Pulmonary embolism : diagnostic management and prognosis

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PULMONARY EMBOLISM

Diagnostic management and prognosis

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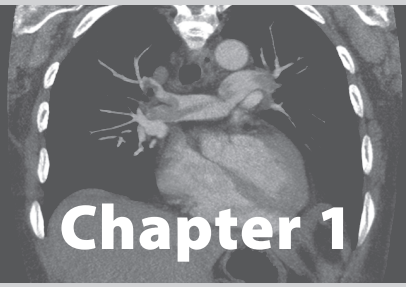
Contents



Chapter 1

Introduction

Even though the first reports on venous thromboembolism date back to the 13th century and the mechanism of acute pulmonary embolism (PE) was unraveled almost 150 years ago by Rudolf Virchow, PE still keeps medical researchers occupied around the globe.[1,2] PE is a disease characterized by obstruction of the pulmonary arteries with thrombotic emboli originating predominantly from pathological thrombi in the deep venous system of the lower extremities.[2] This obstruction of the pulmonary arteries causes an increase in right ventricular afterload that, in combination with the release of several neurohumoral factors, might induce right ventricle enlargement and decreased stroke volume.[3] When the compensatory mechanisms to maintain right ventricular systolic function, i.e. catecholamine-driven tachycardia and the Frank-Starling preload reserve, are utilized, right ventricular cardiac output decreases resulting in decreased left ventricular filling. In turn, this causes left ventricular systolic function impairment and thus decreased coronary perfusion pressure.[3] In the right ventricle, when exposed to increased oxygen demand, decreased coronary perfusion pressure contributes to the relative oxygen deficit and might therefore cause myocardial ischemia and further loss of systolic performance.[3] Depending on comorbid conditions as well as the extent of the embolus load, this vicious circle may have fatal outcome within minutes, or after several hours or days, especially when the patient is left untreated. Hence, accurate and rapid identification and treatment of patients with acute PE is of great clinical importance.

The diagnostic process of acute PE however, represents several challenges. In essence, the physician has to distinguish patients with this disease - and treat them - from patients that are suspected of PE but do not have the disease. Because the signs and symptoms of PE are largely non-specific, many patients presenting with respiratory or chest symptoms are further investigated but do not have PE. As a result of limitations of individual diagnostic tests, mis-management of PE on the basis of the results of single diagnostic tools has been a frequent problem. In addition, invasive diagnostic procedures and exposure to ionizing radiation or nephrotoxic contrast dye should be prevented when possible. The use of well validated diagnostic algorithms combining different non-invasive tests, i.e. clinical decision rules, D-dimer blood tests and radiological imaging, are the solution for these issues.[4] Clinical decision rules predict the probability of having PE for individual patients and aid the clinician in determining the preferred diagnostic approach. D-dimer blood tests should be performed in patients with an unlikely probability since a normal test result safely excludes PE under this condition.[4,5] Because this is not true for patients with a likely probability, D-dimer tests are not useful for these patients and radiological imaging should follow.[4,6] Chapter 2 and 3 of this thesis focus on the clinical validation, simplification and performance of a recently developed clinical decision rule, the revised Geneva score.[7]

Currently, the radiological imaging test of choice for suspected PE is computed tomography pulmonary angiography (CTPA). It has been shown that this test has excellent sensitivity and specificity for diagnosing acute PE.[8] Nonetheless, experts have raised concern for false negative CT results, especially in patients with high clinical probability for PE.[9] For this reason, we have

studied the safety of withholding anticoagulant treatment in patients with suspected PE and a strict indication for CTPA, in whom the CT scan revealed no pulmonary emboli. Furthermore, we have evaluated the additional clinical value of performing compression ultrasonography of the legs subsequent to a normal CTPA to exclude deep venous thrombosis before deciding to withhold treatment. The results of this study are described in chapter 4.

