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A Study to Develop and Validate a Clinical Prediction Rule to Exclude Pulmonary Embolism

by

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UNIVERSITY OF OTTAWA

ABSTRACT

Statement of the Problem

Pulmonary Embolism (PE) is a common, lethal and treatable condition that is only present in a minority of those investigated with suspected PE. This results in inefficient utilization of diagnostic technology for suspected PE. A clinical prediction rule that safely excludes PE could avert the need for many expensive diagnostic tests and improve patient management. None of the published attempts to derive and validate a clinical prediction rule to exclude PE adhered to current methodological standards.

Methods

PHASE I - Using univariate techniques potential predictor variables were identified from a prospective cohort study of patients with suspected PE who subsequently had outcomes measured (Derivation set).

PHASE II - The inter-observer reliability of these individual predictor variables were determined in a second prospective cohort study of patients with suspected PE (Inter-observer reliability study).

PHASE III -Two multivariate techniques (recursive partitioning and logistic regression) were used to derive clinical prediction rules in the derivation set based on those variables that were both significant in univariate analysis ($p<0.20$) (Phase I) and had good inter-observer reliability (kappa>0.5) (Phase II). The

clinical prediction rule with the highest specificity with close to 100% sensitivity was then identified using classification analysis in the derivation set.

PHASE IV - The rule was then retrospectively validated in a third dataset from a previously published prospective cohort study of patients with suspected PE (Validation set).

Results

Phase I

Of 212 eligible and consenting patients with suspected PE who had definitive outcome measures, 49 had PE and 163 did not have PE. The following predictor variables were significant ($p < 0.20$) univariate predictors of PE in patients with suspected PE: Age over 55, male sex, dyspnea, leg pain or swelling, previous deep vein thrombosis or PE, recent surgery, active malignancy, recent immobilization, any risk factor for venous thromboembolic disease, absence of chest pain, heart rate over 110, respiratory rate > 25, systolic blood pressure > 120, loud second heart sound, clinician's impression, non sinus rhythm on ECG, indeterminant axis, incomplete right bundle branch block, increased A - a gradient, alveolar dead space fraction > 0.2 and positive D-Dimer.

Phase II

Loud second heart sound, respiratory rate over 25, clinician's impression and A – a gradient had poor inter-observer reliability (Kappa < 0.5). All other clinical variables had good inter-observer reliability.

Phase III

This study was only adequately powered to enter 10 variables into multivariate analyses to derive a clinical prediction rule. This required that six variables be excluded. Female sex, systolic blood pressure, indeterminate axis on ECG, non-sinus rhythm and incomplete right bundle branch block have inconsistently been shown to be predictors in previously published investigations and hence were selected out. Alveolar deadspace measurement was only available for 70% of the derivation set and hence was omitted due to a high proportion of missing data.

A clinical prediction rule that states:

" The absence of <u>all</u> of the five following clinical variables excludes PE:

1) a positive D-Dimer
2) heart rate over 110 beats per minute
3) leg pain or leg swelling
4) previous venous thromboembolic event
5) recent surgery"

excluded pulmonary embolism with a sensitivity of 100% (95% confidence interval - 91.6% - 100%), negative predictive value of 100.0% (95% confidence interval - 91.4% - 100%) and excluded PE in 26.1% of patients with suspected PE in the derivation set.

Phase IV

In the validation set of 1239 patients with suspected PE the clinical prediction

rule had a sensitivity of 95.3% (95% confidence interval - 91.7% - 97.8%),negative predictive value of 97.8% (95% confidence interval - 96.8% - 99.8%) and safely exclude PE in 35% of patients with suspected PE.

Conclusion

This clinical prediction rule safely excludes pulmonary embolism when compared to currently available diagnostic tools. The application of this clinical prediction rule may obviate the need for further diagnostic testing in one third of patients with suspected PE resulting in improved patient management and savings in resource utilization.

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1.0 INTRODUCTION

1.1 Overall Aim

To develop and validate a safe and clinically useful clinical prediction rule to exclude pulmonary embolism.

1.2 Statement Of The Problem

Pulmonary Embolism (PE) is a common, lethal and treatable condition that is only present in a minority of those investigated with suspected PE.

PE is a common clinical condition as it represents the third leading cause of cardiovascular mortality in North America with an age and sex adjusted estimated incidence rate of 21 to 69 per 100,000 per year in population based studies (1-3). PE is also responsible for 5 to10% of all in-hospital deaths (4-6). PE is an important diagnosis to establish given that undiagnosed PE has a hospital mortality rate as high as 30% which falls to near 8% if diagnosed and treated appropriately (5,7,8). Recent reviews of evidence, however, question these estimates of mortality for untreated PE (9,10).

The diagnosis of pulmonary embolism remains one of the most difficult problems confronting clinicians. Pulmonary embolism is considered in the differential diagnosis of many clinical presentations, including chest pain, hemoptysis and dyspnea, and in a wide variety of clinical settings such as

emergency departments, obstetrical units, surgical wards and intensive care units. Yet, less than 35% of patients suspected of having PE actually have PE (11-14). Therefore, without a simple and reliable way of excluding PE at the bedside, many patients without PE are needlessly hospitalised and anticoagulated while awaiting confirmatory testing with either ventilation-perfusion (V/Q) scans, pulmonary angiograms, non-invasive leg studies or serial non-invasive leg studies. Furthermore, many patients suspected of having PE in smaller centres, without this diagnostic technology, are transferred to larger centres. In larger centres V/Q scans, non-invasive leg studies and pulmonary angiograms are generally only available during weekdays and daytime hours complicating the diagnostic approach for patients with suspected PE seen after hours in these centres.

A ventilation perfusion scan (V/Q scan) is the imaging test most often recommended for the initial investigation of patients with suspected pulmonary embolism (15,16). Only specific combinations of V/Q scan results and pre-test probabilities are considered "diagnostic"; that is conclusively diagnose PE or safely exclude PE. However, most patients (over 70%) who have V/Q scans for suspected pulmonary embolism have non- "diagnostic" results and patients with these non- "diagnostic" V/Q scan results require further investigation for suspected PE (11). The diagnosis of PE can only be made with confidence with an intermediate to high index of pre-test clinical suspicion combined with a high probability V/Q scan (See **Figure 1**) (11). The diagnosis of PE can only be

excluded with confidence with a normal V/Q scan or with a low probability V/Q scan combined with a low pre-test index of clinical suspicion (see **Figure 1**)(11,13,17).

However, even these " diagnostic" V/Q scan interpretations are imperfect. A normal/near normal V/Q scan has a negative predictive value of only 96.4% (95% CI of 91.1% to 97.7%) (11). Also, more recent experience has shown that a patient with a normal V/Q scan can expect a 1.2% (95% CI of 0.3 to 3.0%) chance of having a venous thromboembolic event (PE or its precursor deep vein thrombosis) diagnosed over three months of follow up (12).

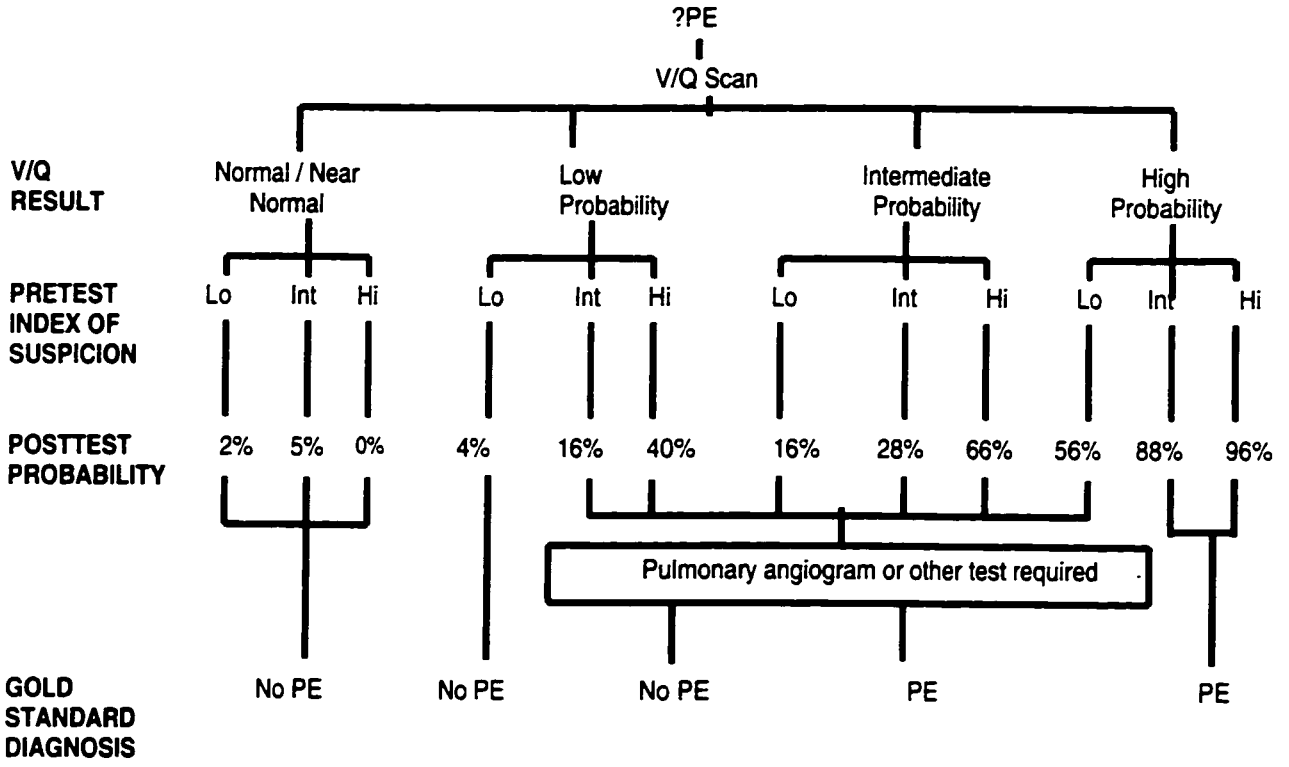

Figure 1. Standard algorithm for investigation of suspected pulmonary embolism. (Data obtained from (11))

Once faced with a non-"diagnostic" V/Q scan result clinicians have several options and each of these options has its limitations:

1) Pulmonary Angiography: The presence or absence of an intravascular filling defect on pulmonary angiography respectively confirms PE or refutes PE (11). Despite remaining the gold standard test for pulmonary embolism many clinicians choose not to pursue pulmonary angiography in patients with non-diagnostic scans (9,10,18,19). The reasons clinicians do not use the gold standard include 1) a fear of the1-2/1000 mortality associated with pulmonary angiography, 2) its limited availability after hours and in smaller centres and 3) the expense and expertise required to perform pulmonary angiography. Further, pulmonary angiography is also an imperfect test. A patient with a normal pulmonary angiogram can expect a 2.2% (95% CI of 0.3 to 8.0%) venous thromboembolic event rate at one year follow-up (13).

2) Serial non-invasive leg studies: Serial non-invasive leg studies examine for the presence or development of deep vein thrombosis. Given that over 90% of pulmonary emboli develop from deep vein thrombosis of the leg, diagnosing deep vein thrombosis in patients with suspected PE is considered indirect evidence for PE (20). Further, the therapeutic question being answered by diagnostic testing for suspected PE is the same as diagnostic testing for deep vein thrombosis, that is, whether or not to anticoagulate for prevention of recurrent venous thromboembolic events (PE or deep vein thrombosis). However, this approach does not answer the diagnostic question of the aetiology of the index pulmonary

symptoms leading to investigation for suspected pulmonary embolism; but it is considered acceptable by most authorities (15). Hull has demonstrated that if serial impedance plethysmograms (a non-invasive test for deep vein thrombosis) remain normal, in patients with non- "diagnostic" V/Q scans, 2.7% develop venous thromboembolism over 3 month follow up (21). Wells has similarly shown that patients with non- "diagnostic" scans, low or moderate pre-test clinical suspicion (assigned by an explicit clinical model) who subsequently have normal serial leg ultrasounds (over a 14 day period) can expect a 0.5% chance of developing recurrent venous thromboembolic events (PE or deep vein thrombosis) over the next three months (12). However, the limited availability of these tests and the inconvenience and expense to patients and health care providers of serial testing limits the use of these approaches.

3) Educated Guess: Many clinicians, unfortunately, resort to making an educated guess about whether PE is present or not in patients with non-diagnostic scans. One author who reported on actual practice, in a large teaching centre, of clinicians investigating suspected pulmonary embolism, demonstrated that only 15% of patients with indeterminate scans went on to further testing and that 28% of patients with indeterminate scans were presumptively anticoagulated long-term (18). Clearly, the approach of an educated guess is unacceptable. Anticoagulation results in significant risk of major bleeding (3 to 6% over 3 months) (22,23). Exposure of a patient without PE to long-term anticoagulation is unacceptable. It

is equally unacceptable to not treat a patient who has PE given its high risk of recurrence and mortality (5,7,8).

4) Other imaging tools have been examined, including spiral Computerised Tomography and Magnetic Resonance Imaging but these tools are not widely available nor have they been validated in large management studies (24-27).

In summary, clinicians in actual practice are hampered by the limitations of traditional diagnostic imaging tests for PE and even current gold standard diagnostic tools are imperfect.

In recent years, interest has been generated in using non- imaging diagnostic tools such as laboratory tests to exclude PE (28). A very recent investigation examined the safety of beginning the diagnostic approach to pulmonary embolism with a rapid ELISA D-Dimer (14). If this test was negative (36% of all patients with suspected PE in this study had a negative rapid ELISA D-Dimer) no further investigations for suspected PE were pursued. If the test was positive standard investigations to determine the presence or absence of venous thromboembolic disease (PE or deep vein thrombosis) were performed. All patients deemed not to have venous thromboembolic disease (negative rapid ELISA D-Dimer or standard tests excluded venous thromboembolic disease) were followed over a three-month period. Only 0.9% (95% CI 0.2 to 2.7%) of these

patients developed venous thromboembolic disease over three month follow-up. However, prior to widespread adoption of this diagnostic strategy it must be validated in other centres and the rapid ELISA will have to become more widely available. Another significant limitation is that in this investigation a large proportion of patients without PE still required diagnostic imaging (i.e. had positive rapid ELISA D-Dimers).

Given the limitations of current diagnostic approaches to suspected pulmonary embolism, a safe clinical prediction rule to exclude pulmonary embolism would be desirable. Clinical prediction rules have been defined as a decision making tool for clinicians that include three or more variables obtained from history, physical examination or simple diagnostic tests and either provide the probability of an outcome or suggest a diagnostic or therapeutic course of action (29). A safe clinical prediction rule could obviate further imperfect and improperly utilized gold standard testing in a significant proportion of patients suspected of PE (eg. imply a diagnostic course of action (no further testing for suspected PE) and a therapeutic course of action (no treatment for PE)). A clinical prediction rule to exclude PE could save scarce health care resources, and eliminate the risks and inconvenience of presumptive anticoagulation, hospital admission for further testing or transfer to a larger hospital for further testing, especially if such a clinical prediction rule could be applied at the bedside in all clinical settings.

2.0 BACKGROUND AND RATIONALE

2.1 Methodological Standards for Clinical Prediction Rules

Wasson published methodological standards for the development of clinical prediction rules (30). These methodological standards have been recently updated (29). In short, studies developing clinical prediction rules should include the following:

1) The outcome or diagnosis to be predicted must be clearly defined, clinically important and the assessment of the outcome must be blinded (i.e. the final arbiter of outcome must have no prior knowledge of potential predictive variables under study).

2) The clinical findings to be used as predictive variables must be clearly defined, standardized and their assessment must be done without knowledge of the outcome (i.e. blinded).

3) The reproducibility of the clinical findings used as predictive variables must be demonstrated and the reproducibility of the rule must be demonstrated.

4) The patients in the study should be selected without bias and should represent a wide spectrum of clinical and demographic characteristics to increase the generalizability of the study results.

5) The statistical techniques used to derive the rule must be identified and valid (i.e. widely accepted).

6) The accuracy of the prediction rule in classifying patients with the outcome (i.e. sensitivity) and without the outcome (i.e. specificity) should be demonstrated.

7) Prospective validation in a second independent set of patients is an essential test of a prediction rule's accuracy and clinical utility (i.e. the effects of clinical use of the rule should be prospectively measured).

8) Clinical prediction rules should be sensible i.e. have a clear purpose, be relevant, demonstrate content validity, be concise, and be easy to use in the intended clinical application. The use of the rule should provide a probability of disease and should imply a course of action.

2.2 Rationale for the Current Study

2.2.1 Characteristics required for bedside method excluding PE

A clinical prediction rule that safely excludes pulmonary embolism needs to: 1) ensure that those who have PE are treated (i.e. the clinical prediction rule has high sensitivity and is safe); and 2) ensure that many of those who do not have PE are not exposed to the hazards and inconvenience of further investigation

and presumptive therapy (i.e. the clinical prediction rule has high specificity and excludes a large proportion of those without PE). In order for clinicians to confidently use a clinical prediction rule to exclude this potentially fatal yet treatable condition the clinical prediction rule should be near 100% sensitive. That is, have very few false negatives and have a high negative predictive value. However, as described above, no diagnostic method (imaging, laboratory assay or otherwise) currently excludes PE with 100% sensitivity or negative predictive value.

The clinical prediction rule developed must rule out a significant portion of patients suspected of having PE if it is to be clinically useful and impact positively on patient care. Throughout this paper I will refer to the excluded proportion as a measure of clinical utility. The excluded proportion can be defined as the number of patients correctly excluded (true negatives) divided by the total number of patients investigated (i.e. d/a+b+c+d from a standard 2x2 table where a= number of true positives, b= number of false positives, c= number of false negatives and d= number of true negatives). The highest potential excluded proportion is 100% minus the prevalence of the disease in the population under study (i.e. given that prevalence = a+c / a+b+c+d and that if a test is 100% specific and 100% sensitive then b=0 and c=0, then the maximum the excluded proportion is d/a+d which is the same as 1 – prevalence(= a/a+d)). In most modern PE studies the prevalence of PE is between 15 to 35% so the highest potential excluded proportion would be 65- 85%. It should be noted that it is

possible to develop a 100% sensitive bedside method that is still clinically useful (i.e. has a high excluded proportion) (e.g. The Ottawa Ankle Rule) (31).

2.2.2 Clinical Predictors of Pulmonary Embolism

The utility of a variety of individual clinical predictors (history, physical examination, laboratory tests, electrocardiogram, pulmonary function and chest X-ray) has been examined in patients with suspected pulmonary embolism. It must be emphasised that a candidate predictor variable must be collected in patients with suspected PE rather than only in patients with actual PE to determine the candidate predictor variable's discriminatory ability in patients with suspected PE. As an example, if chest pain is present in all patients with PE but chest pain is equally prevalent in patients without PE who are suspected of having PE, then chest pain is not a useful predictor variable in a population of patients suspected of PE as it does not allow us to predict which patients have PE. As I will outline in a literature review in the sections that follow (see 2.2.2.1-2.2.2.7), no individual clinical predictor alone is sensitive enough or has a high enough negative predictive value to safely exclude PE. However, the review determines potential predictor variables for further study in an effort to develop a clinical prediction rule.

2.2.2.1 Use of History and Physical Examination to Exclude PE

Stein has reported on the sensitivity and specificity of history and physical examination predictor data collected by non-study personnel and compared it to gold standard diagnostic outcome measures (three-month follow-up events (20) and pulmonary angiography (32,33)). The limitations with Stein's data are: 1) many patients had the history and physical exam after the V/Q scan introducing the possibility of ascertainment bias (11); 2) patients with a history of cardiopulmonary disease were excluded; and 3) the population reported on was a small subset of the potentially eligible pool (365 out of 3016 eligible patients) (11). Two other authors have reported on the sensitivity and specificity of history and physical examination data but the clinical predictors were collected in both studies by study personnel ("experts") and not the clinicians caring for these patients (34,35). Further, one author used imperfect outcome measures (perfusion scans alone) to ascertain outcome (35).

Bearing these limitations in mind we can still consider the predictive value of the individual clinical predictors these studies examined. Patient age is consistently a statistically significant univariate predictor for pulmonary embolism across these studies (see **Table 1**). This is consistent with population based epidemiological data demonstrating an increased incidence of PE with age (36). Patient's sex does not appear to be predictive. Individual presenting symptoms do not reliably differentiate between patients with and without pulmonary embolism, even in those patients without previous cardiopulmonary disease (see **Table 1**) (33). The exceptions in individual studies include pleuritic chest pain and sudden dyspnea. However, pleuritic chest pain was not predictive

in either Stein's or Susec's study. Sudden dyspnea was only reported in the Pisa group's study and was significant. Leg symptoms are consistently more likely in patients with PE but in no study did this reach statistical significance. Interestingly hemoptysis is a rare presenting symptom in suspected PE but across studies is consistently more common in patients with PE although this does not reach statistical significance.

Table 1. Summary of reported prevalence of symptoms and risk factors in patients with suspected pulmonary embolism comparing patients with and without a final diagnosis of pulmonary embolism.

	Percentage With Clinical Predictor					
	PIOPED†		Susec§		Pisa Group‡	
Predictive Factor:	PE (n=117)	No PE (n=248)	PE (n=26)	No PE (n=144)	PE (n=97)	No PE (n=80)
Age (Mean)	54	48*	56.5	41.4*	61.8	55.3*
Female %	51% (41-62%)	68% (62-74%)	73% (52-88%)	64% (65-72%)	53% (45-66%)	57% (46-69%)
Any Chest Pain	----------	----------	58% (37-77%)	78% (71-85%)	65% (55-74%)	61% (50-72%)
Pleuritic Chest Pain	66% (56-74%)	59% (52-65%)	15% (4-35%)	11% (7-17%)	28% (19-38%)	5% (1-12%)*
Hemoptysis	13% (7-20%)	8% (5-12%)	4% (0-20%)	1% (0-5%)	13% (7-22%)	9% (4-17%)
Sudden Dyspnea	----------	----------	----------	----------	58% (48-69%)	35% (25-47%)*
Isolated Dyspnea	22% (15-31%)	21% (16-27%)	92% (75-99%)	69% (61-77%)	----------	----------
Sudden Dyspnea or Chest Pain	----------	----------	12% (2-30%)	13% (8-20%)	----------	----------
Leg swelling	28% (20-37%)	22% (17-28%)	----------	----------	----------	----------
Leg pain	26% (18-35%)	24% (19-30%)	----------	----------	----------	----------
Leg pain or swelling	----------	----------	19% (7-39%)	12% (8-19%)	----------	----------
One or more DVT risk factors	82% (74-89%)	65% (59-71%)*	----------	----------	----------	----------
Immobilization	56% (47-66%)	33% (27-39%)*	35% (17-56%)	13% (8- 20%)	39% (29-50%)	15% (8-25%)*
Trauma	8% (4-15%)	10% (7-15%)	12% (2-30%)	3% (1-8%)	----------	----------
Surgery	54% (44-63%)	31% (26-37%)*	15% (4-35%)	10% (5-16%)	51% (41-62%)	31% (21-43%)
Malignancy	23% (16-32%)	15% (11-20%)	27% (12-48%)	13% (8-20%)	17% (11-27%)	11% (5-20%)
Previous DVT or PE	14% (8-21%)	8% (5-12%)	31% (14-52%)	16% (10-23%)	----------	----------

(95% confidence interval) *p= < 0.05.† from the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) Study (33), § from (34). ‡ from (35)

Risk factors for venous thromboembolic disease are well characterised in the literature (37). In a review of 1231 patients treated for confirmed venous thromboembolic disease one or more risk factors was present in over 96% of patients (see **Table 2**). Furthermore, in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, the presence of one or more risk factors was more common in patients with as opposed to without PE (see **Table 1**). In patients with suspected PE, the only risk factors which are consistently present more often in patients who are ultimately confirmed to have PE are immobilisation, recent surgery, malignancy and previous venous thromboembolic disease. However , only immobilisation and recent surgery reached statistical significance (see **Table 1**).

Table 2. Prevalence of risk factors in patients with confirmed venous thromboembolic events. Data from (37).

Risk factor	**%**	**Risk factor**	**%**
Age over 40	88.5	Fracture (hip or leg)	3.7
Obesity	37.8	Estrogen Treatment	2.0
Previous Venous Thromboembolism	26.0	Stroke	1.8
Cancer	22.3	Multiple Trauma	1.1
Immobilisation greater than 5 Days	12.0	Childbirth	1.1
Major Surgery	11.2	Myocardial infarction	0.7
Congestive Heart Failure	8.2	One or more risk factors	96.3
Varicose Veins	5.8	Two or more risk factors	76.0

Patients with PE are more likely to be tachypneic and tachycardic than patients without PE but these differences were only statistically significantly different in one study (see **Table 3**). In studies reported to date there appears to be

no difference in blood pressures, the presence of a pleural rub on auscultation or temperatures in patients with confirmed and suspected PE. One commonly held misconception is that the presence of chest wall tenderness in patients with pleuritic chest pain excludes pulmonary embolism (38). The presence of a fourth heart sound (S4), loud second pulmonary heart sound (P2), and inspiratory crackles on chest auscultation were more common in patients with pulmonary embolism than patients without pulmonary embolism in one study (33) (see **Table 3**). The reproducibility of these individual clinical findings in this disease setting has not been published.

Table 3. Summary of reported prevalences or means of physical findings in patients with suspected pulmonary embolism comparing patients with and without a final diagnosis of pulmonary embolism.

	Percentage With Clinical Predictor or Mean					
	PIOPED†		Susec§		Pisa Group‡	
Predictive Factor:	PE (n=117)	No PE (n=248)	PE (n=26)	No PE (n=144)	PE (n=97)	No PE (n=80)
Respiratory Rate (breaths/minute)	----------	----------	23	20	27	22*
Tachypnea(>or= 20 breaths/minute)	70% (61-78%)	68% (62-74%)	----------	----------	----------	----------
Tachypnea(>or= 25 breaths/minute)	----------	----------	----------	----------	42% (35-50%)	23% (14-33%)*
Heart Rate (beats/minute)	----------	----------	102	96	97	89*
Tachycardia (>100 beats/minute)	29% (22-39%)	24% (19-30%)	----------	----------	41% (31-52%)	30% 920-41%)
Systolic BP (mm Hg)	----------	----------	128	139	132	135
Diastolic BP (mm Hg)	----------	----------	78	81	----------	----------
Temperature (Degrees Celcius)	----------	----------	36.6	37.1	----------	----------
Temperature > or = 38.5	7% (3-13%)	12% (8-16%)	----------	----------	----------	----------
Temperature > or = 38	----------	----------	----------	----------	20% (12-29%)	21% (13-32%)
Elevated JVP	----------	----------	----------	----------	30% (22-41%)	5% (1-12%)*
Fourth heart sound (S4)	24% (17-32%)	14%(10-19%)*	----------	----------	----------	----------
Loud S2	23% (16-32%)	13%(9-18%)*	----------	----------	40% (30-50%)	23% (14-33%)*
Crackles	51% (42-60%)	40%(33-46%)*	----------	----------	24% (16-33%)	23% (18-33%)
Pleural Rub	3% (1-7%)	2% (1-5%)	----------	----------	23% (15-32%)	16% (9-26%)

(95% confidence interval) * p= < 0.05.† from (33). § from (34). ‡ from (35).

