others do not, resulting in the right ventricular strain and dilatation visible on CTPA. This is evidenced by the large standard deviations seen in the Figure 3 for MMS 12, MMS 13 and MMS 15. The mechanism for this disparity remains unclear and could possibly be due to a number of factors. One suggestion is that those patients without RV dilatation are decompressing their right ventricular afterload through temporary right to left cardiac shunts [18]. Autopsy studies have shown prevalence of patent foramen ovale in the general population of up to 27% [19], whilst echocardiography in both transthoracic and transoesophageal studies has shown incidence of patent foramen ovale (PFO) in the healthy population of 10- 24.3%[20-22]. An unsuspected PFO may open up and allow temporary right to left shunting in the presence of raised right heart pressure, which may reduce the acute right ventricular dilatation on CT. This however is unlikely to equate to a survival benefit: it has previously been shown that those who have a PFO in the setting of PE have an overall mortality of 33% versus 14% in the absence of a PFO, likely to be due to paradoxical embolus and secondary myocardial ischaemia [23]. Another possibility is that patients capable of RV compensation may have a better protected RV myocardium because they do not have pre-existing sub-clinical coronary disease. It is recognised that patients may develop RV ischaemia or infarction as a result of significant increase in RV afterload when PE occurs [24]. Animal studies have also previously shown that right ventricular muscle can hypertrophy fairly rapidly over the course of a couple of weeks in response to increased RV pressure [25]. This could provide a further explanation for why some patients may have increased their right ventricular muscle bulk in response to repeated silent earlier

pulmonary emboli enabling them to avoid right ventricular collapse in the presence of larger thrombus loads.

There are also a small number of outliers in whom there is a raised RV: LV ratio, but with relatively low thrombus loads reflecting the heterogeneous population in whom PE is diagnosed.

We acknowledge that criticism may arise from the choice of study protocol utilised. We chose to utilise MMS and non-cardiac gating as well as axial RV: LV ratios as these were more representative of daily radiology practice than using more complicated thrombus load scores such as the Walsh, Qanaldi or Mastora scores and volumetric RV: LV measurements. Whilst we acknowledge volumetric analysis of RV volume: LV volume has been shown to be the most reproducible measurement [26] and slightly superior in identifying high risk patients with adverse clinical outcomes than uni-dimensional measurements, it is time consuming and requires dedicated software tools which would be disadvantageous in the emergency setting [27]. With non cardiac-gated scans whilst there was a degree of cardiac motion artefact, this did not adversely affect the ventricular wall detection and measurement in diastole. As reported previously by investigators from our institution [10], the patients in the major PE group also exhibited reduced cardiac motion artefact compared to the non-PE group, which is likely to reflect ventricular dyskinesis associated with major PE [28], which allows reproducible measurements as demonstrated by the high inter-observer agreement between the two observers in out study (Bland-Altman analysis, mean 0.04 and SDs 0.22). We acknowledge the limitations of scanner protocol however any inaccuracies in axial measurements would however not be expected

to alter the correlation we have shown between clot burden and the degree of RV dilatation.

This study was designed as purely radiological study and consequently we have not included clinical outcomes of these patients. Studies have consistently demonstrated a poorer prognosis associated with right heart strain [5,6] and data from a number of studies have now confirmed an increased risk of mortality in patients who have evidence of right heart strain, either through biomarkers of cardiac injury through Troponin or BNP [29-32], or radiological and echocardiogram evidence of right heart strain [5, 6, 30]. In this cohort of patients without circulatory collapse, it is still not known whether treatment with thrombolysis is warranted as a recent study [33], currently in press, has noted that whilst pulmonary artery obstruction scores can differentiate between patients with and without RV dysfunction, these were not correlated to adverse clinical outcome. Using only RV: LV ratio or thrombus load measurements in clinical decision making may be misleading as a significant number of patients with either no-PE, or with lower thrombus loads may also have an increased RV: LV ratio. Further work is in progress to correlate this 'tipping point' between thrombus load and right heart strain with eventual clinical outcome in order to help improve the existing treatment algorithms in pulmonary thromboembolism.