After establishing the diagnosis of acute PE, patients should be treated with at least 5 days of either weight based therapeutic doses of low molecular weight heparin or unfractionated heparin aiming at a 1.5 to 2.5 prolongation of the activated partial thromboplastin time, followed by vitamin K antagonists for a period of at least three to six months with a target international normalized ratio (INR) of 2.0 to 3.0.[10] For patients presenting with hemodynamic instability, more aggressive treatment is warranted which may include administration of thrombolytic drugs, thrombosuction or surgical thrombectomy.[10] These latter two are reserved for those patients in whom thrombolysis is contraindicated. Importantly, the clinical condition of apparently stable patients may deteriorate rapidly and unexpectedly to cardiogenic shock of even death in the first hours or days after establishing the diagnosis of acute PE. In most cases, this phenomenon is caused by silent and unnoticed worsening of right ventricular function impairment by the viscous circle described above. It is a challenge to distinguish patients at risk for clinical deterioration from those with relatively mild disease since these first patients might benefit from more intensive clinical surveillance and treatment regimes whereas home treatment may be considered for the latter patient category. It seems pathophysiologically plausible to include specific markers of ventricular function in risk stratification models for patients with acute PE. In chapters 5 to 7 of this thesis, we explore the predictive value for adverse clinical events of several biomarkers of ventricular overload as well as easy obtainable CT-measured indicators of right ventricular function in patients with acute PE.

One other important objective of clinical research in the field of acute PE concerns the patients' prognosis. Patients who survive the acute embolic event face the risk of recurrent venous thromboembolism, bleeding complications from anticoagulant therapy, chronic emboli leading to pulmonary hypertension and in addition arterial cardiovascular events and detection of previously unknown cancer.[11-14] However, despite the increased risk for these serious clinical complications compared to population controls, patients with a first episode of acute PE stop their anticoagulant therapy after three to six months and are from then on referred to their general practitioner. This is mainly due to the absence of evidence-based, well validated guidelines for specific screening programs, intensified clinical surveillance or prolonged treatment regimens. The development of such guidelines is complicated by the lack of knowledge of underlying pathophysiological mechanisms and accurate risk estimates regarding these complications. To further study the long term prognosis of patients with acute PE, we have performed a large cohort study of patients with acute PE, the so called INSHAPE study (INcidence

of Symptomatic chronic thromboembolic pulmonary Hypertension after Acute Pulmonary Embolism). The primary goal of this study was the determination of the incidence of chronic thromboembolic pulmonary hypertension (CTEPH) after acute PE in an unselected patient cohort, which is described in chapter 8. In the subsequent chapter, we have compared various clinical algorithms for managing dyspnoeic patients with previous PE who are suspected of having CTEPH. Analyses regarding the prevalence and causes of exertional dyspnea in the clinical course of acute PE, further evaluation of the risk of cardiovascular events after acute PE and the overall prognosis of patients with acute PE including a pooled survival analysis of different adverse events, are presented in chapters 10, 11 and 12 respectively. Finally, in chapter 13 we describe a newly derived disease specific quality of life instrument for patients with acute PE.

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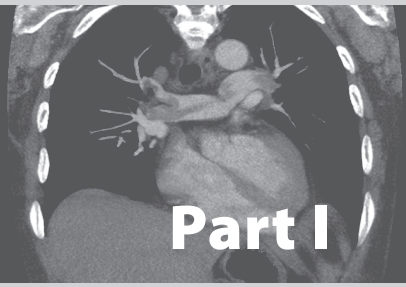
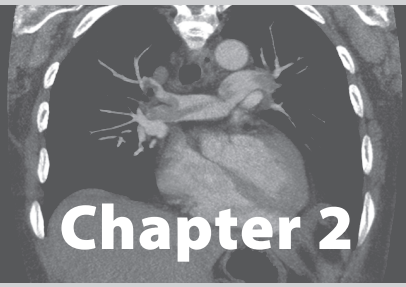


Part I

Diagnostic management of acute pulmonary embolism



Chapter 2

Comparison of the revised Geneva score with the Wells rule for assessing clinical probability of pulmonary embolism

F.A. Klok, E. Kruisman, J. Spaan, M. Nijkeuter, M. Righini, D. Aujesky, P.M. Roy, A. Perrier, G. Le Gal and M.V. Huisman

J Thromb Haemost 2008; 6:40-4

ABSTRACT

Background

The revised Geneva score, a standardized clinical decision rule in the diagnosis of pulmonary embolism (PE), was recently developed. The Wells clinical decision is widely used but lacks full standardization, as it includes subjective clinician's judgement. We have compared the performance of the revised Geneva score with the Wells rule.