2.2.2.2 Use of ECG to Exclude PE

Many authors have reported on the prevalence of ECG changes present in patients with confirmed PE but these authors have not reported on the prevalence of these changes in patients with suspected PE in whom PE is ultimately excluded (32,33,39-41). Two authors have reported on the prevalence of ECG changes in patients with suspected PE. Nazeyrollas reported on ECG changes in a highly select group of 70 patients with suspected PE (patients admitted to a cardiac intensive care unit) and documented outcome with pulmonary angiograms or normal perfusion on scintigraphs (42). Only the S1-Q3 pattern was statistically significantly more prevalent in PE patients than non-PE patients. The presence of sinus rhythm, negative t-waves and right bundle branch block was not statistically significantly different in the patients with and without PE (42). Petruzelli reported on ECG changes in a select group of 245 intensive care unit patients with suspected PE with outcomes measured by perfusion scans only (less than ideal outcome measure). In this study, P-R displacement, late R in AVR, S slurred in V1 and/or V2, S1Q3T3, T inversion in V1-V2 and diffuse T inversion were statistically significantly more common in patients with PE than patients without PE (43). Arrhythmia , tachycardia, AV block, RBBB, P pulmonale, right axis deviation, left axis deviation, low QRS voltage, right ventricular hypertrophy, S1S2S3, ST changes, and t inversion in L2,L3 and AVF did not reach statistical significance (43).

2.2.2.3 Use of Arterial Blood Gases to Exclude PE

One commonly held misconception is that a normal A-a gradient excludes PE (44) despite reports to the contrary (45). Others have tried to improve on the sensitivity of a normal A-a gradient in excluding PE by combining it with either a normal pCO_2 (46) or no prior thromboembolic history (47). Neither rule as reported was 100% sensitive. Further, Stein recently reported that a normal A-a gradient and the absence of risk factors for venous thromboembolic disease had a sensitivity of only 89% (48). A second limitation to these rules is that their clinical utility as measured by their ability to correctly exclude the diagnosis of PE was either not measured (46) or was low (excluded proportion<10%) (47).

2.2.2.4 Use of Chest x-ray to Exclude PE

Stein, using the PIOPED database, examined the use of CXR to diagnose PE. The CXR's were interpreted by study personnel who have potentially more expertise than average clinicians. The most sensitive change was atelectasis or parenchymal abnormality (sensitivity = 68%) (33). However, this radiographic finding only had a specificity of 50% or excluded proportion of 35%. Thus the most sensitive CXR abnormality indicating PE was neither sensitive enough nor specific enough to use in isolation. A group of investigators at the University of Pisa (herein referred to as the Pisa group) has also published on the CXR findings in a population of patients with suspected PE. As described above, this investigation was limited by imperfect outcome measures (use of perfusion scans

only to classify patients) and once again the chest x-rays were interpreted by study personnel (35). Interestingly, the Pisa Group also found that the presence of a parenchymal abnormality was statistically significantly associated with PE (35). Several other findings have been inconsistently found to be significantly associated with PE (See **Table 4**). Further, these other chest x-ray findings lack clear definitions for diagnostic criteria and hence would likely be poorly reproducible.

In another investigation, chest x-rays in patients with suspected PE were interpreted by radiologists; who agreed on the presence of pulmonary embolism in only one third of patients and in only one third of these was the diagnosis correct (49).

Table 4. Summary of reported prevalences of CXR findings in patients with suspected pulmonary embolism comparing patients with and without a final diagnosis of pulmonary embolism.

	Percentage With Clinical Predictor			
	PIOPED†		Pisa Group ‡	
Predictive Factor:	PE (n=117)	No PE (n=247)	PE (n=118)	No PE (n=147)
Atelectasis/Parenchymal abnormality	68% (58-76%)	48% (42-55%)*	----------	----------
Atelectasis	----------	----------	24% (16-32%)	18% (12-25%)
Parenchymal abnormality	----------	----------	32% (24-41%)	8% (4-14%)*
Pleural effusion	48% (39-57%)	31% (25-37%)*	57% (47-66%)	46% (38-55%)
Pleural based opacity	35% (26-44%)	21% (17-27%)*	----------	----------
Pulmonary edema	4% (1-10%)	13% (9-17%)	----------	----------
Elevated diaphragm	24% (16-33%)	19% (14-24%)	64% (65-81%)	52% (44-61%)*
Prominent central pulmonary a.	15% (9-22%)	11% (8-16%)	----------	----------
Descending pulm. a. normal	----------	----------	19% (13-28%)	39% (31-48%)*
Descending pulm. a. sausage shaped	----------	----------	40% (31-49%)	15% (10-22%)*
Cardiomegaly	12% (7-19%)	11% (7-16%)	31% (23-40%)	37% (29-45%)
Right ventricular enlargement	----------	----------	47% (37-56%)	33% (25-40%)*
Biventricular enlargement	----------	----------	6% (2-12%)	15% (10-22%)*
Decreased pulmonary vascularity	21% (14-30%)	12% (8-17%)	----------	----------
Westermark's sign	7% (3-13%)	2% (1-5%)	13% (7-20%)	3% (1-8%)*

(95% confidence interval) *p= < 0.05.† from (33). ‡ from (35)

2.2.2.5 Use of Dead Space Measurements to Exclude PE

Dead space ventilation represents ventilation of those parts of the lung not involved in gas exchange. Gas is exchanged in the alveoli (Alveoli are represented in **Figure 2** as the circles in the Tracheo-Broncho-Alveolar unit schema). In alveoli, oxygen diffuses from the alveolar gas to the blood vessels and carbon dioxide diffuses from the blood vessels to the alveoli (blood vessels represented in **Figure 2** as double lines interfacing with the alveoli). Physiologic dead space has two components: anatomical dead space and alveolar dead space. Anatomical dead space is ventilation of the airways. The airways conduct air from the outside world to the alveoli and are not involved in gas exchange. Alveolar dead space represents ventilation of those alveoli that are not involved in gas exchange i.e. alveoli that are not perfused.

Alveolar Dead Space in PE

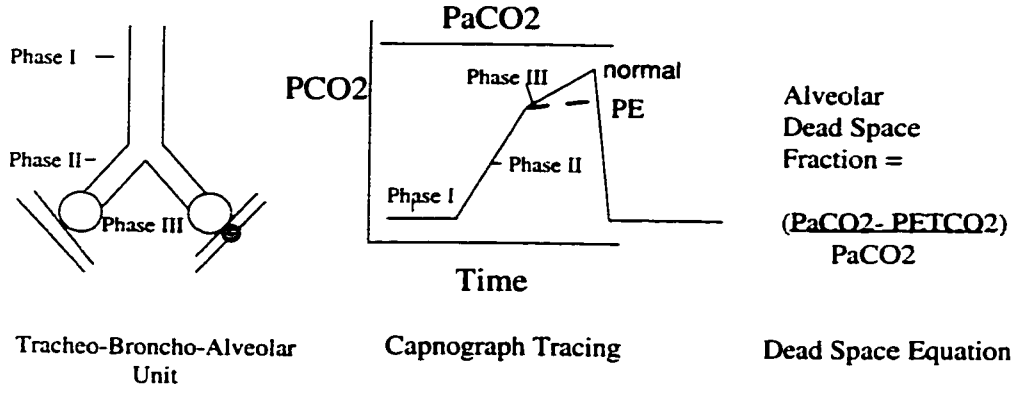

Figure 2. Schematic of Tracheo-Broncho-Alveolar lung unit, a capnograph (CO2 vs Time) tracing and the Alveolar Dead Space Fraction equation.

Robin first published the concept of using the end tidal CO_2 to arterial CO_2 difference in the diagnosis of pulmonary embolism in the New England Journal of Medecine in 1959 (50). He suggested that an estimate of alveolar dead space could be derived from an expired breath capnogram. An expired breath capnograph tracing is shown in **Figure 2**. This tracing demonstrates a carbon dioxide concentration versus time curve for an expired breath. Phase I of the curve is thought to represent the emptying of large airways. These large airways are not involved in gas exchange and hence have the same carbon dioxide concentration as inspired air (i.e. negligible). Phase II represents emptying of a mixture of airways and alveoli and hence has an increasing amount of carbon dioxide. Phase III represents emptying of alveoli (shown as a solid line in normal

patients on the capnograph tracing in **Figure 2**). Alveoli that are involved in gas exchange have high carbon dioxide concentrations. The increased contribution of dead space alveoli to expired alveolar gas in pulmonary embolism patients results in a diminished slope of Phase III (Phase III in pulmonary embolism patients is marked with dashed line in **Figure 2**). Alveolar dead space can be expressed in the form of an equation, the alveolar dead space fraction, as shown in **Figure 2**. $PaCO_2$ represents the arterial blood CO_2 concentration that is obtained routinely at the bedside by arterial blood gas sampling. $PETCO_2$ is the CO_2 concentration obtained from a capnograph tracing at the end of Phase III (i.e. the end tidal CO_2 concentration).

Further interest has been generated in the literature in examining alveolar dead space as a predictor of pulmonary embolism (50-56). Most of these investigations have not demonstrated a technique of alveolar dead space measurement that is near 100% sensitive nor has the reproducibility of these measures been demonstrated. Kline utilized a hybrid of the arterial to end tidal and the arterial to end expired CO_2 differences in a study of 170 ambulatory patients suspected of PE (56). If a plateau was seen on Phase III of the expired breath capnogram during tidal breaths he used the plateau PCO_2 in the alveolar dead space equation. If a plateau was not seen during regular tidal breaths, he asked patients to deeply expire and used the deep expired CO_2 plateau value in the alveolar dead space equation. This method of measuring the alveolar dead space fraction was 88% sensitive (95% CI of 70 to 98%), had a negative

predictive value over 97% (92 to 99%) and a excluded proportion of 78% (56). The reproducibility of Kline's technique has not been published. This is of particular relevance as the author performed all of the dead space measurements himself (personal communication).

2.2.2.6 Use of D-Dimers to Exclude PE

The hemostatic system is finely balanced between thrombus formation and dissolution. D-Dimers are a specific degradation product of cross linked fibrin and are a widely available lab marker of fibrinolysis (clot dissolution). D-Dimers increase in a number of conditions where thrombus is formed and hence are not a specific test for pulmonary thromboembolism (28). A recent review of the safety and utility of D-Dimer levels in excluding the diagnosis of PE has shown that, using an ELISA technique, that normal D - Dimer levels have a sensitivity of 97% in excluding PE and correctly exclude PE in approximately 30% of those patients studied (28). Hence, normal D-Dimer by ELISA technique levels are a relatively reliable predictor of absence of pulmonary embolism. The ELISA assays are relatively expensive and lack specificity. Earlier limitations of the ELISA D-Dimers included the need for the assays to be performed in batches and the results took hours to obtain. These limitations have been improved upon with rapid ELISA's. As indicated above, one study has shown that, despite not being 100% sensitive, if a rapid ELISA D-Dimer is negative in patients with suspected PE, these patients can expect a low risk of symptomatic recurrent venous thromboembolic disease over a three-month period. However, rapid ELISA D-

Dimers are not yet widely available (14). Latex D-Dimer assays are widely available, are relatively inexpensive, quick and easy to perform. The sensitivity of the latex agglutination techniques however is less than the gold standard ELISA technique (sensitivity of latex D-Dimer 92%) (28). A latex D- Dimer test cannot be used alone to exclude PE.

A novel whole blood assay for D-Dimer (SimpliRed), that can be performed and interpreted at the bedside in minutes, has been shown to have a sensitivity of 94% and a specificity of 66% (57). Once again while this assay is not sensitive enough to use alone but may form an important part of a safe and clinically useful bedside method to exclude PE.

2.2.2.7 Use of Clinicians' Overall Impression to Exclude PE

In the PIOPED study clinicians recorded their overall impression based on individual clinical judgement prior to objective investigation with V/Q scanning. When clinicians thought the likelihood of PE was over 80%, over 60% had PE (32,33). When clinicians thought the likelihood of PE was less than 20%, less than 15% had PE (33). However, in most patients the clinicians overall impression was indeterminant (20 to 80%) (33). Perrier similarly demonstrated that when a clinicians' overall impression was that the likelihood of PE was less than 20%, 9% had PE and that when a clinicians impression was that the likelihood of PE was over 80%, 64% had PE (14). However, a recent abstract

presented at an international meeting challenged the utility of a clinician's impression (62). In this study, if a clinician's impression that the likelihood of PE was less than 20%, 19% had PE and if a clinician's impression was that the likelihood of PE was 80%, 46% had PE. None of these studies have demonstrated the inter-rater reliability of a clinician's overall impression.

2.2.3 Previously Published Clinical Prediction Rules for Patients with Suspected PE

Attempts to derive a clinical prediction rule to exclude PE have received little attention in the literature. Stein examined combinations of clinical characteristics and found several that were quite sensitive (32). For example, dyspnea or tachypnea or pleuritic pain was present in 97% of patients with PE. The prevalence of these combinations was comparable in those patients with and without PE. Hence, while some of these combinations may almost safely exclude PE (i.e. are sensitive) none are 100% sensitive. Further, their clinical utility (i.e. excluded proportion) or ability to correctly exclude a significant proportion of patients suspected of having PE is limited. These combinations therefore cannot be used alone as a clinically useful clinical prediction rule.

One approach to the limitation of non- "diagnostic" ventilation-perfusion scans has been to develop clinical decisions rules for patients with non-"diagnostic" results (58-60). However, this approach neither limits the need for

presumptive anticoagulation nor deals with the limited availability and the expense of ventilation-perfusion scanning.

Two separate combinations of predictive factors that appear to safely exclude PE in a large proportion of patients suspected of PE have recently been reported (12,56). Kline, in a population of ambulatory patients, showed that the combination of a negative latex D-Dimer and an alveolar dead space fraction of less than 0.2 had a negative predictive value of 100% (95% CI of 96 to 100%) (56). This combination was 100% sensitive (95% CI of 87 to 100%) in excluding PE. The excluded proportion was 56% (95%CI of 44 to 63%). However, Kline's method has not been prospectively validated and his study was only performed in a single center. Further, as discussed above, the inter-observer reliability of Kline's method of alveolar dead space fraction measurement has not been reported.

Wells has published a clinical prediction model (see **Figure 3**) (12). Only 3.4% of patients with low probability using this clinical model had PE. However, this clinical model uses 28 predictor variables which makes it cumbersome to use (see **Figure 3**). The inter-observer reliability of the individual factors within the model has not been evaluated nor has the inter-observer reliability of the overall method been determined in non-expert clinicians. The effects of clinical use of the rule need to be prospectively measured. To address some of these concerns Wells has simplified the clinical model. Using multivariate techniques he derived

a 7-point clinical prediction rule from the original dataset (see **Figure 4**). The simple 7-point model has not yet been prospectively validated and its inter-observer reliability has not been demonstrated. In fact, a Dutch group has recently attempted to retrospectively validate the 7-point model on an existing data set of patients with suspected PE (62). The results presented in abstract form were discouraging for a: low model score, 28% had PE; for an intermediate model score, 30% had PE; and for a high model score 38% had PE. Despite the limitations of this validation (retrospective, selected subgroup of patients), the 7-point model appears to be imperfect, necessitating further attempts to derive a safe, reproducible and clinically useful clinical prediction rule.

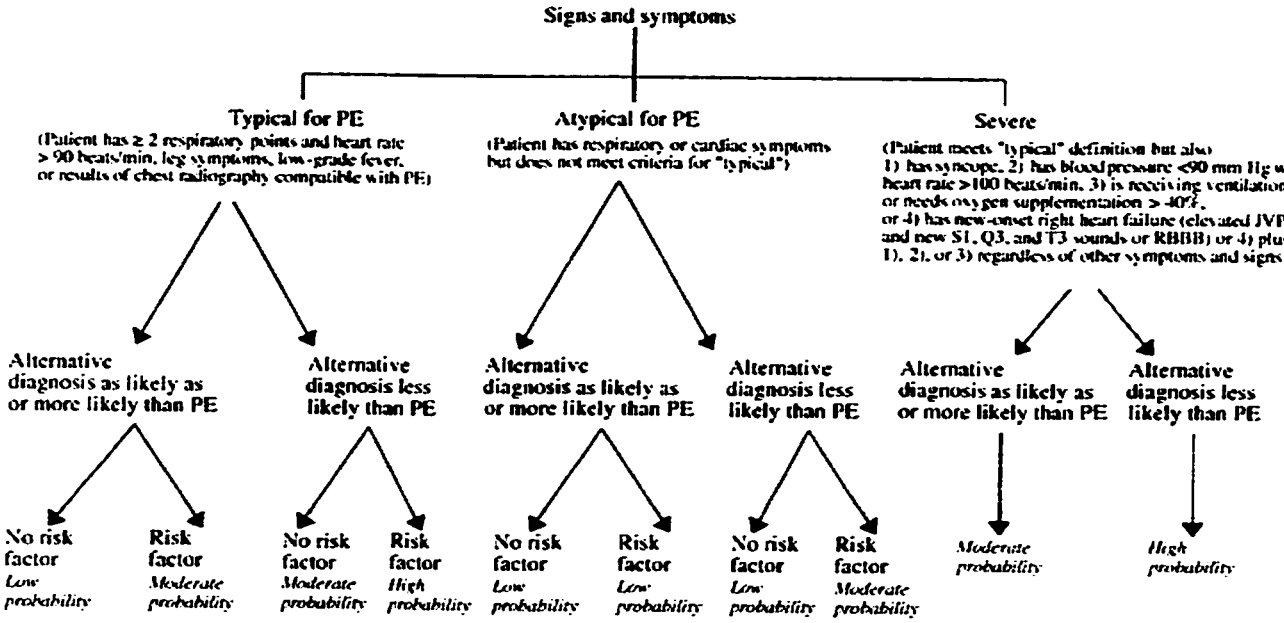

Figure 3. Algorithm for Wells' clinical model to determine the pre-test probability of pulmonary embolism (PE). Respiratory points consist of dyspnea or worsening of chronic dyspnea, pleuritic chest pain, chest pain that is nonretrosternal and nonpleuritic, an arterial oxygen saturation less than 92% while breathing room air that corrects with oxygen supplementation less than 40%, hemoptysis, and pleural rub. Risk factors are surgery within 12 weeks, immobilization (complete bedrest) for 3 or more days in the 4 weeks before presentation, previous deep venous thrombosis or objectively diagnosed pulmonary embolism, fracture of a lower extremity and immobilization of the fracture within 12 weeks, strong family history of deep venous thrombosis or pulmonary embolism (two or more family members with objectively proven events or a first-degree relative with hereditary thrombophilia), cancer (treatment ongoing, within the past 6 months, or in the palliative stages), the postpartum period, and lower-extremity paralysis. JVP = jugular venous pressure; RBBB = right bundle-branch block.

Predictor Variable	Points
Clinical signs or symptoms of DVT	3.0
Alternate diagnosis less likely than PE	3.0
Heart rate over 100	1.5
Previous DVT or PE	1.5
Major surgery or immobilisation within 4 weeks	1.5
Active malignancy	1.0
Hemoptysis	1.0
Total:	

< 4 pts = PE unlikely;
≥ 4pts = PE possible

Figure 4. Wells' Simplified Clinical Model for PE

In summary, many individual clinical predictors have been found to differentiate between patients with and without PE. The studies examining these predictors however have been limited by selection bias or poor outcome measures. Several attempts to derive and validate a clinical prediction rule to exclude pulmonary embolism have been reported. None of these attempts have adhered to methodologic guidelines for clinical prediction rule development and validation.

3.0 GOALS AND OBJECTIVES

1) To identify predictive clinical variables for pulmonary embolism in patients with suspected pulmonary embolism

2) To determine the inter-observer reliability of the predictive clinical variables

3) To derive clinical prediction rules to exclude pulmonary embolism using multivariate techniques

4) To assess the classification performance of the derived clinical prediction rules

5) To validate the clinical prediction rule with the best classification performance in a new study population

4.0 ORGANISATION OF THE STUDY

PHASE I - Using univariate statistical techniques, potential predictor variables were identified from a prospective cohort study of inpatients, outpatients and emergency room patients with suspected PE who subsequently had outcomes measured (Derivation set).

PHASE II The inter-observer reliability of these individual predictor variables were determined in a second prospective cohort study of inpatients, outpatients and emergency room patients with suspected PE (Inter-observer reliability set).

PHASE III -Two multivariate techniques (recursive partitioning and logistic regression) were used to derive clinical prediction rules, in the derivation set, based on those variables that were both significant in univariate analysis ($p<0.20$) and had good inter-observer reliability (kappa>0.5) as per accepted methodological criteria (61). The clinical prediction rules with the highest excluded proportion and with close to 100% negative predictive value were then identified using classification analysis in the derivation set. The rule that was easiest to use was then selected as the final clinical prediction rule.

PHASE IV- The rule was then retrospectively validated in a third independent cohort of inpatients, outpatients and emergency room patients with suspected PE who participated in a previously published multicentre study (12) (Validation set).

5.0 PHASE I-DETERMINING UNIVARIATE PREDICTORS

5.1 Goals and Objectives

To identify predictive clinical variables for pulmonary embolism in patients with suspected pulmonary embolism.

5.2 Patients and methods

5.2.1 Inclusion criteria

Consecutive inpatients and outpatients at the Ottawa General Hospital (a tertiary care hospital) suspected of having pulmonary embolism and referred for a ventilation-perfusion scan or pulmonary angiogram over a 30 month period were approached for consent to participate in the study (January 1996 – August 1998).

5.2.2 Exclusion Criteria

Patients were excluded from the study if they:

1) were less than 18 years of age,
2) were unable to give informed consent,
3) required pulmonary angiography and had a contraindication to pulmonary angiography,
4) were ventilated or
5) were in the final stages of terminal disease.

5.2.3 Sample Size

As per accepted methodological criteria for the development of clinical prediction rules, 5 to10 patients per predictor variable studied are required in the smallest outcome category (29). I estimated (based on the review of published literature) that I would identify 10 significant predictive variables and that five would be found to have high inter-observer reliability. In my study (as in others (11,12,14)), the smallest outcome category was pulmonary embolism. I, therefore, required a minimum of 25 patients and ideally possibly 50 patients with pulmonary emboli.

5.2.4 Ethics

Participating patients signed informed consents approved by the institutional ethics review board (**Appendix I**).

5.3 Standardized Patient Assessment

The referring physician and the study respiratory therapist were asked to complete standardized patient assessments (**Appendix II and III** respectively). The referring physician's standard assessment included history, physical examination, laboratory, ECG and CXR data. The respiratory therapist's standard assessment included alveolar dead space analysis and arterial blood gases.

5.3.1 Referring Physician's Standardized Patient Assessment

The referring physician completed the standardized patient assessments prior to the ventilation perfusion (V/Q) scan (**Appendix II**). Any physician (resident or staff physician but not medical students) could complete the assessment. Physicians were briefly introduced to the standardized patient assessment but there was no systematic attempt to train physicians to complete the standardized patient assessments. Assessments completed after V/Q scan were excluded from analysis.

5.3.1.1 Variables

The referring physician completed a standardized patient assessment that included predictor variables that had previously been shown across studies to consistently predict for PE in patients with suspected PE (see Background). Some selection of these variables was necessary in order to keep the number of variables collected to a minimum to help optimize physician compliance in completing the assessments in and maximize the number of complete datasets. The selected variables were those the author felt were most likely to have high inter-observer reliability and which had previously been shown to be predictive. The final list of variables is shown in **Table 5**.

Table 5. Potential clinical predictors and definitions of potential clinical predictors collected in Phase I.

Predictor Variable	**Definition**	**Predictor Variable**	**Definition**
Presenting History		*Physical Examination*	
- Age	Age in years	- Heart Rate	Heart rate on physical exam
- Sex	Male or female	- Respiratory Rate	Respiratory rate on physical exam
- Any Dyspnea	Any shortness of breath	- Temperature	Temperature on physical exam
- Sudden Dyspnea	Sudden onset shortness of breath	- Blood Pressure	Blood pressure on physical exam
- Any Chest Pain	Any chest discomfort	- JVP	Jugular venous press. (cm above sternum)
- Pleuritic Chest Pain	Chest pain worse with deep breath	- loud P2	S2 louder than S1 at apex
- Sudden Chest Pain	Sudden onset chest pain	- S4	Presence of fourth heart sound
- Hemoptysis	Blood streaked sputum	- Crackles	Presence of crackles on auscultation
- Leg Swelling	Any leg swelling on history or exam		
- Leg Pain	Any leg pain on history or exam	*ECG Changes*	
		- ST Changes	Any ST change > +/- 1mm over T-P interval
VTE Risk Factors		- T Wave Changes	Any T wave flat or inverted except AVR
- Any VTE risk factor	Any of the risk factors below		
- Previous DVT/ PE	Previous DVT or PE	*Chest X-Ray*	
- Family History	Family history of VTE	- Parenchymal Change	Any parenchymal abnormality
- Thrombophilia	Protein C, S, ATIII deficiency or APA		
- Post- Partum	Within 3 months post-partum	*Clinician's Impression*	
- Recent Surgery	Major surgery in the last month	- Likelihood of PE	Clinicians pre-test likelihood in percentages
- Active Malignancy	On treatment in last 6 mo./ palliative	- Alternate diagnosis?	Is an alternated diagnosis more likely (yes or no)
- Recent Immobil.	Immoblised >72hrs in last month		
- Major Trauma	Major Trauma in last 1 month		
- Cong. Heart Fail.	Congestive heart failure		

Data were collected on presenting features and patient sex, despite these variables not having been previously shown to be predictive, in order to identify the baseline characteristics of our population. Leg pain and swelling were included as they were important predictors in Wells' clinical model (12) (see above). Referring clinicians were asked to review two simple ECG changes which have been previously shown to be common in patients with PE, ST wave changes and T wave changes. Of the CXR findings, only the presence or absence of any parenchymal abnormality on CXR was collected given that this finding was quite sensitive and likely reproducible.