Conclusion

Using CT pulmonary angiography, we have demonstrated that in acute pulmonary thromboembolism, the RV: LV ratio remains relatively unchanged with increasing thrombus load until the 'tipping point' of MMS of 12 above which right ventricular

dilatation is more likely to occur. Although further larger studies are required to correlate with clinical outcomes, these findings may contribute to the process of risk stratification for this patient group and affect treatment such as decision for use of fibrinolytic therapy.

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Chapter XIII

Summary

The papers included in this thesis were published over a period of nearly ten years. This has been a time of immense change in the radiological assessment of VTE and also a time which has seen growth in our understanding of the disease. It has been illuminating looking back through these various papers and reflecting on what has been learnt and also what might, in hind-sight, have been done differently in approach to these same issues, knowing what we know now, were we to have our time over again. In this final section the main points of each chapter will be summarised and where lessons have been learnt that might have been applied they will be raised.

The first chapter is a short historical overview is given highlighting the pivotal role of imaging in the diagnosis and understanding of venous thromboembolism. The background to the thesis is explained and the future of VTE and radiological assessment of the disease is explored.

Chapter II looked at the changing practice for investigation of suspected pulmonary embolism shortly after the introduction of CT pulmonary angiography (CTPA). The algorithms for investigation employed, although agreed best practice at the time, now look sadly dated and radiologists and clinicians who did not work through that era will, I am sure, find them somewhat obscure and maybe even perplexing. CTPA, especially with the accuracy in diagnosis afforded by Multi-slice CT scanning, is now largely a' one-stop shop'. Even in the early days it was clear as shown by this paper that radiology would be the victim of its own success. It was shown that with the introduction of CTPA that the total number of investigation rose steadily and that the number of non-diagnostic studies decreased This increase in investigations has continued apace. We are in the process of reviewing the imaging for suspected PE for 2011-12 and have shown the rate of investigation for suspected acute PE has risen over 250% compared to a decade earlier. .

The positive scan rate dropped slightly in this recent study to but the actual incidence of acute PE more than doubled over 10 years. The increased incidence of diagnosed PE maypartly be due to a chaging in patient demographics and a genuine increase in incidence but is likely to primarily reflect more efficient detection of less severe disease. If this is the case, then aggressive treatment may not be appropriate in all cases and further analysis of outcomes, based on a PE severity score, should be considered. Further analysis is required to see if there is a change in PE severity, and to assess patient outcomes, such as recurrent thromboembolism in patients receiving treatment and those with negative scans.

Chapter III looked at the change in patient dose resulting from the change in practice. It was shown that with the increased number of patients investigated, that the total patient dose rose. However the average patient dose did not appear to change significantly as there were less supplementary tests after non-diagnostic studies resulting in less radiological investigations per patient. Looking back at this paper, the most striking thing is that the CTPA dose, although calculated by medical physics, appears rather lower than I would have expected when you consider the doses calculated for current CT scanners. There may be various reasons for this. One reason is that the conversion factor for determining dose has been adjusted in the light of new understanding resulting in higher per study calculated milli-sievert levels. Another reason is that this study, carried out as it was in the early days of CTPA was performed on a single slice CT scanner. For a CTPA it is imperative that the scan is performed during a single breath-hold and to achieve this with a single slice scanner only the middle portion of the chest from aortic arch to tip of

diaphragm was covered, using a high pitch. Both the high pitch and the limited volume included would result in a lower radiation dose. Doses with modern multi-slice CT scanner vary a lot. The routine nowadays would be to cover the whole chest, to benefit from the extra information provided. That, along with the great increase in slices acquired result in increased radiation. Consequently I expect current doses are considerably higher than those quoted in this paper. That said, great efforts are being made to reduce radiation levels, with development of better detectors and iterative reconstruction and it is very likely that doses will drop significantly. Because of the patient safely issue radiation dose is an important issue leaving a lot of scope for further research and evaluation in this field.

Chapter IV looks in depth at a cohort of patients presenting with clinically suspected PE and showed that clinical characteristics, co-morbidities and radiological features were similar when comparing groups with CTPA-proven or CTPA refuted PE. RV dimensions, radiological consolidation on imaging and D-dimer levels were however significantly higher in the PE group. In this outcome study a particularly interesting finding, is that that the cohort of patients investigated for suspected PE have a poorer prognosis, compared with age matched controls, irrespective of whether PE is confirmed. This appears accentuated in patients without PE, a finding which merits wider recognition and further evaluation.