Methods

In 300 consecutive patients with suspected PE, the clinical probability of PE was assessed by the Wells rule and the revised Geneva score. The predictive accuracy of both scores were compared by the area under the curve (AUC) of receiver operating characteristic (ROC) analyses.

Results

The overall prevalence of PE was 16%. The prevalences of PE in the low-, intermediate- and high-probability categories as classified by the revised Geneva score were similar to those of the original derivation set. The AUC of the revised Geneva score was not different from that of the Wells rule. After three months of follow-up, no patient classified into the low or intermediate clinical probability category by the revised Geneva score and a normal D-dimer result was subsequently diagnosed with acute venous thromboembolism.

Conclusions

This study suggests that the performance of the revised Geneva score is equivalent to that of the Wells rule. In addition, it seems safe to exclude PE in patients by the combination of a low or intermediate clinical probability by the revised Geneva score and a normal D-dimer concentration.

INTRODUCTION

Current diagnostic work-up of patients with suspected acute pulmonary embolism (PE) usually starts with the assessment of clinical pretest probability using clinical prediction rules, and plasma D-dimer measurement.[1,2] Indeed, recent studies have demonstrated the safety of rejecting the diagnosis of PE by the combination of a low clinical probability and a normal quantitative D-dimer test result, thereby decreasing the need for further diagnostic radiological imaging in up to 30% of patients.[3]

The best validated and therefore most widely used clinical decision rules are the Wells rule (Table 1) and the Geneva score.[1,2] However, both scores have limitations. The Wells rule includes the physician's judgement of whether an alternative diagnosis is more likely than PE.[1] This criterion, which carries a major weight in the score, is subjective and cannot be standardized. Moreover, it has been suggested that the predictive value of the Wells rule is derived primarily from its subjective component.[4] The Geneva score, based on 13 entirely objective variables, requires a blood gas analysis while breathing room air and has only been evaluated for patients in the emergency ward.[2] Both scores appeared to have a comparable predictive value for PE.

The revised Geneva score is a simple score based entirely on clinical variables and is independent from physicians' implicit judgement (Table 1).[5] The prevalence of PE obtained using the revised Geneva score in the original derivation cohort was comparable to that obtained using the original Geneva score and the Wells rule, i.e. 9.0% in the low clinical probability group,

Table 1. The Wells rule and revised Geneva score.

Wells rule[1]		**Revised Geneva score[5]**	
Items	**Score**	**Items**	**Score**
Clinical signs of DVT	3	Age >65 years	1
Alternative diagnosis less likely than PE	3	Previous DVT or PE	3
Previous PE or DVT	1.5	Surgery or fracture within 1 month	2
Heart rate >100 beats/min	1.5	Active malignancy	2
Surgery or immobilization within 4 weeks	1.5	Unilateral lower limb pain	3
Hemoptysis	1	Hemoptysis	2
Active malignancy	1	Heart rate 74-94 beats/min	3
		Heart rate ≥95 beats/min	5
		Pain on lower limb deep vein palpation and unilateral edema	4
Clinical probability		**Clinical probability**	
Low	<2	Low	0–3
Intermediate	2–6	Intermediate	4–10
High	>6	High	≥11
PE unlikely	≤4		
PE likely	>4		

PE=pulmonary embolism, DVT=deep vein thrombosis.

27.5% in the intermediate clinical probability group and 71.7% in the high clinical probability group. However, this rule has not yet been evaluated by large clinical outcome studies. Therefore, we assessed the revised Geneva score in a convenience sample from a prospective cohort study on the safety of the use of multi-detector row computed tomography (CT) in suspected PE.[6] Furthermore, we compared its performance to that of the Wells rule, which had been routinely assessed in all patients.