To minimize the number of variables collected by the referring physicians, three investigators (the principle investigator and two cardiologists) reviewed all available ECG's for any feature that had previously been commonly found in patients with PE (see **Table 6**).

Table 6. ECG variables reviewed by study physicians

Predictor Variable
Heart Rate on ECG >100
Heart Rate on ECG >90
Any ST or T wave change
Non sinus rhythm
Atrial fibrillation
Premature atrial contraction
Ventricular premature contraction
Right axis deviation (>90 degrees)
Indeterminant axis (180 to -90 degrees)
P Pulmonale
Small QRS (< 5 mm in limb leads)
Incomplete right bundle branch block
Complete right bundle branch block
Right bundle branch block and ST elevation
Transition to V5 or later
Q in III and AVF but not II
S1Q3T3
S slurred in V1 and V2
Late R in AVR
Right ventricular hypertrophy
S1S2S3
ST change
ST depression
T inverted in III and/or AVF
T inverted in V1 or V2
T flat or inverted in any lead but ???
T flat or inverted in any lead but AVR
PR depression
This is PE
Likelihood this is PE

5.3.2 Respiratory Therapist Standardized Patient Assessment

5.3.2.1 Alveolar Dead Space Analysis

Respiratory therapists (RT) performed alveolar dead space analysis. Two methods of end tidal alveolar dead space measurement were used over the course of the study. Both methods were taught in separate two-hour training sessions to the approximately 40 respiratory therapists in our institution. From January 1996 to February 1998, the sitting patient breathed through a Hans Rudolph one way valve with the expiratory side of the valve connected via a three-way stopcock to

a 60 litre Douglas bag. A sidestream port on the Hans Rudolph valve was connected to a Datex CD-102-27-00 capnograph. The capnograph provided continuous expired CO_2 data. The Datex capnograph was calibrated with room air (0.3% CO_2) and 4.0% CO_2 prior to each use. Expired gas was collected for a timed period of 3 minutes once the patient was judged to be relaxed and breathing regularly by the respiratory therapist. At the end of the 3-minute collection, an arterial puncture was performed for arterial blood gas analysis. The blood gas was analysed with a Ciba Corning 278 blood gas analyser, which was calibrated twice daily with standard gases. The mixed expired PCO_2 from the Douglas bag, was measured by 1) the capnograph and 2) the arterial blood gas analyser. If a discrepancy of more than two mmHg was noted in the mixed expired PCO_2 measured by the capnograph and the blood gas analyser then the patient's dead space data was excluded from the study. The end tidal alveolar dead space fraction was calculated as follows:

$$AVDSf = (PaCO_2 - PetCO_2) / PaCO_2$$ (Erikson, 1989 (52))

$PaCO_2$ = Concentration of carbon dioxide in arterial blood

$PetCO_2$ = End tidal CO_2 concentration in last ten breaths prior to end of timed collection.

We modified our methods and equipment after having determined the importance of: 1) patient stability at the time of arterial and end tidal CO_2 sampling and 2) of the accuracy of our end tidal CO_2 monitor. From February

1998 to August 1998, the sitting patient breathed through an airway adapter attached to a mouthpiece. The airway adapter had a mainstream CO_2 and volume sensor (COSMOplus by Novametrix). This device measures breath by breath volume with an accuracy of +/- 50ml and CO_2 with an accuracy of 2 mmHg. The machine was calibrated prior to each use with a known gas (4% CO_2). Once the patient had stabilised (respiratory rate +/- 2 breaths per minute over 2 minutes) the RT recorded this as the stable respiratory rate.

With the patient breathing at the stable respiratory rate, the end tidal CO_2 was recorded if it was stable (+/- 1 mmHg over 2 minutes). Arterial blood gas was obtained by a single arterial blood gas puncture only if the patient was breathing at the stable respiratory rate and the stable end tidal PCO_2. Subsequently, the respiratory therapist calculated the end tidal alveolar dead space fraction as follows:

$$\text{End tidal AVDS Fraction} = \frac{PaC0_2 - PetC0_2}{PaC0_2}$$

$PaCO_2$ = Concentration of arterial carbon dioxide in arterial blood with the patient breathing at the stable respiratory rate and stable end-tidal CO_2.

$PetC0_2$= Stable end tidal PCO_2

The dead space measurements were not provided to either the referring physician or the interpreting nuclear medicine physician.

I calculated A-a gradients in all study patients who had blood gases using the standard equation (45).

5.3.3 D-Dimer Measurement

A latex D-Dimer (Accuclot by Sigma Diagnostics) or a whole blood agglutination D-Dimer (SimpliRED by Agen) were performed on venous blood within 24 hrs of the ventilation-perfusion scan or pulmonary angiogram.

5.4 Outcome Measure

The presence or absence of pulmonary embolism was determined independent of the standardized patient assessments. After the ventilation-perfusion scan, patients with a post-test probability of pulmonary embolism of less than 5% were considered, for study purposes, not to have pulmonary embolism. This group was defined by: 1) patients with normal or near normal ventilation-perfusion scans; 2) patients with a low index of pre-test clinical suspicion, who had low probability ventilation-perfusion scans (11); and 3) patients with low probability scans with a negative leg vein ultrasound result at presentation (12). After ventilation-perfusion scan, patients with a post-test probability of 88% or greater were considered for study purposes to have a pulmonary embolism. This was defined as patients with a high or intermediate index of pre-test clinical suspicion who had high probability ventilation-perfusion scans (11). All other patients were recommended to proceed to pulmonary angiography but this decision was left to the patient's treating physician. Those

patients with indeterminate scans who did not undergo angiography were excluded from the analysis.

5.4.1 Ventilation Perfusion Scan

All patients in the study underwent V/Q scanning. Six views (RAO, LAO, RPO, LPO, anterior and posterior) perfusion scans with 2 mCi of MAA were performed. Ventilation with radioaerosol was performed if the perfusion was abnormal. The 6 views ventilation-perfusion scans were independently interpreted by two nuclear medicine physicians utilizing the PIOPED criteria (11). When a discrepancy in interpretations arose the ventilation-perfusion scan was reinterpreted and a diagnosis assigned by consensus.

5.4.2 Pulmonary Angiography

Pulmonary angiography was performed within 24 hours of V/Q scan in an angiography suite equipped with the digital subtraction-angiography (DSA) equipment (AngioCon 241L, Picker Inc.,Cleveland Ohio). Via a femoral vein approach using 7-8F pigtail catheter the left and right pulmonary arteriograms were obtained in AP projection using intra-arterial DSA technique. These exams were supplemented with selective lobar artery injections in oblique projections when deemed appropriate, after review of the original AP projection and after review of abnormal findings on the V/Q scans. In technically difficult patients film screen angiography was used if DSA and unsubtracted images were deemed to be inadequate.

A total of 100-150 ml of nonionic contrast medium Iohexol with concentration of 350 mg/ml was used during most examinations. Injections were for 2 seconds at a rate of 15-20 ml/s. DSA acquisition were obtained at a rate of 3-5 f/s and filming when necessary at a rate of 3-4 film/s.

Angiograms were interpreted by a single angiographer on recorded fluoroscopic images and reinterpreted by an angiographer (PR) and a study investigator (PW) after reviewing the fixed images obtained on film with laser camera. The diagnosis of pulmonary embolism was based on observation of intraluminal vascular filing defect(s).

5.5 Data Analysis

5.5.1 Univariate analysis

Continuous variables were compared in the patients with PE and the patient without PE by an independent groups t-test with equal variances assumed if Levenes test was not significant. If Levene's test was significant an independent groups t test with unequal variances was performed. Likelihood ratio chi square tests were used to compare proportions between the two groups.

5.6 Results

5.6.1 Baseline Characteristics

Two hundred and ninety three patients were approached of whom 282 were eligible for participation in the study. Of these 282 patients, 246 gave consent. Of 246 eligible and consenting patients 49 had PE and163 did not have PE (see **Table 7**). Thirty four patients could not be classified as clinicians did not further pursue investigations to adequately classify patients. Age, sex and source of referral were not significantly different in comparing unclassified patients from classified patients. Patients with PE were significantly older than patients without PE. Patients with PE were more likely to be male than female. Almost all patients presented with chest pain or shortness of breath.

Table 5. Potential clinical predictors and definitions of potential clinical predictors collected in Phase I.

Predictor Variable	**Definition**	**Predictor Variable**	**Definition**
Presenting History		*Physical Examination*	
- Age	Age in years	- Heart Rate	Heart rate on physical exam
- Sex	Male or female	- Respiratory Rate	Respiratory rate on physical exam
- Any Dyspnea	Any shortness of breath	- Temperature	Temperature on physical exam
- Sudden Dyspnea	Sudden onset shortness of breath	- Blood Pressure	Blood pressure on physical exam
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- Recent Surgery	Major surgery in the last month	- Likelihood of PE	Clinicians pre-test likelihood in percentages
- Active Malignancy	On treatment in last 6 mo./ palliative	- Alternate diagnosis?	Is an alternated diagnosis more likely (yes or no)
- Recent Immobil.	Immoblised >72hrs in last month		
- Major Trauma	Major Trauma in last 1 month		
- Cong. Heart Fail.	Congestive heart failure		

5.6.2 Univariate Predictors of PE

The results of univariate analysis of the standardized physician's assessment are shown in **Table 8** (p values < 0.20 were considered statistically significant for this analysis to select variables for multivariate analysis). Patients with PE were significantly older than patients without PE. Age was re-categorised in intervals of 5 years and a cutoff of 55 years of age resulted in the highest chi square statistic. Female sex was a significant negative predictor for pulmonary embolism. The presence of dyspnea and the absence of chest pain were weak predictors for PE. Leg symptoms were strong predictors of PE. All risk factors except congestive heart failure, recent major trauma, family history, known thrombophilia and the post-partum period were significant. Respiratory rate, heart rate, systolic blood pressure and the presence of loud P2 were the only statistically significant physical examination predictors. Respiratory rate and heart rate were re-categorised in intervals of 5 breaths per minute and 10 beats per minute respectively and a cutoffs of a heart rate of 110 or greater and a respiratory rate of greater than 25 resulted in the highest chi square statistic. None of the ECG or chest x-ray variables was predictive. Clinician's overall impression was statistically significantly predictive as was a clinician's impression that an alternate diagnosis was more likely.

Table 9 shows the results of univariate analysis of the ECG review. Only tachycardia, the absence of sinus rhythm, indeterminant QRS axis and incomplete right bundle branch block were significantly predictive.

Of the respiratory therapist standardized assessment both A-a gradient and alveolar dead space fraction (AVDSf) were predictive with a $p< 0.20$ (see **Table 10**). AVDSf was recategorised in intervals of 0.05 and a cutoff of 0.2 resulted in the highest chi square statistic. The cut-off for A-a gradient used was that which is commonly known to clinicians (48).

Both D-Dimer tests were significant predictors ($p < 0.20$) of pulmonary embolism (see **Table 11**).

Table 8. Phase I results- Univariate analysis of physicians standardized clinical assessment.

	Percentage with or Mean of Predictor Variable		
Predictor Variable	**PE patients** (n=49)	**No PE** (n=163)	**P value**
Presenting History			
- Mean Age (years)	58.9	50.6	0.001*
- Age > 55	33.7%	14.0%	0.001*
- Female Sex %	40.8%	67.5%	0.001*
- Any Dyspnea	85.7%	76.0%	0.151*
- Sudden Dyspnea	56.8%	46.4%	0.243
- Any Chest Pain	69.4%	79.1%	0.162*
- Pleuritic Chest Pain	64.3%	70.2%	0.467
- Sudden Chest Pain	51.2%	57.4%	0.488
- Hemoptysis	6.5%	3.4%	0.558
- Leg Pain or Swelling	62.8%	29.6%	0.000*
VTE Risk factors			
- Any VTE risk factor	80.9%	60.7%	0.011*
- Previous DVT/ PE	34.7%	13.6%	0.001*
- Family History	2.3%	2.2%	0.948
- Thrombophilia	2.4%	0.7%	0.353
- Post- Partum	2.1%	3.9%	0.544
- Recent Surgery	44.9%	19.9%	0.001*
- Active Malignancy	24.5%	15.7%	0.161*
- Recent Immobil.	38.8%	23.2%	0.033*
- Major Trauma	6.1%	4.0%	0.541
- Cong. Heart Fail.	4.4%	5.5%	0.792
Physical Examination			
- Heart Rate (beats/min)	97.7	90.5	0.025*
- Heart Rate > or = 110	51.2%	16.8%	0.000*
- Respiratory Rate (breaths/min)	23.6	21.0	0.009*
- Respiratory Rate >25 (br./min)	41.3%	20.0%	0.004*
- Temperature < 38	88.6%	93.0%	0.387
- Temperature < 38.5	100%	99.2%	0.601
- Systolic Blood Pressure	125.5	132.2	0.146*
- Diastolic Blood Pressure	77.4	77.4	0.996
- JVP (cm above SA)	1.6	1.8	0.545
- loud P2	19.4%	8.3%	0.098*
- S4	10.0%	5.7%	0.417
- Crackles	44.4%	43.4%	0.917
ECG Changes			
- ST Changes	40.9%	47.9%	0.417
- T Wave Changes	36.6%	33.0%	0.681
Chest X-Ray			
- Parenchymal Change	45.0%	53.5%	0.522
Clinician's Impression			
- Likelihood of PE <20%	16.2%	32.7%	0.054*
- Likelihood of PE >80%	29.7%	14.2%	0.032*
- An alternate diagnosis more likely?	31.9%	51.6%	0.021*

*= p< 0.20

Table 9. Phase I results- Univariate analysis of ECG review.

	Percentage with Predictor Variable		
Predictor Variable	**PE patients** (n=49)	**No PE** (n=163)	**P value**
Heart Rate on ECG >100	37.5%	19.0%	0.008*
Any ST or T wave change	68.2%	66.9%	0.874
Non sinus rhythm	8.9%	3.5%	0.156*
Atrial fibrillation	4.4%	2.1%	0.403
Premature atrial contraction	2.2%	1.4%	0.709
Ventricular premature contraction	6.7%	5.0%	0.659
Right axis deviation (>90 degrees)	8.9%	6.4%	0.727
Indeterminant axis (180 to –90 degrees)	8.9%	2.1%	0.038*
P Pulmonale	2.2%	0.7%	0.392
Small QRS (< 5 mm in limb leads)	4.4%	5.0%	0.887
Incomplete right bundle branch block	6.7%	0.0%	0.002*
Complete right bundle branch block	4.4%	3.5%	0.783
Right bundle branch block and ST elevation	2.2%	1.4%	0.709
Transition to V5 or later	13.6%	9.2%	0.400
Q in III and AVF but not II	14.0%	9.2%	0.372
S1Q3T3	11.6%	13.5%	0.753
S slurred in V1 and V2	9.3%	9.2%	0.987
Late R in AVR	0%	0%	-------
Right ventricular hypertrophy	2.4%	2.1%	0.926
S1S2S3	2.3%	6.4%	0.304
ST change	9.3%	12.8%	0.540
ST depression	14.0%	11.3%	0.645
T inverted in III and/or AVF	34.9%	30.0%	0.545
T inverted in V1 or V2	44.4%	44.3%	0.997
T flat or inverted in any lead	76.7%	81.4%	0.499
T flat or inverted in any lead but AVR	41.9%	37.9%	0.637
PR depression	0.0%	0.7%	0.570
This is PE	0%	1.9%	0.601
Likelihood this is PE	18.9%	20.7%	0.583

*P<0.20

Table 10. Phase I results- Univariate analysis of standardized respiratory therapists' assessment.

	Percentage with Predictor Variable		
Predictor Variable	**PE patients** (n=49)	**No PE** (n=163)	**P value**
A-a Gradient > age/4 +4	84.2%	72.6%	0.150*
AVDSf < 0.2	30.8%	79.3%	0.000*

*P<0.20

Table 11. Phase I results- Univariate analysis of D-Dimer measurements

	Percentage with Predictor Variable		
Predictor Variable	**PE patients** (n=49)	**No PE** (n=163)	P value
Latex D-Dimer < 250	30.6%	50.5%	0.037*
SimpliRED D-Dimer negative	18.2%	67.9%	0.000*
Any negative D-Dimer	17.0%	57.6%	0.000*

*P<0.20

Table 12. Phase I results- Summary table of significant univariate predictors of pulmonary embolism in patients suspected of pulmonary embolism.

	Percentage with Predictor Variable		
Predictor Variable	**PE patients** (n=49)	**No PE** (n=163)	P value
Presenting History			
- Age > 55	33.7%	14.0%	0.001
- Female Sex %	40.8%	67.5%	0.001
- Any Dyspnea	85.7%	76.0%	0.151
- Any Chest Pain	69.4%	79.1%	0.162
- Leg Pain or Swelling	62.8%	29.6%	0.000
VTE Risk factors			
- Any VTE risk factor	80.9%	60.7%	0.011
- Previous DVT/ PE	34.7%	13.6%	0.001
- Recent Surgery	44.9%	19.9%	0.001
- Active Malignancy	24.5%	15.7%	0.161
- Recent Immobil.	38.8%	23.2%	0.033
Physical Examination			
- Heart Rate > or = 110	51.2%	16.8%	0.000
- Respiratory Rate >25 (br./min)	41.3%	20.0%	0.004
- Systolic Blood Pressure	125.5	132.2	0.146
- Loud P2	19.4%	8.3%	0.098
Clinician's Impression			
- Likelihood of PE <20%	16.2%	32.7%	0.054
- Likelihood of PE >80%	29.7%	14.2%	0.032
- An alternate diagnosis more likely?	31.9%	51.6%	0.021
ECG Changes			
Incomplete right bundle branch block	6.7%	0.0%	0.002
Indeterminant axis (180 to –90 degrees)	8.9%	2.1%	0.038
Non sinus rhythm	8.9%	3.5%	0.156
RT Data			
A-a Gradient > age/4 +4	84.2%	72.6%	0.150
AVDSf < 0.2	30.8%	79.3%	0.000
D-Dimer			
Any negative D-Dimer	17.0%	57.6%	0.000

5.7 Discussion

Most of the variables I identified as significant univariate predictors of pulmonary embolism have been previously shown to be significant univariate predictors (See Background). Those variables that had not been previously shown

to be significant univariate predictors were only weakly associated (e.g. systolic blood pressure). Interestingly, like Wells, I also found that leg swelling and pain were significant univariate predictors (12). Other authors have not shown this association (33,35). This association makes clinical sense given that most pulmonary emboli develop from leg deep vein thromboses (15). Dyspnea was shown to be a significant positive predictor for PE and chest pain was a significant negative predictor for PE. This would suggest that clinicians should consider PE more often for the differential diagnosis of dyspnea and less often for the differential diagnosis of chest pain. None of the classically described qualifiers for chest pain (sudden, pleuritic) or dyspnea (sudden) were predictive, calling into question the utility of this teaching. In contrast to findings of the Dutch group (62) we found that the referring clinicians overall diagnostic impression was as predictive as has been previously shown (see Background)(14,33). Some predictors that have been previously shown to be predictive but are rarely present in patients with suspected PE (e.g. hemoptysis, post-partum, recent trauma, thrombophilia, family history S1Q3T3) were not found to be predictive in this study. This may reflect this study's inadequate power to detect differences in clinical predictors that are rarely found in patients with suspected PE.

6.0 PHASE II- INTER-OBSERVER RELIABILITY OF SIGNIFICANT UNIVARIATE PREDICTORS

6.1 Goals and Objectives

To identify the inter-observer reliability of each clinical variable identified as a significant predictor by univariate analysis in Phase I.

6.2 Patients and Methods

6.2.1 Inclusion Criteria

Consecutive patients referred for V/Q scanning at the Ottawa General Hospital who were suspected of having pulmonary embolism were approached for consent to participate in the study (same as Phase I see (5.2.1)) between January 1996 to April 1999. Different components of this part of the investigation were conducted at different times eg. inter-observer reliability of standardized physician assessment done October 1998 – April 1999 and standardized RT assessments done April 1998 – August 1998.

6.2.2 Exclusion Criteria

Patients were excluded from the study if they:

1) were less than 18 years of age,

2) were unable to give informed consent,

3) required pulmonary angiography and had a contraindication to pulmonary angiography,

4) were ventilated or were in the final stages of terminal disease.

The exclusion criteria were the same as in Phase I (see 5.2.2).

6.2.3 Standardized Patient Assessment

To measure the inter-observer reliability of each component of the standardized patient assessment, each component was collected on subsets of consecutive study participants by two independent observers. The inter-observer reliability of D-Dimer measurements was not performed in this investigation, as the reproducibility of the tests has been previously published (63). The D-dimer assay has been shown to have excellent inter-observer agreement (kappa (K) = 0.95 [95% CI, 0.88 to 1.0]), between-assay agreement (K = 0.96 [CI, 0.90 to 1.0]), and reproducibility (97%) (63).

6.2.3.1 Physician Standardized Patient Assessment

Duplicate standardized physician patient assessments were completed on all study participants between October 15th 1998 and April 1st 1999 by the refering physician and a study investigator (MR, AK and PW). The physician's standardized patient assessment included the clinical variables found to be significant predictors in Phase I (see **Appendix IV**). Standardized patient assessments were completed blindly and independently of each other. All clinical assessments were performed prior to the ventilation perfusion (V/Q) scan and independent of knowledge of D-Dimer results and alveolar dead space results.

6.2.3.2 Respiratory Therapist Standardized Patient Assessment

Duplicate standardized respiratory therapist patient assessments were completed on all consenting study participants between April 1st 1998 and August 15th 1998. Two respiratory therapists independently and blindly performed alveolar dead space analysis by the technique describe above (see 5.3.2.1) and by the technique described by Kline (56). The results of the alveolar dead space analysis were not provided to the second respiratory therapist performing the tests. Each patient had two separate respiratory therapists perform a blood gas and measure alveolar dead space. The respiratory therapists were also unaware of the outcome of investigations for suspected pulmonary embolism, the physician assessments and the D-Dimer results.

6.2.3.3 ECG review

Two cardiologists independently and blindly interpreted a subset of ECG's of patients suspected of PE included in Phase I of the study (January 1996 – August 1998). Heart rate and indeterminate axis were not examined as these are calculated by modern ECG equipment and printed on the ECG. Hence, the reproducibility of these measures can be expected to be 100%.

6.2.4 Sample size

A sample size of 100 would have been required to obtain a width of 0.2 around our point estimates of kappa for two observers (29,64). Time and resource

constraints did not permit this degree of precision to be achieved but 68 sets of physician assessments, 50 sets of ECG assessments and 34 sets of RT assessments were obtained allowing relatively precise estimates to be obtained.

6.2.5 Data Analysis

The inter-observer reliability of each predictor variable was determined by calculating a two rater unweighted Kappa statistic. Kappa (K) is defined as:

$$K = \frac{Po - Pe}{1 - Pe}$$

where Po is the actual probability of agreement

and Pe is the expected agreement by chance (64).

A kappa score above 0.8 is considered excellent reliability, a kappa score above 0.6 is considered good reliability and a kappa score below 0.4 is considered poor reliability (64). Exact binomial ninety-five percent confidence intervals were calculated for each kappa.

6.3 Results

6.3.1 Standardized Physician Assessments

Sixty eight patients had two blind and independent physician assessments performed. The first physician assessments were mainly completed by residents (44.8%) and emergency room physicians (44.8%). The remainder were completed

by internists (7.5%) and family doctors (3%). The second physician assessment were mainly completed by myself (60.3%), a second internist (AK) (38.2%) and the remaining one completed by a third internist (PW) (3.5%).

History of chest pain and leg swelling had good reproducibility (see Table 13). History of leg pain had poor reproducibility. All venous thromboembolic event risk factors had good reproducibility. Of the physical findings only heart rate had good reproducibility. Not surprisingly loud P2 and S4 had very poor reproducibility. The reproducibility of clinicians overall impression was poor.

Fifty ECGs were independently intrepreted by two cardiologists blinded to physician assessment, D-Dimer data, RT data and outcome measure. The absence of sinus rhythm and incomplete right bundle branch block had a high inter-observer reliability (see Table 14).

6.3.2 Respiratory Therapist Standardized Patient Assessment

Fifty-eight patients were approached to participate in this part of the investigation. Forty-eight consented to a single RT assessment and 34 to two RT assessments. Twenty-three respiratory therapists performed the 68 assessments that are the subject of this analysis.

All of the components of the respiratory therapists standardized assessment had good reproducibility except the A-a gradient and Kline's method of alveolar dead space measurement (see Table 15).

Table 13. Phase II results- Inter-observer reliability of history and physical examination features in patients with suspected pulmonary embolism.

Predictor	Kappa	Standard error	Lower 95% CI	Upper 95% CI
History				
Chest Pain	0.780	0.092	0.600	0.960
Dyspnea	0.511	0.127	0.262	0.759
Leg Pain	0.372	0.169	0.041	0.703
Leg Swelling	0.612	0.144	0.330	0.894
Leg Pain or Swelling	0.520	0.129	0.267	0.773
VTE Risk Factor				
Any VTE risk factor	0.761	0.084	0.596	0.927
Recent Immobilisation	0.505	0.129	0.252	0.758
Malignancy	0.867	0.075	0.720	1.014
Previous VTE	0.783	0.147	0.495	1.071
Recent Surgery	0.798	0.097	0.608	0.988
Recent Major Trauma	1.000	0.000	1.000	1.000
Physical Findings				
Loud P2	0.064	0.148	-0.226	0.354
S4	0.118	0.149	-0.174	0.410
Heart rate >110	0.673	0.106	0.465	0.881
Respiratory rate > 25	0.489	0.102	0.217	0.761
Clinician's impression				
Likelihood of PE	0.455	0.105	0.249	0.661
Other Dx more likely?	0.429	0.12	0.194	0.664

Table 14. Phase II results-Inter-observer reliability of ECG variables.

Predictor	Kappa	Standard error	Lower 95%CI	Upper 95% CI
ECG Changes				
Incomplete right bundle branch block	1.000	0.000	1.000	1.000
Non sinus rhythm	1.000	0.000	1.000	1.000

Table 15. Phase II results- Inter-observer reliability of arterial blood gas and alveolar dead space measurements.