In Chapter V the results of SimliRED a simple beside D-dimer assay are prospectively blindly compared with CTPA results. This study was carried out in the early days of D-Dimer testing, and what was not particularly appreciated at that time and I suspect still not appreciated by all, is that not all D-Dimer tests are the same. Simple yes/no assays such as SimpliRED are much inferior to ELISA D-Dimer assays and a negative SimpliRED D-

dimer assay in isolation does not safely exclude the diagnosis of a pulmonary embolism. We had naively thought that a simple bed-side D-Dimer test on its own might be adequate to rule out PE and to triage patients appropriate for CTPA. Looking back, were I to do this study again, I would have included clinical probability scoring along with D-dimer testing. This is particularly imperative when bed-side assays D-dimer test are assessed.

In **Chapter VI** consecutive enhanced in-patient and in **Chapter VII** consecutive enhanced outpatient non-CTPA chest CT scans, were reviewed to look for unsuspected PEs. These were among the first papers published which looked at large cohorts of unselected patients in this manner and in both a significant number of unsuspected pulmonary emboli were identified. These PEs were generally smaller than PEs identified at CTPA and were more commonly seen in elderly patients. Only about two thirds of these PEs had been reported on the initial scan. The main lesson was that PEs should be routinely sought in all contrast enhanced CTs of the chest irrespective of the indication for the scan, a lesson resulting in change of radiological practice, following publication of these papers. Looking back, the one thing in particular that I would do different if repeating these studies would be to record the Hounsfield Attenuation of the pulmonary arteries to measure enhancement of the main pulmonary artery rather than using the subjective assessment enhancement that was employed. Quantitative measures are better science than objective measures and CT enhancement lends itself to this. It also improves reproducibility.

Chapter VIII used a VTE database to look at distribution of DVT as demonstrated by contrast venography. It was shown that almost a third of positive cases were isolated, below knee thrombi. The importance of this is that these smaller thrombi are more

difficult to detect by non-invasive means such as ultrasound which is now almost universally employed to identify DVT. Our study laid down a reference for relative distribution of below and above knee DVT from pre-US days which can be used as a standard to determine approximately how many below knee DVT are being missed in a given US DVT series. The reviewers of this paper suggested following up these two cohorts of above and below knee DVT to look at incidence of recurrent VTE and development of chronic venous insufficiency. This has been done with interesting results which we plan to publish shortly.

Chapters IX, **X** and **XI** are a Trilogy of papers using the SHIPs database to conduct nationwide, retrospective cohort studies The first assessed the risk of cancer developing in VTE patients diagnosed in Scotland over an eighteen year period and showed significantly elevated risks of cancer which were sustained for two years after VTE diagnosis; most notably for ovarian tumours and lymphomas. Younger patients had a lower overall, but increased relative, risk of this association. The second of these papers linked cases of DVT with metrological variables. The main findings were that low atmospheric pressure, high rainfall and high wind speed are associated with a small but significant increase in the rate of DVT. The correlation is strong, but the cynic might argue that it is simply down to sitting around and immobility resulting from adverse weather. However I am convinced that the association is real and consider this association of DVT with a reduction in atmospheric pressure the most interesting finding in this paper. It may account in part for 'economy class syndrome' in long haul flights, in which a reduction in cabin pressure occurs possibly mimicking this climatic change. In my opinion this merits further evaluation, my expectation being that this effect may not be universal, occurring only in susceptible individuals. The lag between insult and

presentation is also of interest illustrating the time interval it often takes from initial early clot formation to clinical presentation. This time is not fixed but peaks around 9-11 days. Given that PE generally occurs after a DVT it might be expected that the time from initial insult to clinical presentation of PE might be longer and even more variable.

In Chapter XI, the third of the SHIPs based papers, it was shown that the prognosis was significantly poorer in patients in whom VTE occurred up to two years before the diagnosis of a new cancer diagnosis. This association was most notable if cancer was diagnosed in the six months after a VTE. The question which this paper raises is whether this poor outcome is simple due to these patients having more severe disease or whether the presence of preceding DVT is identifying a phenotype of more aggressive malignancy with a poorer outcome. If the answer is the former then it might be argued that these patients should be investigated more thoroughly, if the latter then it may be that extensive investigation for underlying malignancy may not yield a survival benefit in these patients.