METHODS

Patients

The clinical probability of PE was prospectively assessed using the Wells rule in consecutive patients with suspected PE referred to our hospital as part of a large diagnostic study.[6] In contrast to the original publication of the Wells rule that categorized patients in 3 groups of increasing risk for PE, the Christopher study used a dichotomized version of this prediction rule. In all patients with a Wells rule indicating PE unlikely (score of 4 points or less), a quantitative D-dimer test was performed. When the result of this test was within normal ranges, PE was considered to be excluded and patients were left untreated. To establish the final diagnosis of PE, spiral CT-scanning was performed in all remaining patients, i.e. if PE was considered likely (Wells rule greater than 4 points) or in cases of an abnormal quantitative D-dimer test result. All patients were followed for three months to evaluate the recurrence of venous thromboembolism (VTE).[6]

Assessment of the revised Geneva score

The revised Geneva score comprises four variables not included in the Wells rule: 1) age over 65 years, 2) unilateral lower limb pain, 3) heart rate 75–94 beats per minute or more than 94 beats per minute and 4) pain on lower limb deep venous palpation and unilateral edema (Table 1). These items were abstracted from the patient charts after masking the final diagnosis. Values for each item were scored on the day of inclusion. In cases of inaccessibility of patient's files or absence of relevant data, patients were excluded.

Data analysis

Frequencies of PE obtained with the revised Geneva score and original 3-level Wells rule were compared with those of the original Geneva score dataset by comparing the corresponding confidence intervals.[5] The accuracy of the revised Geneva and Wells rule scores was compared by the area under the curve (AUC) in receiver operating characteristic (ROC) analyses.[7] Results from the clinical rule and D-dimer tests were then combined and related to the clinical outcome. In particular, the VTE recurrence rate of patients with a low or intermediate clinical probability as calculated using the revised Geneva score and a normal D-dimer result were

studied. Statistical analyses were performed using SPSS software (SPSS for windows 12.0.1, Inc. 1989–2003, Chicago, IL, USA).

RESULTS

Patients

The study included 300 patients with suspected PE. Medical records of all subjects were obtained and studied. There were no missing data, so the revised Geneva score could be calculated for all patients. Included patients were 47 ±16 years old at the time of diagnosis; 60% were female and 96% were outpatients. The overall incidence of PE was 16%. According to the revised Geneva score, 157 patients (52%) had low clinical probability, 136 (45%) intermediate clinical probability and 7 (2.3%) high clinical probability (Table 2). The incidence of PE was 8.3% (95% confidence interval [CI] 4.0–13), 23% (95% CI 16–30) and 71% (95% CI 35–99.9) respectively for the three probability groups. These frequencies were well comparable to those in the derivation and validation set of le Gal as well as in the Wells rule calculated in the Leiden population (Table 2).[5,6]

Table 2. Proportion of patients classified by, and predictive accuracy of the revised Geneva score in the original derivation and validation set compared to the results of the revised Geneva score and Wells rule in the Leiden study population.

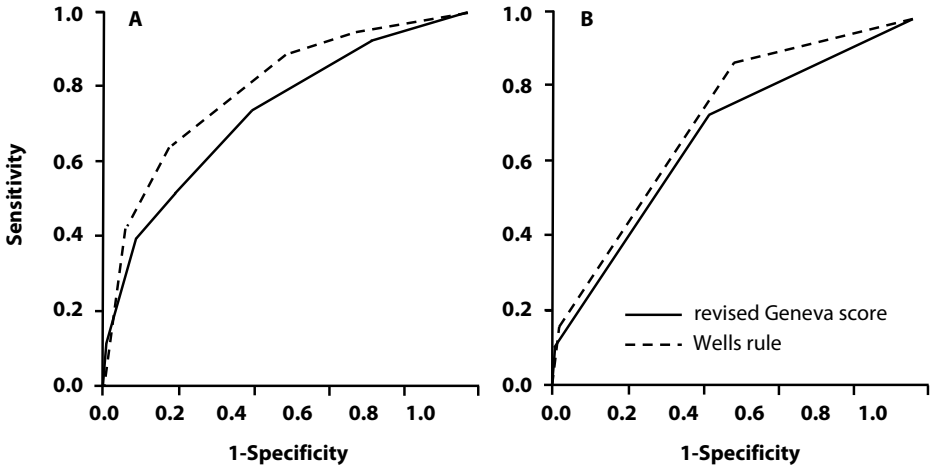
	Derivation set le Gal[5]				**Validation set le Gal[5]**				**Validation set Leiden**				**Wells in Leiden**			
Clinical probability	Patients		Patients with PE		Patients		Patients with PE		Patients		Patients with PE		Patients		Patients with PE	
	n	%	%	95% CI	n	%	%	95% CI	n	%	%	95% CI	n	%	%	95% CI
Low	354	37	9.0	6.6-13	229	31	7.9	5.0-12	157	52	8.3	4.0-13	133	44	4.5	1.7-9.6
Intermediate	549	57	28	24-31	463	62	29	25-33	136	45	23	16-30	154	51	23	16-30
High	53	6	72	58-82	57	8	74	61-83	7	2.3	71	35-99.9	13	3.4	62	32-86