Predictor	Kappa	Standard error	Lower 95%CI	Upper 95% CI
RT Data				
A-a Gradient > age/4 +4	0.464	0.178	0.115	0.813
AVDSf < 0.2 (Kline's method)	0.268	0.258	-0.238	0.774
AVDSf < 0.2 (Our method)	1.000	0.000	1.000	1.000

6.4 Discussion

Overall, history variables had greater reproducibility than physical findings. Recent immobilization had a lower inter-observer reliability than expected but this may reflect a need for more precise definition of immobility (e.g. greater than 90% of a day bedridden for 3 or more days). Pain or tenderness along the distribution of the deep veins had poor reproducibility. This may reflect a lack of knowledge among clinicians of venous anatomy. It came as no surprise that loud P2 and S4 on auscultation of the heart had very poor reproducibility. Heart rate likely had greater reproducibility than respiratory rate given the common clinical use of cardiac monitors or saturation monitors which display heart rate but not respiratory rate. Hence, measurement of respiratory rate involves clinicians observing a patient's breathing (often inducing a change in rate) over a minute or longer (hence often skipped). Not surprisingly, given the

non specific nature of the common presenting complaints for suspected PE (dyspnea and chest pain) clinician's diagnostic impression had poor to moderate reproducibility.

Kline's method of alveolar dead space analysis had poor reproducibility. This likely results from the need for patients to deeply exhale (effort dependent) and a therapists' interpretation of a plateau on a capnograph tracing. Our method, which does not require any alteration in a patient's breathing pattern or a therapist's interpretation, had excellent reproducibility (see **Table 15**). This data calls into question the generalizability of Kline's method of excluding pulmonary embolism at the bedside and should limit this techniques' widespread adoption despite its high negative predictive value in the original study (56).

7.0 PHASE IIII-MULTIVARIATE DERIVATION OF CLINICAL PREDICTION RULE

7.1 Objectives

1) To derive clinical prediction rules to exclude pulmonary embolism using multivariate techniques

2) To assess the classification performance of the derived clinical prediction rules in the derivation set

3) To choose a clinical prediction rule for further validation

7.2 Sample Size

As per accepted methodological criteria for the development of clinical prediction rules, 5-10 patients per predictor studied are required in the smallest outcome category (29). Given that we had 49 patients with PE I was comfortable that I could enter 10 variables into the multivariate analysis without risk of overfitting the data (61).

7.3 Variable selection

Given that 16 variables had met the initial selection criteria of association with PE ($p< 0.20$) and good reproducibility ($k> 0.5$) further variable selection was required to avoid over fitting the data. The final list of variables chosen for multivariate analysis is shown in **Table 16**. Female sex and systolic blood pressure were excluded as these have not been shown to be significant predictors

in previous investigations. Incomplete right bundle branch block, indeterminate axis and non sinus rhythm were excluded from the final analysis as these have not consistently been shown to be predictive in prior investigations. Alveolar dead space was dropped as this variable was missing in 30% of our derivation set. However, given that alveolar dead space analysis with our technique had excellent predictive value and excellent reproducibility this variable will be collected in future investigations given its strong likelihood to form a useful component of a clinical prediction rule that could be applicable in many clinical settings.

Table 16. Variables entered into multivariate analysis and selection criteria.

Predictor Variable	PE	No PE	P value	Valid Cases	Variables in Multivariate Analysis
Presenting History					
- Age > 55	33.7%	14.0%	0.001*	100%	X
- Female Sex %	40.8%	67.5%	0.001*	100%	
- Any Dyspnea	85.7%	76.0%	0.151*	92 %	X
- Any Chest Pain	69.4%	79.1%	0.162*	93%	X
- Leg Pain or Swelling	62.8%	29.6%	0.000*	79%	X
VTE Risk factors					
- Any VTE risk factor	80.9%	60.7%	0.011*	90%	X
- Previous DVT/ PE	34.7%	13.6%	0.001*	91%	X
- Recent Surgery	44.9%	19.9%	0.001*	91%	X
- Active Malignancy	24.5%	15.7%	0.161*	91%	X
- Recent Immobil.	38.8%	23.2%	0.033*	91%	X
Physical Examination					
- Heart Rate > or = 110	51.2%	16.8%	0.000*	98%	X
- Systolic Blood Pressure	125.5	132.2	0.146*	63%	
ECG Changes					
Incomplete right bundle branch block	6.7%	0.0%	0.002*	83%	
Indeterminant axis (180 to –90 degrees)	8.9%	2.1%	0.038*	83%	
Non sinus rhythm	8.9%	3.5%	0.156*	81%	
RT Data					
AVDSf < 0.2	30.8%	79.3%	0.000*	70%	
D-Dimer					
Any negative D-Dimer	17.0%	57.6%	0.000*	90%	X

7.4 Data Analysis and Statistical Methods

Two methods of multivariate analysis, logistic regression and recursive partitioning were used to derive candidate clinical prediction rules. The classification performance of the candidate rules was then assessed.

7.4.1 Logistic Regression

The steps followed in model building were as follows:

1) Full model- A logistic regression was performed on a full model (i.e. all variables and biologically plausible interaction terms).

2) Interaction assessment- First a likelihood ratio test was performed to compare the full model to the full model without interaction terms. If this likelihood ratio test was significant we would then have performed backward elimination of individual interaction terms to identify significant interaction terms. All significant interactions would have been retained in the model.

3) Confounding and precision assessment- Variables were then removed that were not confounders of the remaining variables and did not significantly change the likelihood ratio statistic. We then controlled for the subset of variables that gave the largest gain in precision.

Hosmer Lemeshow test was performed on the final model to assess Goodness of fit.

7.4.2 Recursive Partitioning

Recursive partitioning was used as it has previously been used to develop prediction rules with high sensitivity and specificity (65). Recursive partitioning was performed using Knowledge Seeker Version 3 (Angoss Software,1993) . This software allows a heterogeneous group with and without a specified outcome to be split into increasingly homogeneous strata. The software finds the predictor variables for a specified outcome with statistically significant adjusted chi-squares. The chi-squares are adjusted for multiple comparisons by the method of Bonferroni. The software then partitions the group using the predictor variable with the highest adjusted chi-square. The software permits the operator to choose amongst the significant predictors or force a split with any variable in the dataset.

Our dataset including the outcome variable (PE or No PE) and the predictor variables chosen for multivariate analysis (see **Table 16**), were entered into a recursive partitioning process. Recursive partitioning was guided to correctly classify PE patients at the expense of specificity. The predictor variable with the highest adjusted chi-square was used to split the group into a group at high risk of PE and lower risk for PE. In other words, cases positive for the predictor variable were set aside as being at high risk for PE. Cases negative for the predictor variable were then grouped and formed the dataset for the next partition. The software then found the predictor variable within this lower risk group with the highest chi-square. This predictor variable was then used to partition this lower risk group into an even lower risk group for PE and a higher

risk group for PE. This process was continued until a subgroup with very few or no PE cases is identified. Those predictor variables responsible for partitioning the dataset were integrated into a candidate clinical prediction rule. Multiple solutions were found and hence multiple candidate rules were identified.

7.4.3 Classification Performance

Negative predictive value and the corresponding exact binomial 95% CIs were calculated for each candidate decision rule. Excluded proportions were calculated for each candidate rule. The rule with the best combination of high negative predictive value, excluded proportion and ease of use was then selected.

7.5 Results

7.5.1 Logistic Regression

No significant interactions were found (see **Table 17**). Dyspnea, malignancy, any risk, chest pain, immobility and age 55 could all be removed without significantly altering the model's precision. Recent surgical procedure, heart rate over 110, positive D-Dimer, leg pain or swelling and previous venous thromboembolic event could not be removed and were kept in the final logistic regression model. Hosmer and Lemeshows test was not significant (p=0.33) indicating a good goodness of fit for the final model.

Assigning each variable in the final model a point score proportional to each variables regression coefficient (see **Table 18**) yields a clinical prediction model (Regression model).

Table 17. Steps in model building by logistic regression.

Model	Deviance	G	df	P value for G
Full model	99.59	--	19	--
Full model minus interaction terms	108.302	8.71	8	0.36
Full model minus interaction terms and dyspnea	108.306	0.004	1	0.95
Full model minus interaction terms, dyspnea and malignancy	108.321	0.015	1	0.90
Full model minus interaction terms, dyspnea, malignancy and any risk factor	112.25	3.929	1	0.05
Full model minus interaction terms, dyspnea, malignancy, any risk factor and chest pain	112.99	0.74	1	0.38
Full model minus interaction terms, dyspnea, malignancy, any risk factor, chest pain and immobility	115.96	2.97	1	0.08
Full model minus interaction terms, dyspnea, malignancy, any risk factor, chest pain, immobility and age<55	118.86	2.97	1	0.08
Full model minus interaction terms, dyspnea, malignancy, any risk factor, chest pain, immobility, age<55 and HR<110	131.93	13.07	1	0.000*
Full model minus interaction terms, dyspnea, malignancy, any risk factor, chest pain, immobility, age<55 and Previous DVT	123.82	4.96	1	0.026*
Full model minus interaction terms, dyspnea, malignancy, any risk factor, chest pain, immobility, age < 55 and recent surgery	125.83	6.97	1	0.008*
Full model minus interaction terms, dyspnea, malignancy, any risk factor, chest pain, immobility, age < 55 and leg pain or swelling	157.71	38.85	1	0.000*
Full model minus interaction terms, dyspnea, malignancy, any risk factor, chest pain, immobility, age < 55 and DDimer	147.32	28.46	1	0.000*

***p<0.05**
G= Likelihood ratio test stastistic,.df= degrees of freedom for G.

Table 18. Regression coefficients and odds ratios for variables in the final regression model.

	Regression Coefficent	Odds Ratio	Odds Ratio Lower 95% CI	Odds Ratio Upper 95% CI	Model Points
D-Dimer Positive	2.09	8.1120	2.7991	23.5090	2.0
Heart Rate greater than 110	1.79	6.0274	2.1090	17.2256	2.0
Leg Pain or Swelling	1.64	5.1977	2.0524	13.1631	1.5
Previous VTE	1.17	3.2288	1.1416	9.1326	1.0
Recent Surgery	0.98	2.6736	1.0384	6.8839	1.0

Fewer than 1.0 model point results in a sensitivity and negative predictive value of 100% and safely excludes PE in 26.1% of the derivation set (see **Figure 5**).

	PE	NO PE
One or more Logistic Regression Model Points	42	74
Less than one Logistic Regression Model Points	0	41

Sensitivity = 100.0%(91.6-100%)
Specificity = 35.7% (27.7-46.1%)
Negative predictive value = 100.0%(91.4-100%)
Excluded proportion = 26.1%

Figure 5. 2x2 table and classification performance of the final logistic regression model with a less than one point cut-off.

Using one and a half points as the cut-off yields a clinical prediction model with a lower sensitivity but higher specificity (see **Figure 6**). A cut-off of two model points or higher yielded an unacceptably low negative predictive value (96.8%) (not shown).

	PE	NO PE
1.5 or more Logistic Regression Model Points	41	66
Less than 1.5 Logistic Regression Model Points	1	49

Sensitivity = 97.6%(87.4-99.9%)
Specificity = 42.6% (33.4-52.2%)
Negative predictive value = 98.0%(89.4-99.9%)
Excluded proportion= 31.2%

Figure 6. 2x2 table and classification performance of the final logistic regression model with a less than one and a half point cut-off.

An automated backward stepwise logistic regression yielded a clinical prediction model similar to the above but an additional variable (age>55) was included in the model (Regression coefficient- 0.95, significance of Wald's test 0.055). The classification performance of this six variable model was assessed (see **Figures 7 and 8**).

Using a cutoff of two points or more yields a high negative predictive value and a high specificity (see **Figure 7**). A cut-point of two and half or more points resulted in an unacceptably low negative predictive value (97.1%) (not shown).

	PE	NO PE
Two or more Logistic Regression Model Points	42	63
Less than two Logistic Regression Model Points	0	52

Sensitivity = 100.0%(91.6-100%)
Specificity = 45.2% (35.9-54.8%)
Negative predictive value = 100.0% (93.1-100%)
Excluded proportion= 33.3%

Figure 7. 2x2 table and classification performance of an automated backward stepwise logistic regression model with a less than one and a half point cut-off.

Using a cutoff of one point or more yields a high negative predictive value but a much lower specificity (see **Figure 8**).

	PE	NO PE
One or more Logistic Regression Model Points	42	83
Less than one Logistic Regression Model Points	0	32

Sensitivity = 100.0%(91.6-100%)
Specificity = 27.8% (19.9-36.9%)
Negative predictive value = 100.0% (89.1-100%)
Excluded proportion = 20.4%

Figure 8. 2x2 table and classification performance of an automated backward stepwise logistic regression model with a less than one point cut-off.

7.5.2 Recursive Partitioning

The variable with the highest adjusted chi-square was D-Dimer. After examining many possible alternatives it became clear that the only alternatives that resulted in almost complete partitioning out of PE patients had to include D-Dimer. Given that this was the strongest predictor in the univariate analysis it was reassuring that it should predominate. As can be seen in **Appendix** V, after D-Dimer 3 further splits were found that had significant chi-squares: Leg pain or swelling, any risk factor and recent surgical procedure. Further recursive partitioning allowed the author to identify several candidate prediction rules and assess the classification performance of these prediction rules (see **Table 19**).

Several three variable rules with 100% sensitivity were identified but most of these had low specificity. Further, given clinical experience the author felt that it was highly unlikely that any of these three variable rules would have high

sensitivity and high negative predictive value in validation studies. As the number of variables was increased (see four and six variable rules) the specificities dropped off dramatically. To increase specificity several two step combinations were examined (see **Table 19**).

Table 19. Clinical prediction rules developed by recursive partitioning and their classification performance.

Model	Sensitivity (95%CI)	Specificity (95%CI)	Negative Predictive Value	True Negative Proportion
Negative D-Dimer, no leg pain or swelling and no previous venous thromboembolic event	100% (92.7-100%)	31.3% (24.3-39.0%)	100% (93.0-100%)	24.1%
Negative D-Dimer, absence of any risk factor and no leg pain or swelling	100% (92.7-100%)	25.2% (18.7-32.6%)	100% (91.4-100%)	19.3%
Negative Ddimer, no leg pain or swelling and heart rate less than 110	98.0% (89.1-99.9%)	30.7% (23.7-38.4%)	98.1% (89.4-99.9%)	23.6%
Negative D-Dimer, no recent surgical procedure and age less than 55	100% (92.7-100%)	29.4% (22.6-37.1%)	100% (92.6-100%)	22.6%
Negative D-Dimer, no recent surgical procedure, no pain or swelling and no previous venous thromboembolic event	100% (92.7-100%)	28.8% (22.0-36.5%)	100% (92.5-100%)	22.1%
Negative D-Dimer, no leg pain or swelling, age less than 55, no previous venous thromboembolic event, no recent surgery and heart rate less than 110	100% (92.7-100%)	19.6% (13.8-26.6%)	100% (89.1-100%)	15.1%
Negative D-Dimer, no leg pain or swelling and age less than 55 or Negative D-Dimer, no leg pain or swelling, age greater than 55 and absence of any risk factor	100% (92.7-100%)	29.5% (22.6-37.1%)	100% (92.6-100%)	22.6%
Negative D-Dimer and no leg pain or swelling And 1. No previous venous thromboembolic event or 2. No recent Surgery or 3. Age less than 55	98.0% (89.1-99.9%)	33.7% (26.6-41.5%)	98.2% (90.3-99.9%)	25.9%
Negative D-Dimer and no leg pain or swelling And Three of four negative (previous venous thromboembolic event, recent surgery, age over 55 and heart rate over 110)	100% (92.7-100%)	29.5% (22.6-37.1%)	100% (92.6-100%)	22.6%

7.5.3 Final model selection

Given the multitude of potential clinical prediction rules to choose from, the author surveyed 20 clinicians to ascertain what thresholds for negative predictive value, number of variables in a model and excluded proportions were acceptable to clinicians (see **Appendix VI**). It appears that a five variable model, with an over 96% negative predictive value and excluded proportion near 40% would be acceptable to most clinicians (over 80%). This degree of acceptance provides some assurance that the final model chosen would be utilized.

Reviewing the candidate models (see **Tables 18 and 19** and **Figures 5 to 8**) I chose the 5 variable regression model with a one point cut off (summarized in **Figure 9**). Given that a one point cut off is used the relative weights are not meaningful in applying the rule. Further ignoring these relative weights makes applying the rule easier. I believe the 5 point regression model rule has the best combination of 1) likelihood to have high negative predictive value in validation, 2) high excluded proportion invalidation, 3) ease of use and 4) ease to commit to memory.

The absence of all the five following clinical variables excludes PE:
1. Positive D-Dimer
2. Heart rate over 110 beats per minute
3. Leg pain or leg swelling
4. Previous venous thromboembolic event
5. Recent surgery

Figure 9. The five point clinical prediction rule.

7.6 Discussion

The final model includes five variables which have consistently been shown to be predictive of PE in patients with suspected PE. D Dimer as a biologic by product of clot dissolution make sense as a clinical predictor. PE often results in tachycardia from chest pain and changes in hemodynamics (reduced venous return resulting in increased heart rate to maintain cardiac output). Ninety percent of PE originate from thrombi in deep leg veins. Proximal thrombus (popliteal vein or higher) often results in leg pain or tenderness from inflammation of the veins or increased tissue pressures from diminished venous return. Similarly leg swelling results from reduced venous return. The two consistently strongest clinical risk factors are previous venous thromboembolic events and recent surgery. These five variables are easy to remember and conventional wisdom and teaching are that they are independent predictors of PE. The final model had

excellent negative predictive value in the derivation set. Disappointingly, the excluded proportion was not very high (26.1%). However, given the great expense of admission and diagnostic tests to exclude suspected PE, excluding one quarter of patients with suspected PE at the bedside would result in enormous savings in resource utilization.

8.0 PHASE IV- VALIDATION OF THE CLINICAL PREDICTION RULE

8.1 Goals and Objectives

To validate the following clinical prediction rule: "The absence of all the five following clinical variables excludes PE: 1) a positive D-Dimer, 2) heart rate over 110 beats per minute, 3) leg pain or swelling (on history and physical exam), 4) previous venous thromboembolic event and 5) recent surgery" .

8.2 Patients and methods

The validation dataset is a pre-existing dataset taken from a previously published investigation of the management of patients with suspected pulmonary embolism (12). This study of over 1300 patients was conducted in 5 centers (Ottawa Civic, McMaster, London, Halifax, Victoria). The center in which the rule was derived (Ottawa General) did not participate in this study. Detailed methodology including inclusion and exclusion criteria can be obtained from the original publication (see **Appendix VII**).

8.3 Standardized Patient Assessment

8.3.1 Clinicians Standardized Patient Assessment

All patients were evaluated by a physician or a nurse practioner. A checklist of signs and symptoms was completed that included pulse rate, leg pain or swelling (leg pain = history of leg pain or tenderness on exam and leg swelling = history of or exam finding of leg swelling (including pitting edema), history of

previously documented PE or DVT and major surgery within the previous four weeks.

8.3.2 D-Dimer Measurement

Blood was taken and processed by a research assistant for quantitation of D-Dimer by the SimpliRED assay. Results were categorized as normal or abnormal on the basis of the absence (normal) or presence (abnormal) of erythrocyte agglutination. The results of the D-dimer assay were not disclosed to caregivers and were obtained independently of the pretest probability assessment and results of other diagnostic tests.

8.4 Outcome Measure

The management approach used in the patient population is summarized in the **Figure 10**. Ventilation-perfusion lung scanning was done in all patients within 24 hours of presentation using a technique described elsewhere (13). Scans were classified as normal (that is, the perfusion scan was normal), high probability (one or more segmental or larger perfusion defects with normal ventilation) or non-"diagnostic" (perfusion defects not meeting criteria for a high-probability scan) (11). All patients also had bilateral compression ultrasonography from the common femoral vein to the calf trifurcation within 24 hours of presentation. Lack of vein compressibility was considered diagnostic of deep vein thrombosis.

Patients with non- "diagnostic" lung scans, low or moderate pretest probability, and a normal initial compression ultrasonogram had repeated compression ultrasonography on days 3 to 5, 6 to 8, and 13 to 15. Anticoagulation was withheld provided that the results of compression ultrasonography remained normal. If the initial or serial ultrasonogram was abnormal, pulmonary embolism was diagnosed. Patients with non-"diagnostic" scans, high pre-test probability, and normal initial compression ultrasonograms underwent venography; if the results of this test were normal, pulmonary angiography was done.

If the perfusion lung scan was normal, compression ultrasonography was performed; if ultrasonography results were normal, no further testing was done and pulmonary embolism was considered excluded. If the results were abnormal, pulmonary embolism was diagnosed. Patients with a high-probability lung scan and a high or moderate pre-test probability were considered to have pulmonary embolism regardless of compression ultrasonography results. Patients with a high-probability scan, low pre-test probability, and normal initial compression ultrasonograms had venography; if venograms were normal, these patients also underwent pulmonary angiography. All patients who did not receive anticoagulants were followed-up for 3 months for the presence or absence of symptomatic venous thromboembolism by clinical evaluation. This consisted of a careful history to elicit symptoms of pulmonary embolism or deep venous thrombosis and appropriate investigation if such symptoms occurred.

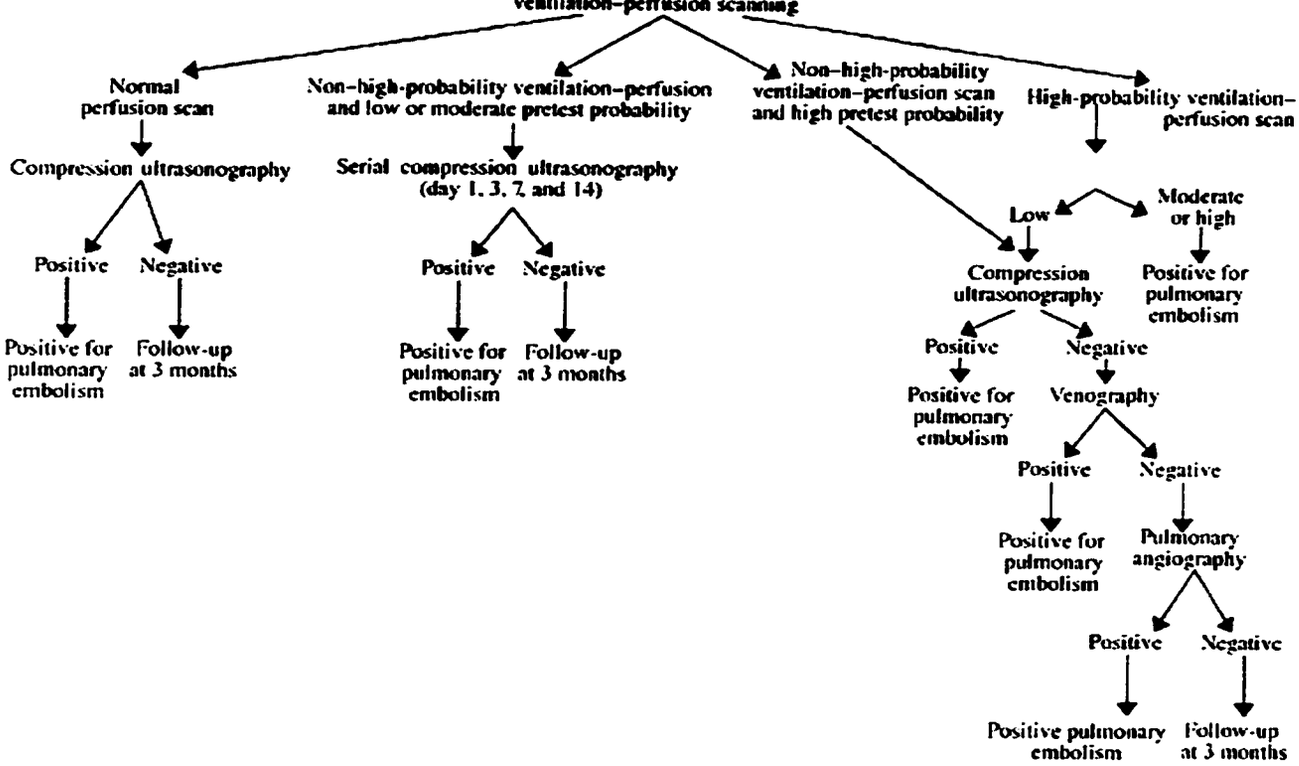


Figure 10. Diagnostic strategy used in patients with suspected pulmonary embolism. Reproduced from (12) with permission of the author.

Patients were classified as having PE if one or more of the following occurred: positive pulmonary angiogram; positive compression ultrasonogram (at any time) or positive contrast venogram; high-probability perfusion lung scan plus moderate or high pretest probability; or symptomatic, objectively confirmed venous thromboembolism during the 3-month follow-up. All other patients were classified as negative.

Patients considered positive for pulmonary embolism received full-dose intravenous heparin or subcutaneous low-molecular-weight heparin followed by at least 3 months of oral anticoagulation. Patients who were considered negative for pulmonary embolism did not receive anticoagulant therapy.

8.5 Data Analysis

8.5.1 Baseline Characteristics

Continuous variables were compared in the patients with PE and the patient without PE by an independent groups t-test. Likelihood ratio chi square tests were used to compare proportions between the two groups.

8.5.2 Classification performance of clinical prediction rule

Negative predictive value, sensitivity, specificity and their corresponding exact 95% CIs were calculated by using the binomial distribution. Excluded proportions were also calculated.

8.6 Results

8.6.1 Baseline Characteristics

The validation set was comparable in age and sex distribution to the derivation set (see **Table 20**). Patients with PE were significantly older than patients without PE. Patients with PE were more likely to be male than female. Similar to the derivation set almost all patients presented with chest pain or dyspnea.

Table 20. Baseline characteristics of validation set

	All patients (n=1239)	**PE patients (n=216)**	**No PE patients (n=1023)**
Mean Age in years (sd)	56.6 (18.6)	61.2 (16.2)	55.6 (18.9)*
Female % (95% CI)	62.0% (59.2-64.7%)	54.2% (47.2-60.9%)	63.6% (60.6- 66.4%)*
Outcome determined by....		• Positive angiogram n= 2 • High prob. V/Q with intermed/ high pretest n= 142 • Day 1 to Day 14 testing positive for DVT n= 67 • Follow-up event n= 5	• Normal V/Q and initial U/S and no follow up events n=330 • Non-high scan, normal Day1 to Day 14 U/S and no follow-up events n= 662 • Normal pulmonary angiogram n= 31
Chest pain or Dyspnea	97.3% (96.3-98.1%)	95.4% (91.6-97.8%)	94.2% (96.6-98.5%)

8.6.2 Classification performance of clinical prediction rule

The 5-point clinical prediction rule derived in Phase III, had a higher specificity in the validation set but a lower sensitivity and negative predictive value than the derivation set (see **Figure 11**). The rule had resulted in a higher excluded proportion in the validation set (35%), than in the derivation set (26%).