It would have been useful to have been able to include staging information for these patients to help clarify this point. Unfortunately this was not available at the time of this paper, however it is now available for linkage and would make a valuable follow up study to clarify the situation. The data presented in Chapters IX and XI may also be useful for health economists and epidemiologists to calculate the cost effectiveness of screening VTE patients for underlying malignancy

Chapter XII assessed the correlation between increasing pulmonary embolism thrombus load and right ventricular dilatation as demonstrated by CTPA and assessed the thrombus load threshold which indicates impending right ventricular decompensation. It was shown that in acute pulmonary thromboembolism, the RV: LV ratio remains relatively unchanged with increasing thrombus load until the ‘tipping point’ of MMS of 12 above

which right ventricular dilatation is more likely to occur. It was concluded that these findings may contribute to the process of risk stratification for this patient group and affect treatment such as decision for use of fibrinolytic therapy. In this paper we developed our understanding of the relationship between thrombus load and right ventricular strain. In chapter IV a similar but smaller group of patients had been examined and in that paper a quadratic curve was applied to the scatter plot. The 'tipping point' hypothesis presented in chapter XII better explains the findings and complies with what might be expected physiologically in light of Starling's Law of myocardial contractility.

In conclusion, deep venous thrombosis and pulmonary embolism are part of the same disease spectrum of venous thrombo-embolism. VTE is a common disease whose presentation mirrors many other pathologies and the diagnosis cannot be made with any confidence without imaging input. It is a much feared disease which is still poorly understood but whose understanding has been improved with the help of imaging and of clinical databases. By using imaging derived data and data from both local and national databases the understanding of various aspects of this common, but still relatively poorly understood, disease process have been evaluated and advanced. The work has laid the foundation for further investigation in the field some of which is already underway with other aspects planned.

Acknowledgment

The focus of this project is venous thromboembolism, a topic which I first caught my interest as a radiology trainee at Edinburgh Royal Infirmary. That interest was generated by the enthusiasm that **John Reid,** who was a consultant radiologist in the department at that time, had for the topic. John was instrumental in setting up a database of patients transiting the department with suspected venous thrombo-embolism and I was fortunate to be invited by him to assist with that database which formed the basis of my earliest venous thrombo-embolism publications. **John Reid** not only first introduced me to the vast ongoing potential for VTE research but has over the years been inspirational in focussing many of the VTE based studies in which I have been involved. John has been, and continues to be, an invaluable collaborator in many of my paper on venous thromboembolism with further collaborative VTE projects at various stages of completion and my greatest thanks in this field are due to him.

Databases are an invaluable tool when it comes to quantifying and evaluating disease. As well as our radiology VTE database I have also made use of the Scottish Hospital and In-Patients Statistics (SHIPS) database for several of these publications. This is a resource which I first encountered as a medical Senior House Officer at the Gastro-Intestinal Unit at the Western General Hospital Edinburgh whilst carrying out a research project under the supervision of **Professor Anne Ferguson** for whose help I am very grateful. The remit of that post also included attending courses on epidemiology and statistics, disciplines which have proved useful for publications included for this PHD. Several

papers started off as student Special Study Module projects and my thanks are due to students who participated in data collection and initial analysis for these projects including **Gordon Cowell, Lynne Wylie, Asam Akram,** and **Louise Logan**. It has been encouraging to see how some of those who have chosen radiology SSM projects as students have gone on to pursue a career in radiology.

Research is seldom purely radiological and often multidisciplinary. I am grateful for the clinical support given for some of these publications. I wish to thank **Professor Derek Bell** for his help with the Simpli-RED D-dimer CTPA study and **Professor John Simpson** who was an enthusiastic and perceptive collaborator in several of the PE projects before moving to take up his chair in Newcastle. I am also greatly indebted to Professor **Bill McNee** and to **Nik Hirani**, for the opportunities they have afforded me to collaborate in respiratory research in their specialist fields when a radiology perspective has been required. It was a very welcome boost to have **Professor Edwin van Beek** come to Edinburgh to take up the SINAPSE Chair of Radiology. Edwin, particularly in his role as supervisor, has been very supportive of this project and, the phone calls, letters and e-mails which he wrote to chivvy things along, the support he has provided, and his advice in the preparation of this manuscript, are much appreciated.

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