	PE	NO PE
PE Possible	206	618
PE Excluded	10	449

Sensitivity = 95.3% (91.7-97.8%)
Specificity = 42.1% (39.1-45.1%)
Negative predictive value = 97.8% (96.0-99.0%)
Excluded proportion= 35.0%

Figure 11. 2x2 table and classification performance of the five point clinical prediction model in the validation set.

9.0 DISCUSSION

In this study I have derived and validated a clinical prediction rule that excludes pulmonary embolism at the bedside with high negative predictive value in one third of patients with suspected PE.

The negative predictive value of the 5-point clinical prediction rule (97.8% (95% CI-96.0 to 99.0%) is comparable to that of a normal V/Q scan (98.8% (95% confidence interval-97.0 to 99.7%)) (12), is better than that of a near normal V/Q scan (96.1% (95% confidence interval-91.1 to 98.7%)) (11) and is clearly better than that of a low probability V/Q scan (86% (95% confidence interval-82 to 90%) (11)). Unfortunately, on a daily basis clinicians use low probability scans alone to exclude PE (18).

The diagnosis and exclusion of pulmonary embolism remains problematic. The diagnostic gold standard is pulmonary angiography. Pulmonary angiography is an invasive and expensive procedure, with limited availability and potentially serious complications. Ventilation-perfusion scans provide a definitive diagnosis in less than 40% of cases (11). These limitations result in many clinicians not pursuing definitive objective tests in patients with suspected pulmonary embolism (18,19). Given that 13.4% of our population, in the context of a study, were unclassified, provides further evidence that alternate diagnostic approaches, more acceptable to clinicians and patients, must be developed.

Developing a clinical prediction rule with 100% sensitivity in this disease is likely impossible. Clinicians reluctance, even in the setting of a clinical trial, to use the gold standard (pulmonary angiography) necessitates that investigators must use imperfect outcome measures. Hence, it is implausible that a prediction rule with true 100% sensitivity will be developed when the outcome measures are not 100% sensitive. Even if a group of investigators were able to convince clinicians to obtain pulmonary angiograms on all patients with suspected PE, as was done in the PIOPED study, it is likely that a highly selected study group would remain, as occurred in the PIOPED study (1493 patients consenting out of 3016 eligible patients) (11). This degree of selection almost certainly results in a biased study sample and would likely result in difficulty with generalizability of the derived prediction rule.

One approach to the limitation of ventilation-perfusion scanning resulting in many non diagnostic scans has been to develop clinical prediction rules for patients with non- "diagnostic" scans (58-60). This approach, however, does not limit the need for presumptive anticoagulation nor deal with the limited availability and expense of ventilation-perfusion scanning.

Three authors have developed bedside techniques that claim to safely exclude pulmonary embolism (12,14,56). It is unlikely that Kline's technique will be generalisable given that his method of alveolar deadspace analysis (an integral

part of his bedside method) had such poor reproducibility in my inter-observer reliability study. Perrier, utilized rapid ELISA D-Dimer's to exclude PE at the bedside (14). This excluded PE in 159 out of 444 study patients (i.e. excluded proportion of 35.8%) and none of these 159 patients had a recurrent venous thromboembolic event over three months (negative predictive value 100% (95% CI- 97.7 to 100%). However, this method of D-Dimer measurement will have to become more widely available and these findings will have to be validated prior to acceptance of this bedside technique to exclude PE. Wells has developed a clinical prediction tool that partitions patients with suspected PE into low, (3.4% had PE), intermediate (27.8% had PE) and high (78.4% had PE) pre-test probability (12). However, this tool has 28 predictor variables making it cumbersome to use. Further, many of the variables in this tool (eg. clinicians' impression) have poor reproducibility and hence it is likely that the tool itself will have poor reproducibility. In an effort to simplify the clinical model, Wells derived a simple 7 point model by logistic regression. However, the simple model uses clinicians' impression, which I have shown to be poorly reproducible, hence this model may not be generalisable. In keeping with this a Dutch group has recently retrospectively validated this tool and demonstrated disappointing results (62).

My study adhered to most of the methodological guidelines for clinical prediction rule development and validation. The strengths of my study design are that: 1) the outcome to be predicted (PE vs no PE) was clearly defined and

clinically important; 2) the assessment of the outcome was blinded; 3) the clinical findings used as predictive variables were clearly defined, standardized and their assessment was done without knowledge of the outcome; 4) the reproducibility of the clinical findings used as predictive variables was demonstrated; 5) The patients in the study were selected without bias and represented a wide spectrum of clinical and demographic characteristics ensuring generalizability of the study results. However, not all patient data sets were complete, including 34 patients who were unclassified. The result of incomplete data sets may be that the study population is not representative of the total population of patients suspected of pulmonary embolism. Reassurance that the unclassified and classified patients are comparable is given by the fact that these groups were not statistically significantly different in gender or age. However, other important differences between these groups may exist (e.g. proportion with comorbidities); 6) the statistical techniques used to derive the rule were identified and valid; 7) the accuracy of the prediction rule in classifying patients with the outcome (i.e. sensitivity) and without the outcome (i.e. specificity) was demonstrated; 8) validation in a second independent set of patients was conducted and confirmed a high negative predictive value and high excluded proportion; 9) the clinical prediction rule is sensible i.e. has a clear purpose, (to safely exclude PE at the bedside), is relevant, (less than 35% of patients suspected of PE have PE) demonstrates content validity (all our predictors make biological sense), is concise (5 variables) and is easy to use in the intended clinical application; and

10) The use of the rule provides a probability of disease and implies a course of action (no further testing).

Clinical prediction rules often do not perform as well in validation studies as in their derivation studies (67). This was the case in our study. This often results from differences in surveillance strategies and definitions of outcome between the original studies and the validation studies (67). Our derivation study only used "diagnostic" V/Q scan results, pulmonary angiograms or low probability scans combined with negative initial ultrasounds. The validation set used less definitive standard initial diagnostic methods (e.g. accepting that a confirmed DVT in a suspected PE patient is evidence for PE) but complemented these with rigorous three month follow-up. Given that the therapeutic question being answered by diagnostic testing for suspected PE is whether to anticoagulate for prevention of recurrent events, three month follow-up is considered an acceptable alternative to gold standard testing when investigating diagnostic tools for venous thromboembolic disease (20). Nonetheless, these differences in outcome measures may have resulted in the decreased sensitivity seen on validation of the prediction rule.

A significant limitation of this study is that this study was not adequately powered to enter all of the reproducible and predictive variables. It may be that using the six variables I excluded (female sex, systolic blood pressure, incomplete right bundle branch block, indeterminate axis, non sinus rhythm and alveolar dead

space measurement) would have yielded a better prediction rule. I am reassured by the fact that, with the exception of alveolar dead space, all the other variables have not been consistently shown to be predictors of PE in patients with suspected PE. It is plausible that alveolar dead space would have entered final model given its strong predictive value and reproducibility. This variable will be collected in future studies and may enter a refined model in the future.

Further work is required prior to widespread adoption of this clinical prediction rule. A prospective implementation study will be required to further validate the rule, demonstrate the inter-observer reliability of the rule itself and to determine the effects of clinical use of the rule.

The possibility that the clinical prediction rule does not perform as well in a prospective validation study is minimized by the fact that I utilized rigorous diagnostic techniques as outcome measures in the derivation set and that I developed the bedside techniques in consecutive inpatients, outpatients and emergency room patients suspected of pulmonary embolism
(ie. a wide spectrum of clinical patients). Further, collection of clinical data, on which the clinical prediction rule was based, was performed by referring physicians with varying degrees of expertise in the diagnosis of pulmonary embolism (including interns and residents). Hence the clinical prediction rule is pertinent to all clinicians and not limited to those with a high degree of expertise in the diagnosis of pulmonary embolism.

The excluded proportion gives us an indication of the proportion of patients that could be excluded without further testing and hence is proportional to both the clinical and economic impact a clinical prediction rule will have once validated and adopted into clinical practice. An excluded proportion of 35% in the validation study represents significant number of patients that could safely be excluded at the bedside without further testing if our clinical prediction rule is validated and adopted. Given the expense of the current diagnostic strategies for suspected PE adoption of this rule will likely result in significant cost savings to the health care system.

10.0 CONCLUSION

The clinical prediction rule presented in this study, " The absence of all of the five following clinical variables excludes PE:

1. a positive D-Dimer
2. heart rate over 110 beats per minute
3. leg pain or leg swelling
4. previous venous thromboembolic
5. recent surgery"

appears to be as safe in excluding pulmonary embolism, as currently available diagnostic tools applicable by clinicians with varying degrees of expertise and could easily be made widely available. The clinical prediction rule safely rules out PE in 1 out of three 3 patients suspected of pulmonary embolism.

REFERENCES

1. Anderson FA, Wheeler Brownwell H, Goldberg J, Hosmer DW, Patwardan NA, Jovanovic B, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. Arch.Intern.Med. 1991;151:933-8.

2. Silverstein M.D., Heit J, Mohr DN, Petterson TM, O'Falloon WM, Melton LJ. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Int Med 1998;158:585-93.

3. Nordstrom M, Lindblad B. Autopsy-verified venous thromboembolism within a defined urban population--the city of Malmo, Sweden. APMIS.1998.Mar. 106:378-84.

4. Dismuke SE and Wagner EH. Pulmonary embolism as a cause of death. The changing mortality in hospitalised patients. JAMA 1986;2552039-42.

5. Dalen JE, Alpert JS. Natural history of pulmonary embolism. Prog.Cardiovasc.Dis.1975.Jan.-Feb. 17:257-70.

6. Nordstrom M, Lindblad B. Autopsy-verified venous thromboembolism within a defined urban population--the city of Malmo, Sweden. APMIS.1998.Mar. 106:378-84.

7. Carson JL, Kelley MA, Duff A, Weg JG, Fulkerson WJ, Palevsky HI, Schwartz JS, et al. The clinical course of pulmonary embolism. N Engl J Med 1992;326(19):1240-5.

8. Alpert J.S., Smith R.et al. Mortality in patients treated for pulmonary embolism. JAMA 1976;236(13):1477-80.

9. Egermayer P, Town GI. The clinical significance of pulmonary embolism: uncertainties and implications for treatment--a debate [published erratum appears in J Intern Med 1997 Apr;241(4):341]. J Intern Med 1997 Jan 241:5-10.

10. Egermayer P, Town GI. The mortality of untreated pulmonary embolism in patients with intermediate probability lung scans. Chest 1998;114(5):1497-.

11. PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism.Results of the prospective investigation of

pulmonary embolism diagnosis study (PIOPED). JAMA 1990;263(20):2753-9.

12. Wells PS, Ginsberg JS, Anderson DR, Kearon C, Gent M, Turpie AG, Bormanis J, Weitz J, Chamberlain M, Bowie D, et al. Use of a clinical model for safe management of patients with suspected pulmonary embolism. Ann Intern Med 1998 Dec 15;129(12):997-1005 1998;

13. Hull RB, Hirsh J, et al. Pulmonary angiography, ventilation lung scanning, and venography for clinically suspected pulmonary embolism with abnormal perfusion lung scan. Ann.of Intern.Med. 1993;98(6):891-9.

14. Perrier A, Desmarais S, Miron MJ, de Moerloose P, Lepage R, Slosman D, Didier D, Unger PF, Patenaude JV, Bounameaux H. Non-invasive diagnosis of venous thromboembolism in outpatients. Lancet 1999.Jan.16. 1999;353:190-5.

15. Ginsberg JS. Management of venous thromboembolism. N Engl J Med 1996;335:1816-28.

16. Goldhaber SZ. Pulmonary embolism [see comments]. N Engl J Med 1998 Jul 9 339:93-104.

17. Hull RD, Raskob GE, Coates G, Panju AA. Clinical validity of a normal perfusion lung scan in patients with suspected pulmonary embolism [see comments]. Chest 1990.Jan 97:23-6.

18. Schluger N, Henschke C, King T, Russo R, Binkert B, Rackson M, Hayt D. Diagnosis of pulmonary embolism at a large teaching hospital. Journ.of Thoracic Imaging 1994;9:180-4.

19. van Beek EJR., Buller HR., Brandjes DP., Rutten GC., ten Cate JW. Diagnosis of Clinically Suspected Pulmonary Embolism: A Survey of Current Practice in a Teaching Hospital. Netherlands J of Med 1997;44(2):50-5.

20. Kearon C. Noninvasive diagnosis of deep venous thrombosis. McMaster Diagnostic Imaging Practice Guidelines Initiative. Ann Intern Med.1998 Apr 15 128:663-77.

21. Hull RD, Raskob GE., Coates G., Panju AA., Gill GG. A new noninvasive management strategy for patients with suspected acute pulmonary embolism. Arch Intern Med 1989;149:2439-55.

22. Rodger MA, Bredeson CN, Wells PS, Beck J, Kearns B, Huebsch LB. Cost-effectiveness of low molecular weight heparin versus

unfractionated heparin in the treatment of deep vein thrombosis. CMAJ 1998;Submitted

23. Simonneau G, Sors H, Charbonnier B, Page Y, Laaban JP, Azarian R, Laurent M, Hirsch JL, Ferrari E, Bosson JL, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. The THESEE Study Group. Tinzaparine ou Heparine Standard: Evaluations dans l'Embolie Pulmonaire. N Engl J Med 1997 Sep 4;337(10):663-9

24. Kauczor HU. Contrast-enhanced magnetic resonance angiography of the pulmonary vasculature - A review. Investigative Radiology 1998;33(9):606-17.

25. Beigelman C, Chartrand-Lefebvre C, Howarth N, Grenier P. Pitfalls in diagnosis of pulmonary embolism with helical CT angiography. American Journal Of Roentgenology 1998;171(3):579-85.

26. Burkill G, Bell J. Spiral CT and ventilation perfusion scintigraphy for the diagnosis of pulmonary embolism. Clinical Radiology 1998;53(10):784-.

27. Cross JL. Spiral CT and ventilation perfusion scintigraphy for the diagnosis of pulmonary embolism - reply. Clinical Radiology 1998;53(10):784-.

28. Bounameaux H, de Moerloose P, Perrier A, Reber G. Plasma measurement of DDimer as a diagnostic aid in suspected venous thromboembolism: An Overview. Thrombosis and Hemostasis 1994;71:1-6.

29. Laupacis A, Sekar N, Stiell IG. Clinical prediction rules. A review and suggested modifications of methodological standards. JAMA 1997;277:488-94.

30. Wasson JH, Sox HC, Neff RK, Goldman L. Clinical prediction rules. Application and methodological standards. New Engl J Med 1985;313:793-9.

31. Stiell IG, Greenberg GH, McKnight RD, Nair RC, McDowell I, Reardon M, Stewart JP, Maloney J. Decision rules for the use of radiography in acute ankle injuries. Refinement and prospective validation [see comments]. JAMA 1993 Mar 3;269(9):1127-32 1999;

32. Stein PD., Saltzman HA., Weg JG. Clinical Characteristics of Patients with Acute Pulmonary Embolism. Am J Cardiol 1991;68:1723-4.

33. Stein PD., Terrin ML., Hales CA., Palvesky HI., Saltzman HA., Thompson BT., Weg JG. Clinical, Laboratory, Roentgenographic and Electrocardiographic Findings in Patients with Acute Pulmonary Embolism and No Prexisting Cardiac or Pulmonary Disease. Chest 1991;100:598-607.

34. Susec O, Boudrow D, Kline JA. The clinical features of acute pulmonary embolism in ambulatory patients. Acad Emerg Med 1997;4(9):891-7.

35. Manganelli D, Palla A, Donnamaria V, Giuntini C. Clinical features of pulmonary embolism. Doubts and certainties. Chest 1995 Jan 107:25S-32S.

36. Anderson FA, Wheeler Brownwell H, Goldberg J, Hosmer DW, Patwardan NA, Jovanovic B, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. Arch.Intern.Med. 1991;151:933-8.

37. Anderson F.A., Wheeler H.B. Venous Thromboembolism. Risk factors and Prophylaxis. Clinics in Chest Med. 1995;16(2):235-51.

38. Hull RD, Raskob GE, Carter CJ, Coates G, Gill GJ, Sackett DL, Hirsh J, Thompson M. Pulmonary embolism in outpatients with pleuritic chest pain. Arch.Intern.Med 1988.Apr. 148:838-44.

39. Ferrari E, Imbert A, Chevalier T, Mihoubi A, Morand P, Baudouy M. The ECG in pulmonary embolism. Chest 1997;111(3):537-43.

40. Sreeram N., Cheriex EC., Smeets JLRM., Gorgels AP., Wellens HJ. Value of the 12 Lead Electrocardiogram at Hospital Admission in the Diagnosis of Pulmonary Embolism. Am J Cardiol 1994;73:298-303.

41. Stein PD, Dalen JE, McIntyre KM, Sasahara AA, Wenger NK, Willis PW. The electrocardiogram in acute pulmonary embolism. Prog.Cardiovasc.Dis.1975.Jan-Feb 17:247-57.

42. Nazeyrollas P, Metz D, Jolly D, Maillier B, Jennesseaux C, Maes D, Chabert JP, Chapoutot L, Elaerts J. Use of transthoracic Doppler echocardiography combined with clinical and electrocardiographic data to predict acute pulmonary embolism. Eur Heart J 1996 May 17:779-86.

43. Petruzzelli S, Palla A, Pieraccini F, Donnamaria V, Giuntini C. Routine electrocardiography in screening for pulmonary embolism. Respiration 1986. 50:233-43.

44. McFarlane MJ, Imperiale TF. Use of the alveolar-arterial oxygen gradient in the diagnosis of pulmonary embolism [see comments] [published erratum appears in Am J Med 1998 Nov;105(5):458]. Am J Med 1994 Jan 96:57-62.

45. Stein PD., Goldhaber SZ., Henry JW. Alveolar-Arterial Oxygen Gradient in the Assessment of Acute Pulmonary Embolism. Chest 1995;107(1):139-43.

46. Cvitanic O, Marino PL. Improved use of arterial blood gas analysis in suspected pulmonary embolism. Chest 1989;95:48-51.

47. McFarlane MJ, Imperiale TF. Use of the alveolar-arterial oxygen gradient in the diagnosis of pulmonary embolism. Am J Med 1994;96:57-62.

48. Stein PD, Goldhaber SZ, Henry JW, Miller M. Arterial blood gas analysis in the assessment of suspected acute pulmonary embolism. Chest 1996;109:78-81.

49. Greenspan RH, Ravin CE, Polansky SM, McLoud TC. Accuracy of the chest radiograph in diagnosis of pulmonary embolism. Invest.Radiol 1982.Nov-Dec 17:539-43.

50. Robin ED., Julian D., Travis D., Crump C. A physiologic approach to the diagnosis of acute pulmonary embolism. New Engl J Med 1959;260(12):586-91.

51. Hatle L., Rokseth R. The arterial to end-expiratory carbon dioxide tension gradient in acute pulmonary embolism and other cardiopulmonary diseases. Chest 1974;66(4):352-7.

52. Erikson L, Wollmer P, Olsson CG, Albrechtsson U, Larrusdottir H, Nilsson R, et al. Diagnosis of pulmonary embolism based on alveolar dead space analysis. Chest 1989;96:357-62.

53. Burki NK. The dead space to tidal volume ratio in the diagnosis of pulmonary embolism. Am Rev Respir Dis 1986;133:679-85.

54. Burton G.G. and Grosbois J.M. Effect of posture on arterial-alveolar carbon dioxide gradient and physiologic dead space measurements. Case report. 1965; 806-809.

55. Massumi R.A., Nutter DO. The arterial to end-expiratory carbon dioxide tension gradient in acute pulmonary embolism and other cardiopulmonary diseases. Chest 1974;66(4):352-7.

56. Kline JA, Meek S, Boudrow D, Warner D, Colucciello S. Use of the alveolar dead space fraction (Vd/Vt) and plasma D-dimers to exclude acute pulmonary embolism in ambulatory patients. Acad Emerg Med 1997 Sep;4(9):856-63 1997;

57. Wells PS, Ginsberg JS, Brill-Edwards P., Donovan D., Panju A., van Beek EJR, Patel A. Application of a novel and rapid whole blood assay for D-Dimer in patients with clinically suspected pulmonary embolism. Thrombosis and Hemostasis 1995;73(1):35-8.

58. Bowine CM, Kuijer PMM, McDonnell J, vanBeek EJR, Rutten FFH, Buller HR. The role of a decision rule in symptomatic pulmonary embolism patients with a non-high probability ventilation perfusion scan. Thromb Haemo 1997;78:794-8.

59. Celi A, Palla A, Petruzzelli S, Carrozzi L, Jacobson A, Cella G, et al. Prospective study of a standardized questionnaire to improve clinical estimate of pulmonary embolism. Chest 1989;95:332-7.

60. Hoellerich VL, Wigton RS. Diagnosing pulmonary embolism using clinical findings. Arch Inten Med 1986;146:1699-704.

61. Concato J. The risk of determining risk with multivariable models. Ann Intern Med.1993 Feb 1 118:201-10.

62. Sanson BJ, Lijmer JG, Prins MH, et al. Comparison of a clinical probability estimate with a clinical model in the diagnosis of pulmonary embolism. [Abstract] Thromb Haemost 1999;82 (Supplement):(1)406-.

63. Turkstra F, van Beek EJ, Buller HR. Observer and biological variation of a rapid whole blood D-dimer test. Thromb Haemost 1998 Jan 79:91-3.

64. Flack VF, Afifi AA, Lachenbruch PA, Schouten HJA. Sample size determinations for the two rater kappa statistic. Psychometrika 1988;53(3):321-5.

65. Stiell I.G., Greenberg G.H., McKnight RD., Nair CR., McDowell I., Reardon M., Stewart JP., Maloney J. Decision rules for the use of radiography in acute ankle injuries. JAMA 1993;269(9):1127-31.

66. Charlson M.E., Ales K.L.et al. Why predictive indexes perform less well in validation studies. Arch.Intern.Med. 1987;147:2155-61.

LIST OF APPENDICES

APPENDIX I

HÔPITAL GÉNÉRAL D'OTTAWA OTTAWA GENERAL HOSPITAL

PATIENT INFORMATION SHEET

Title: "A Study to Develop a Method to Diagnose and Exclude Pulmonary Embolism"

I understand that my physician suspects that I may have had a blood clot go to my lungs (pulmonary embolism). This event may cause shortness of breath, chest pain, coughing up blood or dizziness. I understand that I may be at risk for this event to occur again and that the recurrence of this event can be life threatening.

I understand that the only way doctors can currently prove or disprove that a blood clot has gone to my lungs is for me to undergo a Ventilation / Perfusion Scan (a Nuclear Medicine blood flow and breath test) and or a Pulmonary Angiogram (a radiology test where dye is injected into the main arteries to my lungs). These tests are part of standard care for this condition. Both tests are only available during weekdays and daytime hours. I understand that my doctor may have to admit me to hospital and treat me with blood thinners until I can have a Ventilation/ Perfusion scan and or a Pulmonary/ Angiogram. If I do have a blood clot in my lungs I realize that blood thinners are the treatment necessary and blood thinners are part of standard care. Blood thinners could prevent another blood clot traveling to my lungs and possibly save my life.

The research doctors are trying to show that a simple combination of bedside tests can exclude a blood clot in my lungs. If they are able to show this they may be able to prevent some future patients from having to undergo Ventilation/ Perfusion scans or Pulmonary Angiograms. Some future patients may also be able to avoid admission to hospital and treatment with blood thinners. I will derive no direct benefit from participating in the study however I may contribute to the development of better patient care.

I will have the usual standard initial evaluation of patients suspected of pulmonary embolism. In addition, as part of the study protocol a respiratory therapist will perform breath and blow tests that are not part of the standard initial evaluation. These breath and blow tests are minimally uncomfortable, done at my bedside, pose no risk to me and take about 20 minutes of my time. An additional blood test requiring a teaspoon of blood will be performed and where possible will be added to the routine blood tests. These additional tests will not delay my usual investigations or usual treatment. I also understand that I may be called at home in the next year to find out how I am doing. If I agree, I may see the study doctors in a follow up clinic at some point in the next year. Both the telephone and clinic follow up are for research purposes only.

I will then undergo the usual standard tests, which are part of routine care, to prove or disprove whether I have a blood clot in my lungs, that is, the Ventilation/ Perfusion scan and/ or the Pulmonary Angiogram. These confirmatory tests are part of standard medical care for this disease and are not experimental. The Ventilation/Perfusion scan is a radioactive dye injection and radioactive gas breath test (total radiation is less than a chest x ray). This poses virtually no risk. The Pulmonary angiogram is test where a radiologist places a small tube in my groin vein and passes this tube to my lung arteries and injects dye to see if a blood clot is present. The pulmonary angiogram has a risk of death of about 2 people in 1200 in patients like myself without life threatening heart or lung disease. The major complications of the Pulmonary angiogram test are heart rhythm disturbances, allergic reaction to the dye, kidney damage and lung artery rupture. A minor complication is bleeding at the site where the catheter is inserted. I again understand that these tests are not part of the study protocol but part of the standard care for this disease and that I will require them so that my doctor and I know whether or not I have a blood clot in my lungs and whether I am at risk for a possibly life threatening recurrence. If I have a blood clot in my lungs I will likely be treated with blood thinners to prevent a recurrence.

Dr Christopher Bredeson, Dr Marc Rodger or Dr Gwynne Jones or one of their associates, has explained this research project to me, and has offered to answer any questions that I have. I know that I can call Dr Christopher Bredeson at 737-8158, or Dr Marc Rodger at 782-7777, or Dr Gwynne Jones at 737-8978.

I understand that I am free to withdraw from this study at any time and that my withdrawal will not influence my subsequent care. I understand that complete confidentiality will be kept in terms of my medical and outpatient records and that my records will be put together with similar records from other patients at the Ottawa General Hospital. I will receive a copy of my consent form and this patient information sheet and may contact the above physicians if I have further questions about this study now or in the future.

APPENDIX II

C.T.R.U.
Division of Haematology

PHYSICIAN ASSESSMENT
PULMONARY EMBOLISM STUDY

Date : _____ Time: _____

HISTORY

		Yes	No	Don't Know
1-	Chest pain	☐	☐	☐
	Sudden onset	☐	☐	☐
	Pleuritic	☐	☐	☐
2-	Dyspnea	☐	☐	☐
	Sudden onset	☐	☐	☐
	Worsening or New	☐	☐	☐
3-	Hemoptysis	☐	☐	☐
4-	Active Lung Disease	☐	☐	☐
	COPD ☐			
	Asthma ☐			
	Other: _____			

Time since onset of symptoms: _____

DVT RISK FACTORS Yes ☐ No ☐

		yes	no	Don't know
1-	Previous documented DVT/PE	☐	☐	☐
2-	Recent major surgical procedure (<1 mo.)	☐	☐	☐
3-	Active malignancy (< 6 mo.) or palliative	☐	☐	☐
4-	Pregnancy/Postpartum < 3 mo.	☐	☐	☐
5-	Activated protein C,S,APCR,AT III anti-phospholipid antibody	☐	☐	☐
6-	Immobilization > 72 hr. within previous 4 weeks	☐	☐	☐
7-	Major trauma < 1 mo. specify: _____	☐	☐	☐
8-	Paralysis, Paresis or Plaster cast immobilization < 4 weeks	☐	☐	☐
9-	Family history of thrombosis (documented in 1st degree relatives)	☐	☐	☐
10-	Congestive heart failure	☐	☐	☐

PHYSICAL EXAMINATION

Heart Rate : _____
Respiratory Rate: _____
JVP: _____
Temperature: _____
Blood Pressure: _____

	yes	no
Leg swelling > 3 cm calf, > 2 cm thigh	☐	☐
Leg tenderness along deep veins	☐	☐

	Yes	No	Don't Know
Loud P2 (S2 > S1 @ apex of heart)	☐	☐	☐
S4	☐	☐	☐
Crackles	☐	☐	☐
Pleural Rub	☐	☐	☐

EKG CHANGES

		yes	no
1-	Presence of ST changes (> 1 mm increased/decreased compared to TP interval)	☐	☐
2-	Presence of T wave changes (Any flat or inverted except AVR)	☐	☐

CHEST X-RAY FINDINGS

Normal ☐
Abnormal ☐ (any parenchymal abnormality) Specify: _____
Don't know ☐

Is ANOTHER diagnosis more likely than PE yes ☐ no ☐

If so, specify: _____

Your Index of Clinical Suspicion of Pulmonary Embolism: **(Percentage chance that the diagnosis is PE)**

(Can't be PE) 0% 10 20 30 40 50 60 70 80 90 100% (Is definitely PE)

APPENDIX III

RESPIRATORY THERAPIST ASSESSMENT SHEET
ULMONARY EMBOLISM STUDY QUESTIONNAIRE

PATIENT NAME: _____

BAROMETRIC PRESSURE: _____ mmHg

FI02 _____

ABG RESULTS: **(INFORMATION TO BE DISCLOSED TO REFERRING PHYSICIAN)**

pH _____ PaC02 _____ Pa02 _____

HC03 _____ Sa02 - calc _____

-meas (co-ox) _____

EDSIDE FLOW RATE:

FVC: _____ FEV1: _____

(BEST OF 3) or AS INDICATED BY RT

INFORMATION FOR STUDY PURPOSES ONLY:

3 MINUTE TIMED EXPIRED GAS COLLECTION RESULTS:

EXPIRED GAS VOLUME _____ L MINUTE VENTILATION: _____

		TEST 1	TEST 2
MIXED EXPIRED C02 (PeC02)	A) CAPNOGRAPHE MEASUREMENT	_____ mmHg	_____ mmHg
	B) ICU ABG MACHINE MEASUREMENT	_____ mmHg	_____ mmHg

MIXED EXPIRED 02 (Pe02) _____ mmHg

PETC02 (End tidal C02 from Capnograph) _____

PvC02 _____ RESPIRATORY RATE: _____

RESPIRATORY THERAPIST: _____

DATE _____

PLEASE APPEND CAPNOGRAPH PRINTOUT AND GIVE TO HELENE
This sheet does not remain with the patient chart - please mail to Room 7232

APPENDIX IV

.nbosis Assessment and Treatment Unit
L'unité d'évaluation et traitement de thrombose

Clinical Trials and Research Unit / L'unité d'essais cliniques et de recherches
Division of Hematology / Division d'Hématologie
The Ottawa Hospital, General Site / L'Hôpital d'Ottawa, Site Général

BIOPED Study

(Bedside Investigation of Pulmonary Embolism Diagnosis)

✧ RETEST ✧

✧ Patient Assessment Sheet ✧

Randomization No.:

To be filled in by Study Personnel

✧ **RETEST** ✧
Patient Assessment Sheet

Total Score

HISTORY

	Yes/True	No	Not Sure
yspnea	O	O	O
ny Chest Pain	O	O	O
udden Chest Pain	O	O	O
leuritic Chest Pain	O	O	O
emoptysis	O	O	O
igns & Symptoms of DVT:			
Swelling of legs	O	O	O
Pain along the distribution of deep veins (if you're not sure, call us)	O	O	O
VT Risk Factors:			
Immobilization (> 72 hrs continuously bedridden in the last month)	O	O	O
Surgery (major surgery in the last month)	O	O	O
Major Trauma (in the last month)	O	O	O
Malignancy (on treatment; treated in the last six months or palliative)	O	O	O

PHYSICAL EXAM

Heart Rate:	_____ beats per minute		○ Not Sure
Respiratory:	_____ breaths per minute		○ Not Sure
Diastolic blood pressure:	_____ mmHg		○ Not Sure
Temperature:	○ < 38.0 °	○ ≥ 38.0 °	○ Not Sure
Loud P_2 (S_2 louder at apex than S_1)	○ Yes	○ No	○ Not Sure
S_4	○ Yes	○ No	○ Not Sure

YOUR IMPRESSION

- *I think that the likelihood that this patient has a PE is:*

  ○ 0 - 20% ○ 21 - 80% ○ 81 - 100%

- *How likely is an **alternate diagnosis**?*

  ○ An alternate diagnosis is more likely than PE.

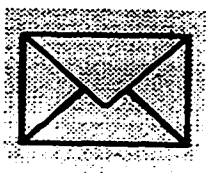
  ○ PE is more likely than any other diagnosis.

  ○ PE and alternate diagnosis are equally likely.

.Please specify the most likely alternate diagnosis:

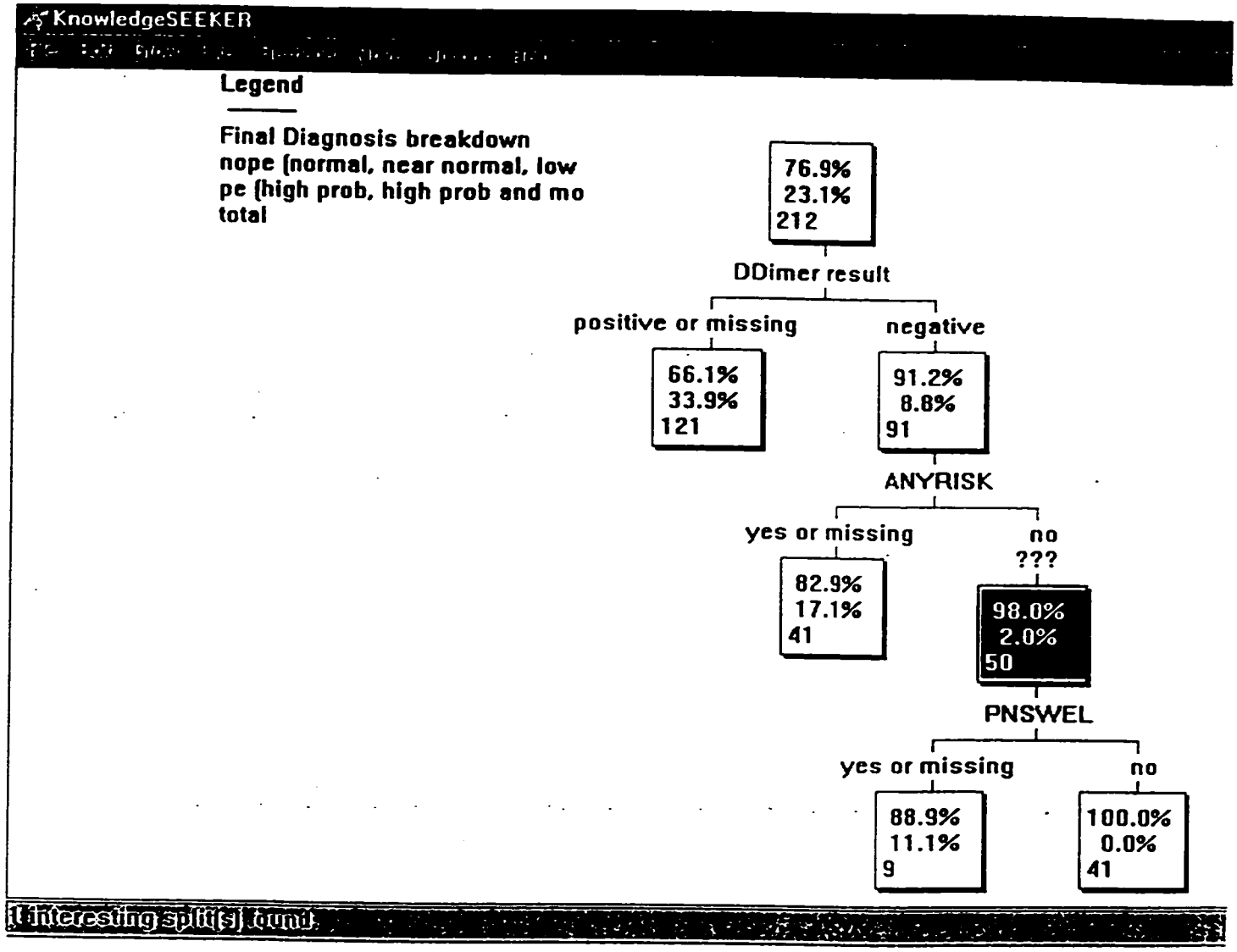
Physician: _____

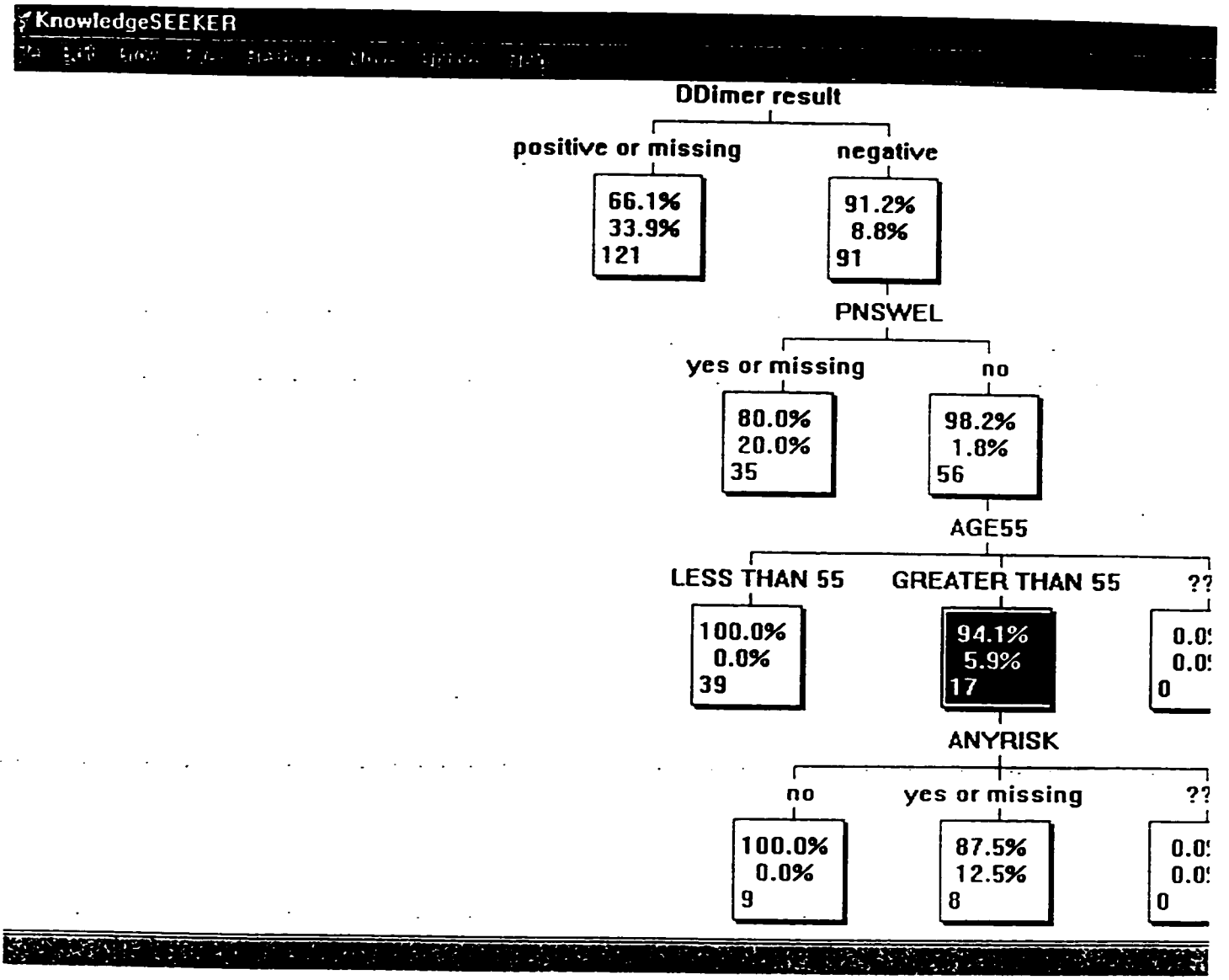
Date: _____ Time: _____



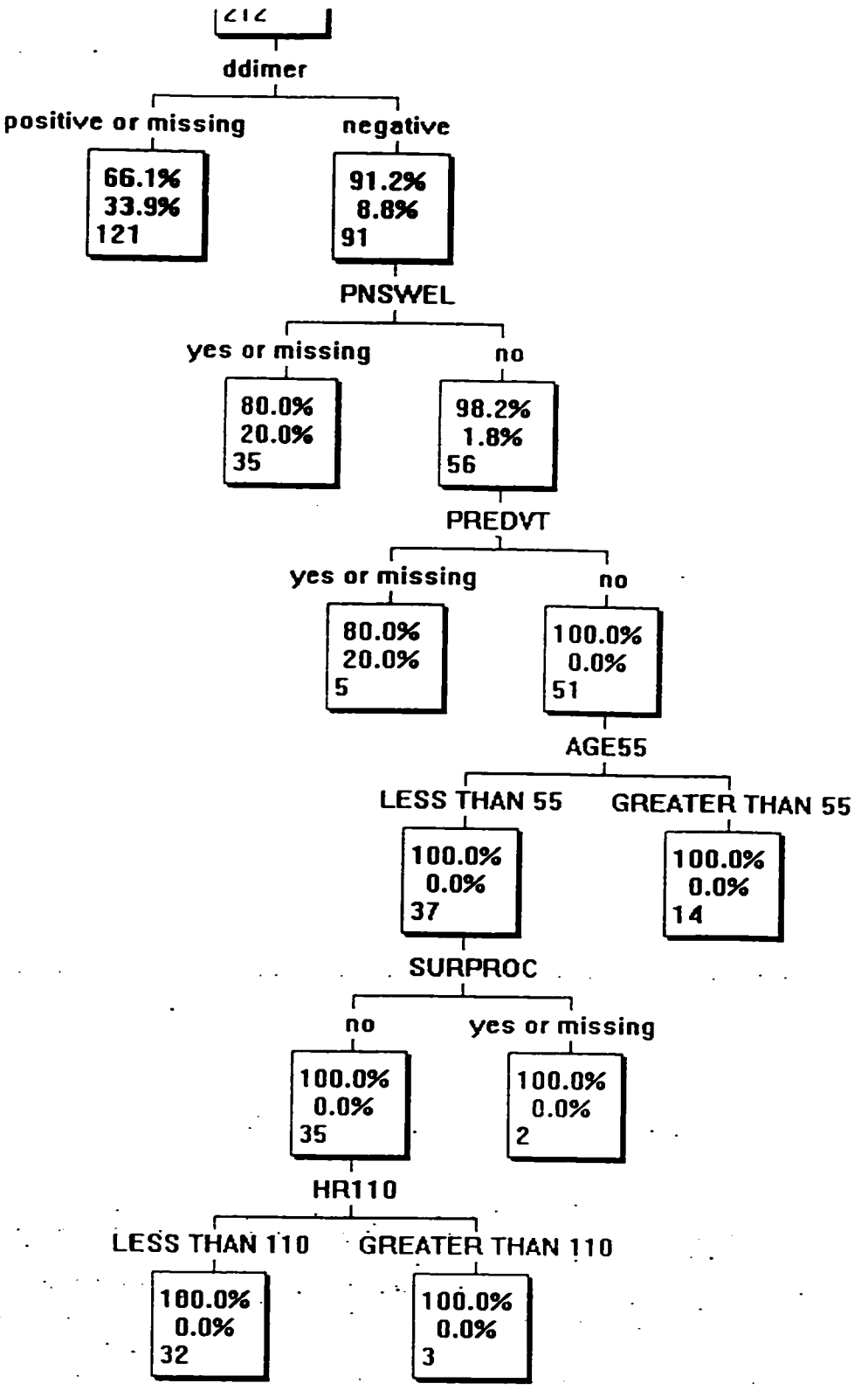
Please give this sheet to Julie Beck
Thanks very much!

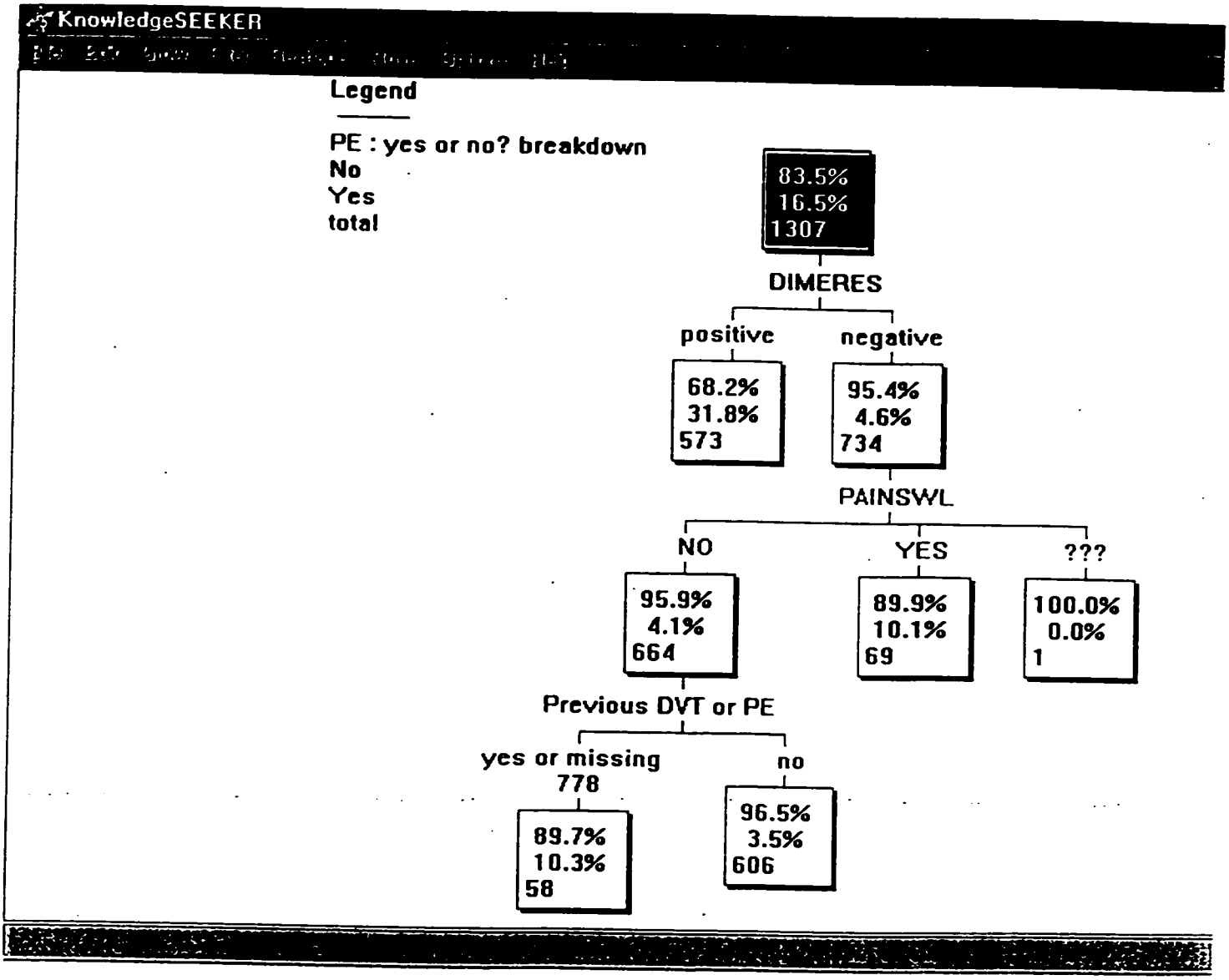
APPENDIX V


KnowledgeSEEKER
Legend
Final Diagnosis breakdown
nope (normal, near normal, low
pe (high prob, high prob and mo
total
76.9%
23.1%
212
DDimer result
positive or missing
negative
66.1%
33.9%
121
91.2%
8.8%
91
ANYRISK
yes or missing
no
???
82.9%
17.1%
41
98.0%
2.0%
50
PNSWEL
yes or missing
no
88.9%
11.1%
9
100.0%
0.0%
41
1 interesting split(s) found


KnowledgeSEEKER
DDimer result
positive or missing
negative
66.1%
33.9%
121
91.2%
8.8%
91
PNSWEL
yes or missing
no
80.0%
20.0%
35
98.2%
1.8%
56
AGE55
LESS THAN 55
GREATER THAN 55
??
100.0%
0.0%
39
94.1%
5.9%
17
0.0
0.0
0
ANYRISK
no
yes or missing
??
100.0%
0.0%
9
87.5%
12.5%
8
0.0
0.0
0

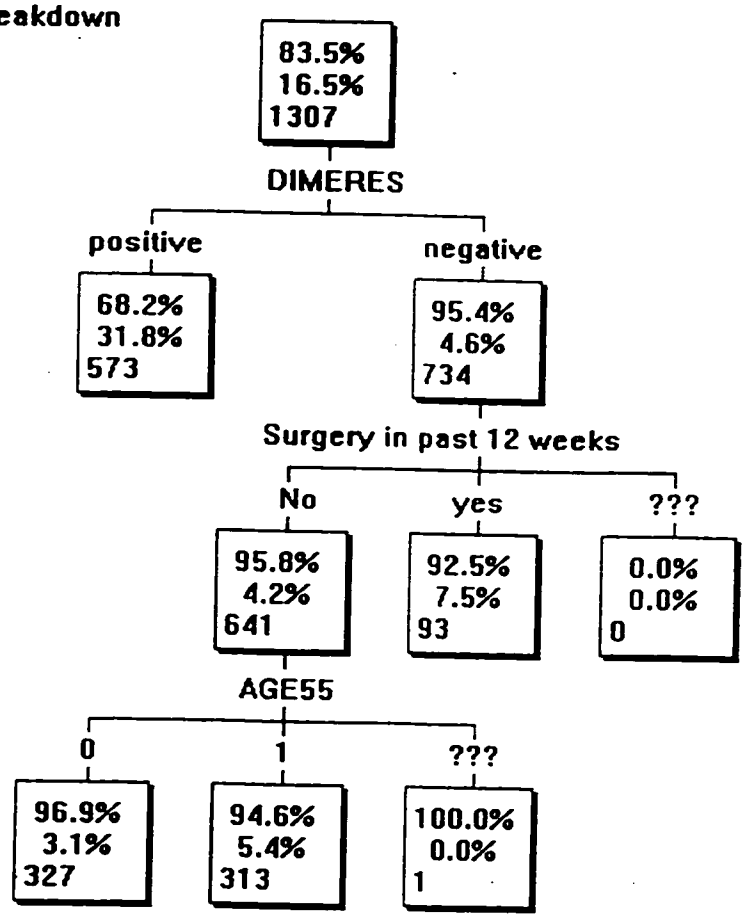
total


212
ddimer
positive or missing
negative
66.1%
33.9%
121
91.2%
8.8%
91
PNSWEL
yes or missing
no
80.0%
20.0%
35
98.2%
1.8%
56
PREDVT
yes or missing
no
80.0%
20.0%
5
100.0%
0.0%
51
AGE55
LESS THAN 55
GREATER THAN 55
100.0%
0.0%
37
100.0%
0.0%
14
SURPROC
no
yes or missing
100.0%
0.0%
35
100.0%
0.0%
2
HR110
LESS THAN 110
GREATER THAN 110
100.0%
0.0%
32
100.0%
0.0%
3


KnowledgeSEEKER
Legend
PE : yes or no? breakdown
No
Yes
total
83.5%
16.5%
1307
DIMERES
positive
negative
68.2%
31.8%
573
95.4%
4.6%
734
PAINSWL
NO
YES
???
95.9%
4.1%
664
89.9%
10.1%
69
100.0%
0.0%
1
Previous DVT or PE
yes or missing
778
no
89.7%
10.3%
58
96.5%
3.5%
606

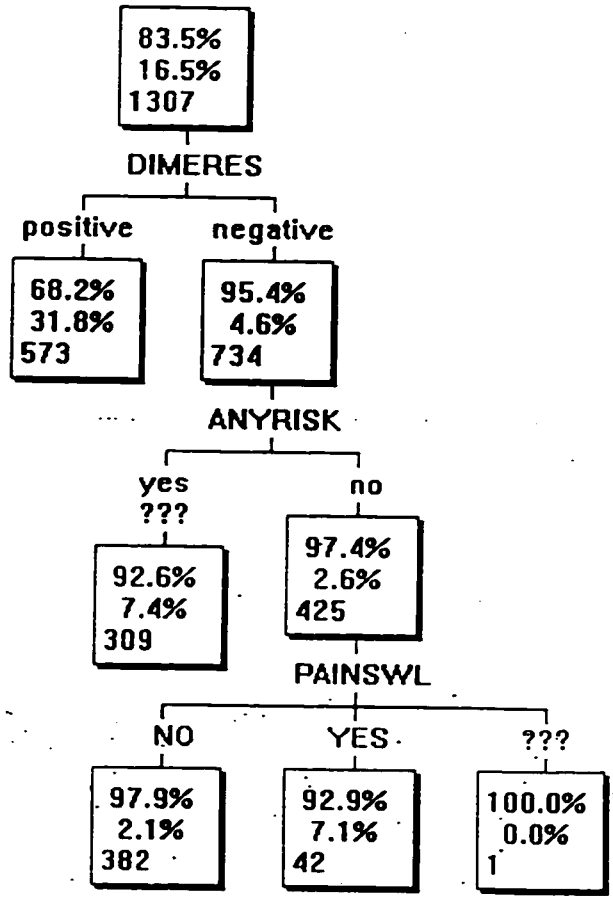
Legend

PE : yes or no? breakdown
No
Yes
total



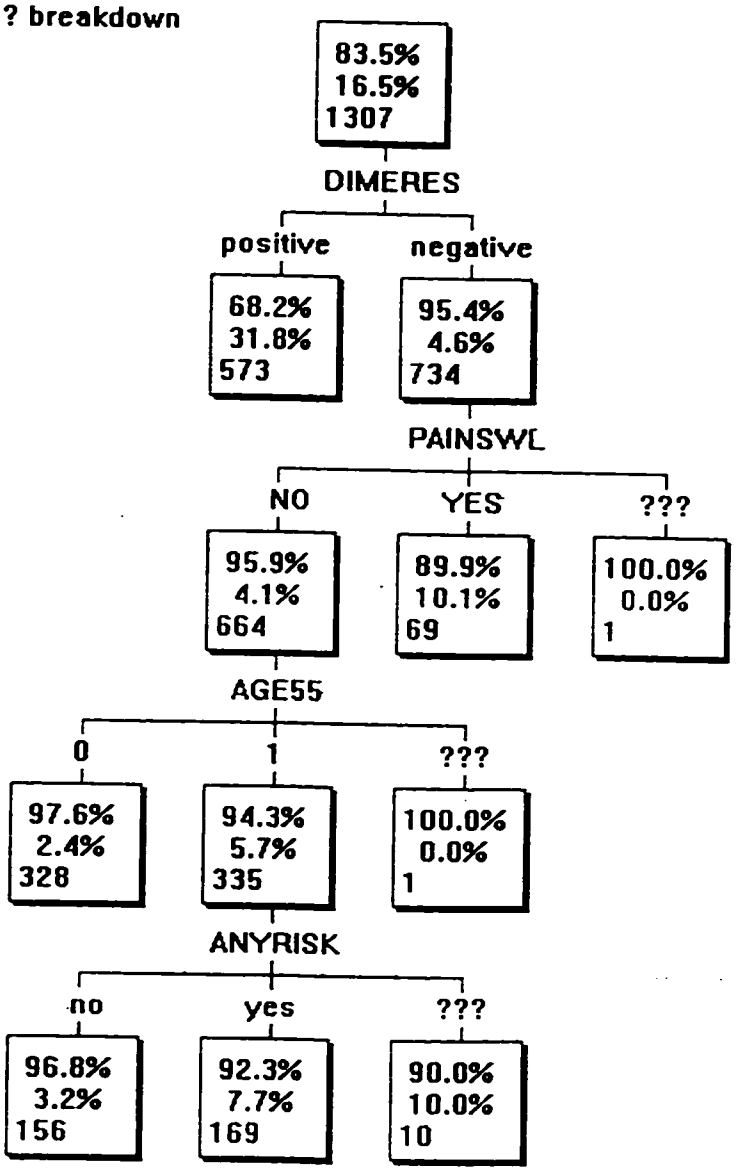
Legend

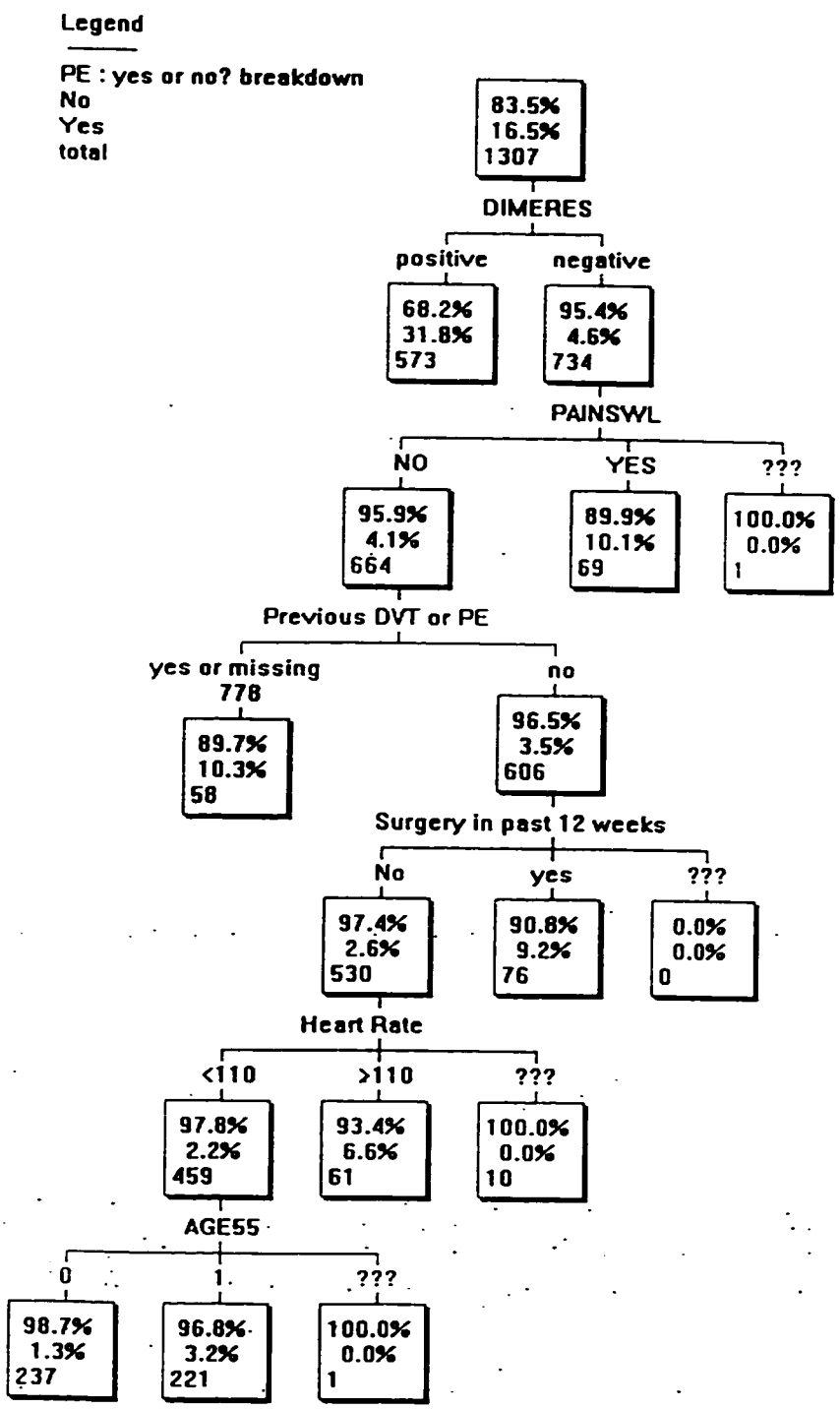
PE : yes or no? breakdown
No
Yes
total



Legend

PE : yes or no? breakdown
No
Yes
total




Legend
PE : yes or no? breakdown
No
Yes
total
83.5%
16.5%
1307
DIMERES
positive
negative
68.2%
31.8%
573
95.4%
4.6%
734
PAINSWL
NO
YES
???
95.9%
4.1%
664
89.9%
10.1%
69
100.0%
0.0%
1
Previous DVT or PE
yes or missing
778
no
89.7%
10.3%
58
96.5%
3.5%
606
Surgery in past 12 weeks
No
yes
???
97.4%
2.6%
530
90.8%
9.2%
76
0.0%
0.0%
0
Heart Rate
<110
>110
???
97.8%
2.2%
459
93.4%
6.6%
61
100.0%
0.0%
10
AGE55
0
1
???
98.7%
1.3%
237
96.8%
3.2%
221
100.0%
0.0%
1

APPENDIX VI

Given a patient with suspected PE and considering that:

1. A **normal V/Q scan** has a negative predictive value of 99% (i.e.1% of patients with a **normal V/Q** have PE) but that you only get a **normal V/Q scan** 10-20% of the time.

2. A **normal/near normal V/Q** has a negative predictive value of 96% (i.e. 4% of patients with a **normal/near normal scan** have PE) but that you only get a **normal /near normal** scan 15-20% of the time.

3. A **low probability scan** has a negative predictive value of 86% (i.e. 4% of patients with a **low probability scan** will have PE) and you get a **low probability scan** result 30-40% of the time.

Would you confidentiy and enthusiastically use....

1. A prediction rule with six variables with a negative predictive value of 98% (2% of patients with negative rule have PE) but you only get a negative result 15-20% of the time.

   Definitely Yes Maybe No

2. A prediction rule with five variables with a negative predictive value of 96% (4% with a negative rule have PE) and you get a negative result 40% of the time.

   Definitely Yes Maybe No

3. A prediction rule with three variables with a negative predictive value at 90% (10% of patients with a negative rule will have PE) and you get a negative result 50-60% of the time.

   Definitely Yes Maybe No

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Annals of Internal Medicine

Use of a Clinical Model for Safe Management of Patients with Suspected Pulmonary Embolism

Philip S. Wells, MD, MSc; Jeffrey S. Ginsberg, MD; David R. Anderson, MD; Clive Kearon, MD, PhD; Michael Gent, MSc; Alexander G. Turpie, MD; Janis Bormanis, MD; Jeffrey Weitz, MD; Michael Chamberlain, MD; Dennis Bowie, MD; David Barnes, MD; and Jack Hirsh, MD

Background: The low specificity of ventilation–perfusion lung scanning complicates the management of patients with suspected pulmonary embolism.

Objective: To determine the safety of a clinical model for patients with suspected pulmonary embolism.

Design: Prospective cohort study.

Setting: Five tertiary care hospitals.

Patients: 1239 inpatients and outpatients with suspected pulmonary embolism.

Interventions: A clinical model categorized pretest probability of pulmonary embolism as low, moderate, or high, and ventilation–perfusion scanning and bilateral deep venous ultrasonography were done. Testing by serial ultrasonography, venography, or angiography depended on pretest probability and lung scans.

Measurements: Patients were considered positive for pulmonary embolism if they had an abnormal pulmonary angiogram, abnormal ultrasonogram or venogram, high-probability ventilation–perfusion scan plus moderate or high pretest probability, or venous thromboembolic event during the 3-month follow-up. All other patients were considered negative for pulmonary embolism. Rates of pulmonary embolism during follow-up in patients who had a normal lung scan and those with a non–high-probability scan and normal serial ultrasonogram were compared.

Results: Pretest probability was low in 734 patients (3.4% with pulmonary embolism), moderate in 403 (27.8% with pulmonary embolism), and high in 102 (78.4% with pulmonary embolism). Three of the 665 patients (0.5% [95% CI, 0.1% to 1.3%]) with low or moderate pretest probability and a non–high-probability scan who were considered negative for pulmonary embolism had pulmonary embolism or deep venous thrombosis during 90-day follow-up; this rate did not differ from that in patients with a normal scan (0.6% [CI, 0.1% to 1.8%]; $P > 0.2$).

Conclusion: Management of patients with suspected pulmonary embolism on the basis of pretest probability and results of ventilation–perfusion scanning is safe.

This paper is also available at http://www.acponline.org.

Ann Intern Med. 1998;129:997-1005.

Because the signs and symptoms of pulmonary embolism are nonspecific, objective diagnostic tests are warranted when this event is suspected (1, 2). Many algorithms have been suggested for the diagnosis of pulmonary embolism, but there is no standardized approach. Pulmonary angiography is the gold standard diagnostic test, but this technique is invasive, expensive, not readily available, and labor intensive. Moreover, its results can be difficult to interpret. In addition, 1.6% of patients with a normal pulmonary angiogram develop pulmonary embolism during 1-year follow-up, usually in the first month (3, 4). Consequently, noninvasive ventilation–perfusion lung scanning is usually performed first in patients with suspected pulmonary embolism. A normal scan essentially rules out the diagnosis of pulmonary embolism (5), and a high-probability scan has a high positive predictive value (except in patients with a low pretest probability) (6, 7). However, more than 50% of patients with suspected pulmonary embolism have so-called non–high-probability ventilation–perfusion scans; angiography would demonstrate pulmonary embolism in less than 25% of these patients. Given the limitations of angiography and the fact that most pulmonary emboli originate from thrombi in the deep veins of the leg (7), investigation for deep venous thrombosis by using ultrasonography is an alternative. It is relatively safe to withhold anticoagulation in patients with suspected pulmonary embolism who have no evidence of deep venous thrombosis on serial impedance plethysmography (8); however, impedance plethysmography is not widely used, and we recently demonstrated that it is significantly less sensitive

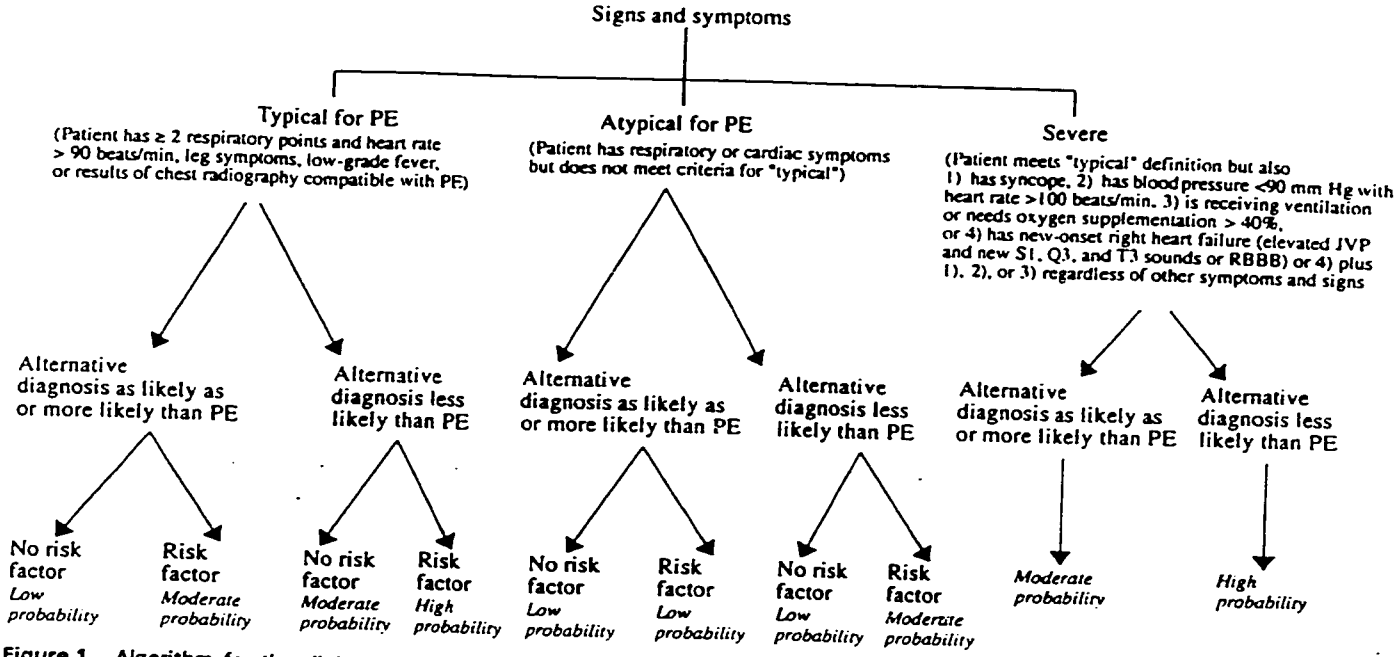

Figure 1. Algorithm for the clinical model to determine the pretest probability of pulmonary embolism (*PE*). Respiratory points consist of dyspnea or worsening of chronic dyspnea, pleuritic chest pain, chest pain that is nonretrosternal and nonpleuritic, an arterial oxygen saturation less than 92% while breathing room air that corrects with oxygen supplementation less than 40%, hemoptysis, and pleural rub. Risk factors are surgery within 12 weeks, immobilization (complete bedrest) for 3 or more days in the 4 weeks before presentation, previous deep venous thrombosis or objectively diagnosed pulmonary embolism, fracture of a lower extremity and immobilization of the fracture within 12 weeks, strong family history of deep venous thrombosis or pulmonary embolism (two or more family members with objectively proven events or a first-degree relative with hereditary thrombophilia), cancer (treatment ongoing, within the past 6 months, or in the palliative stages), the postpartum period, and lower-extremity paralysis. JVP = jugular venous pressure; RBBB = right bundle-branch block.

than ultrasonography (9, 10). Two studies (6, 11) have demonstrated that clinical assessment of the pretest probability of pulmonary embolism may be a useful adjunct to lung scanning, but neither study used explicit criteria.

The optimal strategy for investigating patients with suspected pulmonary embolism should combine clinical assessment, ventilation–perfusion scanning, and venous ultrasonography of the lower extremities. We reasoned that patients with non–high-probability ventilation–perfusion scans and a low or moderate pretest clinical probability of pulmonary embolism (as determined by a clinical prediction rule) could be safely managed with serial ultrasonography. Further testing would be required in patients with a high clinical probability and a non–high-probability scan and in patients with a low clinical probability and a high-probability scan.

Methods

Development of the Clinical Model

Our group (consisting of physicians trained in respiratory medicine, hematology, thrombotic diseases, epidemiology, and radiology) previously developed a useful clinical model for patients with suspected deep venous thrombosis by reviewing the literature and coming to a consensus on a scoring system. The system combined well-established risk factors for venous thrombosis, clinical signs and symptoms, and determination of whether an alternative diagnosis was likely (12). We applied the same strategy in patients with suspected pulmonary embolism. We used criteria from the published literature (13, 14) to establish a pilot model by consensus. This preliminary model was tested in a pilot study of 91 patients with suspected pulmonary embolism and was subsequently refined. The final clinical model is shown in **Figure 1.**

First, a history was taken and a physical examination was performed; the latter included chest radiography, oxygen saturation tests, and electrocardiography (if indicated). A checklist of signs and symptoms was completed to determine whether the patient met our definition of a severe, typical, or atypical clinical presentation. The presence of an alternative diagnosis that was as likely as or more likely than pulmonary embolism to account for the patient's signs and symptoms was determined. This determination was based on signs and symptoms and results of routine tests (blood gas, chest X radiography, or electrocardiography). We defined an alternative diagnosis as any other illness that could fit the patient's symptom complex if it was supported by the history or by physical, laboratory, and radiologic findings. The alternative diagnosis did not have to be related to previous disorders. F

ple, it was possible to enroll a patient with an alternative diagnosis of pneumonia if the physician still thought that pulmonary embolism could not be ruled out. Finally, established risk factors for venous thromboembolism were totalled. Patients could then be classified as having a low, moderate, or high probability of pulmonary embolism.

Management Study

Patient Sample

Five Canadian centers (McMaster University Medical Centre and the Hamilton Civics Hospitals, Hamilton; Ottawa Civic Hospital, Ottawa; and Queen Elizabeth II Health Sciences Centre, Halifax) participated in the study from September 1993 to May 1996. Consecutive inpatients and outpatients with suspected pulmonary embolism whose symptoms had lasted less than 30 days were potentially eligible. Exclusion criteria were 1) suspected upper-extremity deep venous thrombosis as the source of the pulmonary embolism, 2) no symptoms of pulmonary embolism for more than 3 days before presentation, 3) use of anticoagulation for more than 72 hours, 4) expected survival of less than 3 months (a criterion introduced halfway through the study because the death rate, albeit not due to pulmonary embolism, was higher than expected), 5) contraindication to contrast media, 6) pregnancy, 7) geographic inaccessibility precluding follow-up, 8) age younger than 18 years, and 9) inability to obtain permission from the patient or the patient's attending physician.

Investigations on the Day of Presentation

After informed consent was obtained, all patients were evaluated by a physician to determine the pretest clinical probability of pulmonary embolism by using the clinical model. Ventilation–perfusion scanning was performed, and the results were interpreted by the hospitals' nuclear medicine physicians. These physicians had no knowledge of other results or the patients' signs, symptoms, or risk factors. Their scan interpretations were used to manage patients. Ventilation–perfusion scans were interpreted as 1) normal (no perfusion defects), 2) high probability (≥1 segmental or greater perfusion defects with normal ventilation or ≥2 large subsegmental perfusion defects [>75% of a segment]) with normal ventilation, or 3) non–high probability (ventilation–perfusion defects that did not qualify as high probability or normal) (7). A lung segment reference chart was used to interpret the scans (15). In a random sample of 570 patients, the scans were interpreted by using the revised Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) criteria (16) and were compared with the

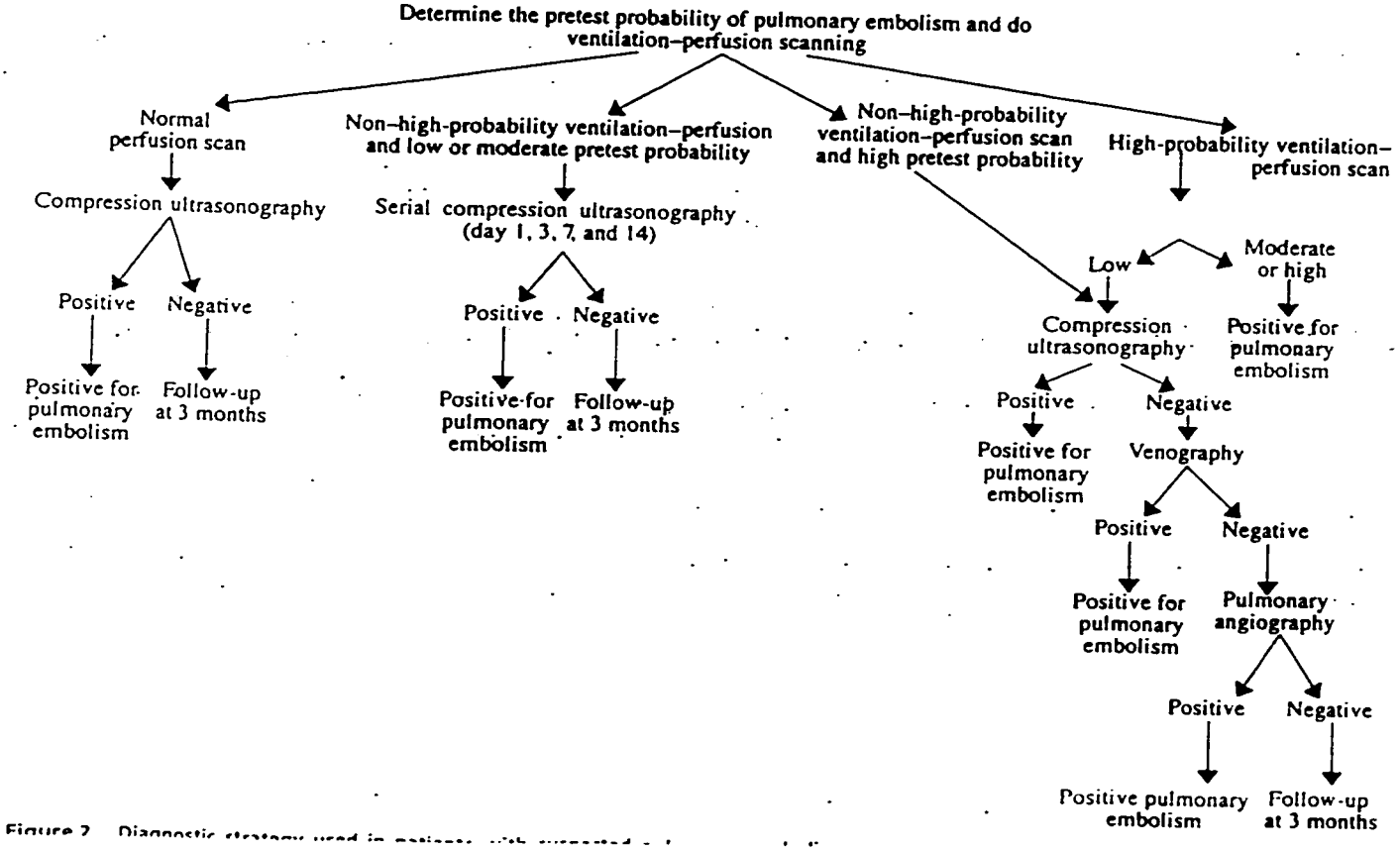

Figure 2. Diagnostic strategy used in patients with suspected

results derived by using the criteria described above. After ventilation–perfusion scanning was completed, bilateral compression ultrasonography from the common femoral vein to the trifurcation of the calf veins (but not below) was performed. Lack of vein compressibility was considered diagnostic of deep venous thrombosis.

Subsequent Management Strategy

Patient management was based on the results of clinical pretest probability, ventilation–perfusion scanning, and ultrasonography (**Figure 2**). In our management strategy, patients underwent contrast venography and pulmonary angiography if the clinical pretest probability and ventilation–perfusion scan were discordant (high clinical probability with a non–high-probability ventilation–perfusion scan or low clinical probability with a high-probability ventilation–perfusion scan). Contrast venography was performed as described elsewhere (17). If the venogram was normal, patients received intravenous heparin and pulmonary angiography was performed within 24 hours. Pulmonary angiography was performed by using standard techniques (11). Pulmonary embolism was diagnosed if there was a constant intraluminal filling defect or an abrupt cut-off in vessels larger than 2.5 mm in diameter. Low- and moderate-probability patients with non–high-probability ventilation–perfusion scans are statistically the most likely group to have false-positive results on ultrasonography. Therefore, we attempted to perform confirmatory venography in these patients. If the venogram was inadequate or could not be obtained, the final diagnosis was made on the basis of the result of ultrasonography or angiography was performed.

Patients were classified as positive for pulmonary embolism if one or more of the following occurred: an abnormal result on pulmonary angiography, ultrasonography, or venography; a high-probability ventilation–perfusion scan plus moderate or high pretest probability; or a venous thromboembolic event within the 3-month follow-up period. All other patients were classified as negative for pulmonary embolism.

Treatment and Follow-up

Anticoagulant therapy was withheld in patients who were negative for pulmonary embolism. Patients were followed for 3 months and were instructed to return at once if they developed symptoms or signs suggestive of pulmonary embolism or deep venous thrombosis. If at any time venous thromboembolism was suspected, patients were investigated by using a standardized approach (**Figure 3**). After 3 months, all patients returned for a follow-up appointment or were contacted by telephone.

Statistical Analysis

The primary analysis was a comparison of the rate of venous thromboembolism during the 3-month follow-up in patients who had a low or moderate pretest probability, non–high-probability ventilation–perfusion scans, and normal serial compression ultrasonograms with the rate in patients who had normal perfusion scans and normal initial ultrasonograms. This comparison was performed because a normal ventilation–perfusion scan is usually considered to exclude pulmonary embolism and we hypothesized a priori that the rates of venous thromboembolism in these two groups would be the same. Sample size was determined by adapting the equivalence test procedure described by Dunnett and Gent (18). We believed that an acceptable rate of deep venous thrombosis or pulmonary embolism in the follow-up period after normal serial testing in patients with non–high-probability ventilation–perfusion scans and low or moderate pretest clinical

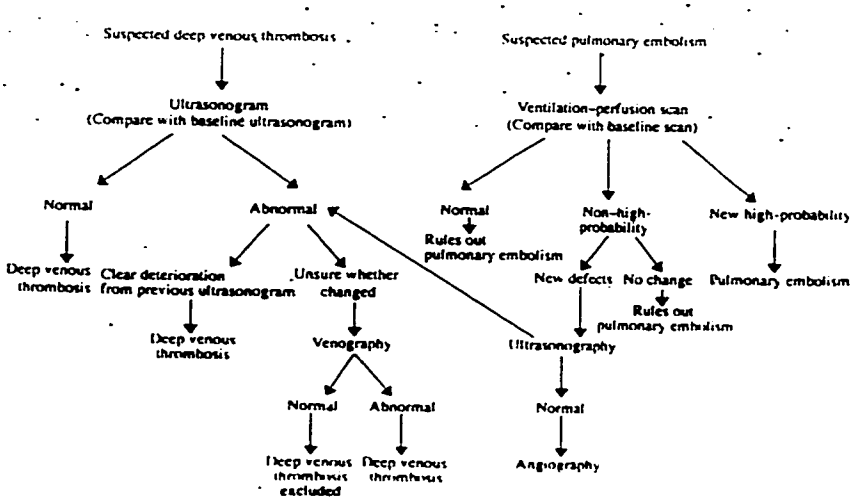

Figure 3. Algorithm for investigation of patients with suspected deep venous thrombosis or pulmonary embolism.

Table 1. Rates of Pulmonary Embolism According to Pretest Probability of Pulmonary Embolism and Results of Ventilation–Perfusion Lung Scanning

Pretest Probability of Pulmonary Embolism	Normal Perfusion (95% CI)	Lung Scanning Result (95% CI)		Total (95% CI)
		Non–High Probability	High Probability	
	←	%	→	
Low	1.2 (0.2–3.4)	2.9 (1.5–4.9)	33 (17–54)	3.4 (2.2–5.0)
Moderate	0 (0–4.9)	12.1 (8.0–16.2)	100*	27.8 (23.4–32.2)
High	13 (3.2–52.7)	47 (37.9–72)	100*	78.4 (69.2–86.0)
Total	1.2 (0.3–3.0)	8.4 (6.5–10.7)	89.3 (83.7–93.6)	17.5 (15.4–19.6)

* By definition, the probability of pulmonary embolism was 100% in these groups

probability would be 4%; this was the rate of pulmonary embolism in the normal/near-normal category used in PIOPED. Most physicians seem to consider such scan results acceptable to exclude pulmonary embolism. We accepted that the rate of events on follow-up in the patients with normal perfusion scans would be 1%. In this case, with the null hypothesis (probability of pulmonary embolism during follow-up in patients with non–high-probability lung scans minus the probability of pulmonary embolism during follow-up in patients with a normal lung scan = 3%) and the alternative hypothesis (probability = 1%), 550 patients with non–high-probability lung scans would provide a power of 84% to demonstrate that the difference between the two groups is unlikely to be more than 3%. We judged that a 3% difference would be clinically acceptable.

Results were assessed by using a chi-square test. Confidence intervals were calculated from the binomial distribution. To determine the interobserver reliability of the clinical model, two independent observers obtained same-day assessments in 58 patients. Agreement was determined by using a weighted κ test. The rates of abnormal ultrasonography results in the three pretest probability categories were compared by using a 3×2 chi-square test. This analysis was performed for all patients regardless of lung scanning results and in patients with high-probability lung scans.

Results

Patients

A total of 1885 consecutive, symptomatic patients were evaluated, of whom 484 were ineligible because of prolonged anticoagulant therapy ($n = 158$), expected survival less than 3 months ($n = 89$), geographic inaccessibility ($n = 68$), contraindication to contrast media ($n = 60$), inability to contact the attending physician ($n = 57$), pregnancy ($n = 23$), suspected upper-extremity deep venous thrombosis ($n = 17$), symptoms resolved for more than 72 hours ($n = 7$), and age younger than 18 years ($n = 5$). Of the 1401 eligible patients, 147 declined to participate, 2 had inadequate ventilation–perfusion scans, and 13 moved from the study region and were lost to follow-up. Thus, 1239 patients were evaluated.

Pretest Probability and Rates of Pulmonary Embolism

Of the 1239 evaluable patients, 734 were determined to have a low pretest probability (of whom 25 [3.4%] had pulmonary embolism), 403 had a moderate pretest probability (of whom 112 [27.8%] had pulmonary embolism), and 102 had a high pretest probability (of whom 80 [78.4%] had pulmonary embolism). **Table 1** shows the breakdown of patients with pulmonary embolism according to pretest probability and result of ventilation–perfusion scanning. The difference in the prevalence of pulmonary embolism in the three categories was statistically significant ($P < 0.001$).

The proportion of patients with pulmonary embolism in the three pretest probability categories was compared among centers. The clinical model performed similarly in all five centers ($P > 0.2$). Sixteen physicians were involved in the study. The weighted κ value for interobserver reliability for the clinical model was determined in a subset of 58 patients to be 0.86; this value represents an excellent level of agreement.

Ventilation–Perfusion Lung Scanning

Of the 1239 patients analyzed, 334 (27%) had normal ventilation–perfusion scans, 736 (59%) had non–high-probability scans, and 169 (14%) had high-probability scans. When events in the 3-month follow-up period were included, 4 patients (1.2%) in the normal ventilation–perfusion scan group, 62 patients in the non–high-probability scan group (8.4%), and 151 patients (89%) in the high-probability scan group were positive for pulmonary embolism. Results obtained by using the PIOPED cri-

Table 2. Rates of Pulmonary Embolism According to Pretest Probability of Pulmonary Embolism and Results of Ventilation–Perfusion Lung Scanning (by PIOPED Criteria)*

Pretest Probability of Pulmonary Embolism	Normal Perfusion	Lung Scan Result			Total†
		Low Probability	Intermediate Probability	High Probability	
	← n/n →				n/n (%)
Low	2/162	0/113	1/69	4/13	7/357 (2 [0.8–4.0])
Moderate	0/40	5/54	8/41	32/33	45/168 (27 [20.3–34.2])
High	0/3	2/8	5/8	21/24	28/43 (65 [49.1–79.0])
Total‡	2/205 (1 [0.1–3.5])	7/175 (4 [1.6–8.1])	14/118 (12 [6.6–19.1])	57/70 (81.4 [70.3–89.7])	

* PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis.
† Values in square brackets are 95% CIs.
‡ Values in parentheses and square brackets are (percentage of patients [95% CI])

Management Strategy

Primary Analysis

Rates of venous thromboembolic events during the 3-month follow-up did not differ between patients with normal perfusion scans and normal initial ultrasonograms (2 of 332 [0.6%; 95% CI, 0.3% to 3.0%]) and those with non–high-probability ventilation–perfusion scans, low or moderate pretest probability, and normal serial ultrasonograms (3 of 665 [0.5%; CI, 0.1% to 1.3%]; $P > 0.2$). Normal serial ultrasonography had a negative predictive value of 99.5%. The results of ultrasonography are shown in **Figure 4**. Serial conversion occurred in 14 of 679 patients (2.0%): 7 on day 3, 4 on day 7, and 3 on day 14. Thus, if the day 7 and 14 ultrasonograms had not been obtained, the follow-up event rate could have been as high as 1.3%. Three-month follow-up information was obtained by telephone for 58% of patients. All other patients were interviewed for their follow-up visit and underwent ultrasonography at 3 months. Asymptomatic deep venous thrombosis was not detected in any of these patients.

Secondary Analyses

Twenty-seven of the 169 patients (16%) with high-probability ventilation–perfusion scans had a low pretest probability. Eight patients were initially confirmed to have pulmonary embolism (by ultrasonography in 5 patients, venography in 1, and angiography in 2). One patient had pulmonary embolism during follow-up, but this patient did not comply with the protocol by declining to undergo venography and angiography. A comparison of ultrasonographic results in patients with high-probability ventilation–perfusion scans showed that the ultrasonogram was abnormal in 5 of 27 patients (19%) with low pretest clinical probability, 31 of 75 patients (40%) with moderate pretest probability, and 35 of 60 patients (58%) with high pretest probability. These differences are statistically significant ($P < 0.001$). When all ventilation–perfusion scan groups are combined, ultrasonograms were abnormal in 17 of 734 patients (2.3%) with low pretest probability, 56 of 396 patients (14.1%) with moderate pretest probability, and 46 of 102 patients (45%) with high pretest probability ($P < 0.001$) (**Table 3**).

Seventy-two patients died during the study. Sixteen of these patients had an initial diagnosis of pulmonary embolism, and 56 were considered negative for pulmonary embolism. All deaths were adjudicated by an independent panel, and none was judged to have been caused by pulmonary embolism (**Table 4**).

Discussion

We developed a clinical model for use in patients with suspected pulmonary embolism. The model accurately classified patients as having low, moderate, or high probability of pulmonary embolism. Reproducibility of the model is suggested by the similar accuracy in the five centers, and the interobserver reliability of the model was validated. The validity of the clinical model is further suggested by the significantly different rates of deep venous thrombosis detected by ultrasonography in patients with low, moderate, and high pretest probability of pulmonary embolism. We recognize that our model may overestimate the overall rate of pulmonary embolism in patients whom we considered to have a moderate pretest probability, because these patients were considered positive for pulmonary embolism if the ventilation–perfusion scan indicated high probability. However, almost 90% of these patients have angiographic evidence of pulmonary embolism (6), and treatment is generally recommended in these patients. By incorporating the pretest probability into the diagnostic approach for patients with suspected pulmonary embolism, we tested a management strategy that reliably diagnosed pulmonary embolism in more than 96% of patients by using only ventilation–perfusion scanning and bilateral leg vein ultrasonography. The strategy outlined in **Figure 2** resulted in only 46 of 1239 patients (3.7%) requiring

venography or angiography, and only 6 of 1022 (0.6%) patients considered negative for pulmonary embolism had events on follow-up. None of these events was massive pulmonary emboli or iliofemoral deep venous thrombosis.

It is difficult to estimate the number of tests that our strategy avoids. In the PIOPED study, 54% of patients with suspected pulmonary embolism had moderate or high pretest probabilities and nondiagnostic scans. It would not be unreasonable to perform angiography in all of these patients. Another study demonstrated that only 15% of patients with non–high-probability scans go on to angiography, but a remarkable proportion (28%) were treated with anticoagulants without receiving a final diagnosis (19). In our study, only 3.7% of patients required angiography or venography; thus, our strategy provides a marked reduction in the need for invasive tests. It is evident that our approach is a safe, noninvasive strategy for the management of patients with non–high-probability ventilation–perfusion scans. We validated the use of serial ultrasonography in patients with non–high-probability ventilation–perfusion scans and a low or moderate pretest probability, a group that represented more than 95% of our patients with non–high-probability ventilation–perfusion scans. Because pulmonary embolism and deep venous thrombosis are manifestations of the same disease and because this approach is safe in patients with suspected deep venous thrombosis, it seemed reasonable to hypothesize that serial ultrasonography would be safe (20–22). In addition, we identified two small but clinically important subgroups in which further invasive diagnostic tests are justified: 1) patients with a low pretest clinical probability of pulmonary embolism, a high-probability ventilation–perfusion scan, and a normal ultrasonogram and 2) patients with high pretest clinical probability of pulmonary embolism, a non–high-probability scan, and a normal ultrasonogram.

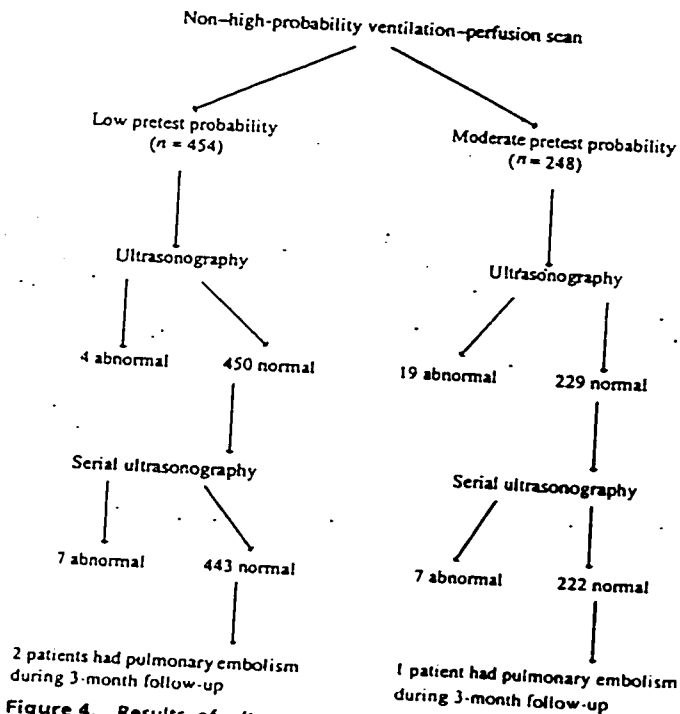

Figure 4. Results of ultrasonography in patients with non–high-probability ventilation–perfusion scans and low or moderate pretest probability of pulmonary embolism.

Table 3. Rates of Abnormal Results on Initial Ultrasonography According to Ventilation–Perfusion Scanning Results and Pretest Probability

Pretest Probability of Pulmonary Embolism	Normal Perfusion	Lung Scan Result		Total
		Non–High Probability	High Probability	
	← n/n (%) →			
Low	1/253 (1.2)	11/454 (2.4)*	5/27 (19)	17/734 (2.3)
Moderate	0/73 (0)	26/248 (10.5)†	30/75 (40)‡	56/396 (14.1)‡
High	1/8 (13)	10/34 (29)	35/60 (58)	46/102 (45)
Total	2/334 (0.6)	47/736 (6.3)	70/162 (43)	119/1232 (9.7)

* Seven of 11 patients had an abnormal result on serial testing
† Seven of 26 patients had an abnormal result on serial testing
‡ Three patients had inadequate ultrasonography results and four did not undergo ultrasonography.

Because physicians are willing to rule out pulmonary embolism in patients with normal ventilation–perfusion scans (5), we believed that the rate of venous thromboembolism during 3-month follow-up in patients with normal perfusion scans should be equivalent to that found with any strategy in which angiography is limited. We chose to use Hull diagnostic criteria for scan interpretation instead of the PIOPED criteria because a previous noninvasive management strategy had used these criteria; a high degree of observer agreement has been demonstrated with these criteria; and Hull criteria, which make no distinction between low- and intermediate-probability scans, are easier to remember. Nonetheless, because we expected that some physicians would be more familiar with the PIOPED criteria, we also scored the ventilation–perfusion scans of 570 randomly selected patients according to the PIOPED system. We found no advantage to using the PIOPED criteria. None of the 113 patients (CI, 0% to 3.2%) with a low pretest probability and a low probability scan according to the PIOPED criteria had pulmonary embolism; this does not statistically significantly differ from the 3.4% rate of pulmonary embolism (CI, 2.2% to 5.0%) in patients with low pretest probability and non–high-probability scans according to Hull criteria. Thus, either the PIOPED or Hull criteria can be used in our strategy, with the same results.

The role of ultrasonography in patients with suspected pulmonary embolism is

Table 4. Cause of Death According to Whether Pulmonary Embolism Was Initially Diagnosed

Cause of Death	Deaths		
	Patients with Pulmonary Embolism Initially	Patients with No Pulmonary Embolism Initially	Total
	← n →		
Metastatic cancer	8	34	42
Congestive heart failure	0	11	11
Renal failure	2	2	4
Pneumonia	0	5	5
Liver failure	1	1	2
Sepsis	1	0	1
Myocardial infarction	3	3	6
Stroke	0	1	1

high rates of deep venous thrombosis detected by ultrasonography in patients with non–high-probability scans, their study was limited by small numbers (20 patients) and selected enrollment. In another study, Turkstra and colleagues (24) indicated that ultrasonography may be of low usefulness in patients apparently similar to those in our study. However, we believe that Turkstra and colleagues' study was limited because ultrasonography was done only on the day of presentation and only in the common femoral vein and popliteal vein regions. We performed serial testing and more extensive imaging of leg veins in our study. This may account for the fact that 43% of our patients with high-probability ventilation–perfusion scans had an abnormal ultrasonogram compared with only 30% in the study by Turkstra and colleagues. In addition, the latter study may have overestimated the rate of pulmonary embolism by considering all high-probability scans positive. The PIOPED study showed that the rate of pulmonary embolism with high-probability scans was 96% if clinical probability was high, 88% if clinical probability was moderate, and 50% if clinical probability was low. It is unlikely that all patients in Turkstra and colleagues' study had high clinical probability. In addition, false-positive ultrasonographic results are more likely with the two-region compression used by Turkstra and colleagues, but no attempt was made to adjust for this in the study design or interpretation (10). These limitations all bias toward a lower usefulness for ultrasonography. We used venography to confirm cases in which the ultrasonographic result was statistically most likely to be false-positive (low or moderate pretest probability with non–high-probability ventilation–perfusion scans). Thus, false-positive results are not likely to be common with our approach. However, in our study, only 10% of all patients with suspected pulmonary embolism had an abnormal ultrasonogram, and serial conversions occurred in only 2% of patients.

Our study has some limitations. Because the clinical model was used predominantly by physicians who have expertise in thromboembolic diseases, it may not be suited for use by all physicians. Patients were entered consecutively, and we included both hospitalized and ambulatory patients; nonetheless, the demographic characteristics of our patients may differ from those of patients presenting in other centers. Although the eligibility criterion was simply "suspected pulmonary embolism," it was informally agreed that patients should have dyspnea or chest pain not clearly due to another condition. This lack of a definable symptom complex as an eligibility criterion may limit the generalizability of our findings. Another potential limitation is the critical role of determining whether an alternative diagnosis that was as likely as or more likely than pulmonary embolism accounted for the patient's signs and symptoms. This depends on the physician judgment, which will vary according to physician experience. Overall, 60% of patients had an alternative diagnosis (such as pneumonia, musculoskeletal pain, viral pleuritis, postoperative atelectasis, pulmonary neoplasm, or anxiety). An alternative diagnosis was made in 65% of the patients without pulmonary embolism and 29% of those with pulmonary embolism. Our strategy is designed to reduce invasive tests and, as such, it may be best to assume that an alternative diagnosis does not exist in cases of doubt.

Despite these potential limitations, the model seems to be reproducible and most of the necessary information easily elicited. The high frequency of telephone follow-up did not allow us to determine the frequency of asymptomatic events during follow-up, but no events were detected in patients who reported for ultrasonography at 3 months. Therefore, we cannot accurately comment on asymptomatic events during the 3-month follow-up, but it is unlikely that a significant number of events occurred. Moreover, we were more concerned with symptomatic events during follow-up, and it is unlikely that telephone follow-up would miss symptomatic events.

Depending on local costs of ultrasonography and angiography, the serial ultrasonography approach, although very safe, may not save money. On the other hand, it is important to note that only 3.4% of all patients with a low clinical probability had pulmonary embolism. Because this rate is not dissimilar to the rate of pulmonary embolism in patients with normal and near-normal ventilation–perfusion scans, it may not be worthwhile to perform lung scans or ultrasonography in such patients. However, we believe that the optimal strategy may include the high negative predictive value of certain D-dimer

with suspected deep venous thrombosis (26). Decreasing the number of serial tests performed (that is, eliminating the test on day 7 or 14) would also increase efficiency and decrease the cost of our approach with almost no loss in safety.

We have shown that our clinical model can be used to select patients with non–high-probability ventilation–perfusion scans in whom serial ultrasonography is appropriate. When the pretest probability is discordant with the result of ventilation–perfusion scanning (high pretest probability but non–high-probability ventilation–perfusion scan or low pretest probability but high-probability ventilation–perfusion scan) and the ultrasonogram is normal, pulmonary angiography is indicated. In our study, venography was performed in the hope that it would eliminate the need for angiography, but this was not the case. Therefore, patients in whom more invasive testing is indicated can proceed directly to angiography. Application of the model and its use in the strategy that we described represent a safe, effective, and largely noninvasive means of managing patients with suspected pulmonary embolism.

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References

1. **Hildner FJ, Ormond RS.** Accuracy of the clinical diagnosis of pulmonary embolism. JAMA. 1967;202:567-70.
2. **Sasahara AA, Sharma GV, Barsamian EM, Schoolman M, Cella G.** Pulmonary thromboembolism. Diagnosis and treatment. JAMA. 1983;249:2945-50.
3. **Stein PD, Athanasoulis C, Alavi A, Greenspan RH, Hales CA, Saltzman HA, et al.** Complications and validity of pulmonary angiography in acute pulmonary embolism. Circulation. 1992;85:462-8.
4. **Henry JW, Relyea B, Stein PD.** Continuing risk of thromboemboli among patients with normal pulmonary angiograms. Chest. 1995;107:1375-8.
5. **Hull RD, Raskob GE, Coates G, Panju AA.** Clinical validity of a normal perfusion lung scan in patients with suspected pulmonary embolism. Chest. 1990;97:23-6.
6. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). The PIOPED Investigators. JAMA. 1990;263:2753-9.
7. **Hull RD, Carter CJ, Jay RM, Ockleford PA, Hirsh J, et al.** Pulmonary angiography, ventilation lung scanning, and venography for clinically suspected pulmonary embolism with abnormal perfusion scan. Ann Intern Med. 1983;98:891-9.
8. **Hull RD, Raskob GE, Coates G, Panju AA, Gill GJ.** A new noninvasive management strategy for patients with suspected pulmonary embolism. Arch Intern Med. 1989;149:2549-55.
9. **Anderson DR, Lensing AW, Wells PS, Levine MN, Weitz JI, Hirsh J.** Limitations of impedance plethysmography in the diagnosis of clinically suspected deep-vein thrombosis. Ann Intern Med. 1993;118:25-30.
10. **Wells PS, Hirsh J, Anderson DR, Lensing AW, Foster G, Kearon C, et al.** Comparison of the accuracy of impedance plethysmography and compression ultrasonography in outpatients with clinically suspected deep vein thrombosis. A two centre paired-design prospective trial. Thromb Haemost. 1995; 74:1423-7.
11. **Perrier A, Bounameaux H, Morabia A, de Moerloose P, Slosman D, Didier D, et al.** Diagnosis of pulmonary embolism by a decision analysis-based strategy including clinical probability, D-dimer levels, and ultrasonography: a management study. Arch Intern Med. 1996;156:531-6.
12. **Wells PS, Hirsh J, Anderson DR, Lensing AW, Foster G, Kearon C, et al.** Accuracy of clinical assessment of deep-vein thrombosis. Lancet. 1995; 345:1326-30.
13. **Celi A, Palla A, Petruzzelli S, Carrozzi L, Jacobson A, Cella G, et al.** Prospective study of a standardized questionnaire to improve clinical estimate of pulmonary embolism. Chest. 1989;95:332-7.
14. **Hoellerich VL, Wigton RS.** Diagnosing pulmonary embolism using clinical findings. Arch Intern Med. 1986;146:1699-704.
15. **Lensing AW, van Beek EJ, Demers C, Tiel-van Buul MM, Yakemchuk V, van Dongen A, et al.** Ventilation-perfusion lung scanning and the diagnosis of pulmonary embolism: improvement of observer agreement by the use of a lung segment reference chart. Thromb Haemost. 1992;68:245-9.
16. **Gottschalk A, Sostman HD, Coleman RE, Juni JE, Thrall J, McKusick KA, et al.** Ventilation-perfusion scintigraphy in the PIOPED study. Part II. Evaluation of the scintigraphic criteria and interpretations. J Nucl Med. 1993; 34:1119-26.
17. **Rabinov K, Paulin S.** Roentgen diagnosis of venous thrombosis in the leg. Arch Surg. 1972;104:134-44.
18. **Dunnett CW, Gent M.** Significance testing to establish equivalence between treatments, with special reference to data in the form of 2 × 2 tables. Biometrics. 1977;33:593-602.
19. **Schluger N, Henschke C, King T, Russo R, Binkert B, Rackson M, et al.** Diagnosis of pulmonary embolism at a large teaching hospital. J Thorac Imaging. 1994;9:180-4.
20. **Huisman MV, Büller HR, ten Cate JW, van Royen EA, Vreeken J, Kersten MJ, et al.** Unexpected high prevalence of silent pulmonary embolism in patients with deep venous thrombosis. Chest. 1989;95:498-502.
21. **Kruit WH, de Boer AC, Sing AK, van Roon F.** The significance of venography in the management of patients with clinically suspected pulmonary embolism. J Intern Med. 1991;230:333-9.
22. **Sluzewski M, Koopman MM, Schuur KH, van Vroonhoven TJ, Ruijs JH.** Influence of negative ultrasound findings on the management of in- and outpatients with suspected deep-vein thrombosis. Eur J Radiol. 1991;13: 174-7.
23. **Bradley MJ, Alexander L.** The role of venous colour flow Doppler to aid the non-diagnostic lung scintigram for pulmonary embolism. Clin Radiol. 1994; 50:232-4.
24. **Turkstra F, Kuijer PM, van Beek EJ, Brandjes DP, ten Cate JW, Buller HR.** Diagnostic utility of ultrasonography of leg veins in patients suspected of having pulmonary embolism. Ann Intern Med. 1997;126:775-81.
25. **Ginsberg JS, Wells PS, Brill-Edwards P, Donovan D, Panju A, van Beek EJ, et al.** Application of a novel and rapid whole blood assay for D-dimer in patients with clinically suspected pulmonary embolism. Thromb Haemost. 1995;73:35-8.
26. **Wells PS, Anderson DR, Bormanis J, Guy F, Mitchell M, Lewandowski B.** SimpliRED D-dimer can reduce the diagnostic tests in patients with suspected deep vein thrombosis [Letter]. Lancet. 1998;351:1405-6.