CI=confidence interval, n=number.

Performance of the revised Geneva score

We compared the AUC of the ROC analysis for the revised Geneva score and Wells rule (Figure 1A and B). The AUC of the continuous prediction rules between the Wells rule (0.79; 95% CI 0.72–0.87) and the revised Geneva score (0.73; 95% CI 0.65–0.81) were comparable (difference 0.06, 95% CI -0.03-0.09). The AUC of the categorized rules was 0.72 (95% CI 0.65–0.80) for the Wells rule and 0.67 (95% CI 0.59–0.76) for the revised Geneva score. These AUCs were not significantly different as well (difference 0.05, 95% CI -0.04-0.13).

In total, 134 (45%) patients were classified differently using the Wells rule and the revised Geneva score (Table 3, κ=0.16). In almost all patients (97%), this disagreement was due to the decision



Figures 1A and 1B. Receiver operating characteristic curves of the continuous (A) and categorized (B) outcome of the revised Geneva score and Wells rule.

of awarding or not awarding 3 points for the item 'alternative diagnosis less likely than PE' in the Wells rule. Extreme disagreement, defined as patients classified into the low clinical probability group by one score and into the high clinical probability category by the other score, did not occur. In patients with CT-proven PE, 20 patients were categorized differently by the two rules: the Wells rule classified 15 patients into a higher clinical probability category than the revised Geneva score; in 5 patients it was the other way around. Among patients with a higher Wells rule classification, the CT-scan indicated central embolus location in four, segmental location in eight, and subsegmental embolus in three. Among cases of higher classification by the revised Geneva score, one patient had central emboli and four patients had segmental emboli. There was no difference between these two groups (p=0.5).

Table 3. (dis-) Similarities in clinical probability between the Wells rule and revised Geneva score in individual patients from our study population.

revised Geneva score	**Wells rule**		
	Low	Intermediate	High
Low	85	48	0
Intermediate	72	78	4
High	0	10	3

D-dimer testing was performed in all patients (233) with a Wells rule of 4 points or less. After three months of follow-up, no patient with a low (0/98; 95% CI 0.0–2.7) or intermediate (0/34; 95% CI 0.0–7.4) clinical probability score by the revised Geneva score and a normal D-dimer result at inclusion was subsequently diagnosed with VTE.

DISCUSSION

Our study confirms the good performance of the revised Geneva score. This conclusion is based on 4 observations. First, the predictive accuracy of the revised Geneva score in our study population was comparable to that of the original derivation and validation set of the score. Second, the comparison of the AUCs of the ROC analyses, a validated instrument for weighing the discrimination ability of a statistical method for predictive purposes, showed the equivalence of the revised Geneva score and Wells rule in our study population.[8] Third, our data suggest that the combination of a low or intermediate clinical probability by the revised Geneva score with a normal D-dimer result can safely rule out the diagnosis of PE. Fourth, cases of disagreement between the Wells rule and the revised Geneva score were not explained by embolus location. Therefore, neither score tended to overestimate clinical probability in cases of subsegmental PE.

There are several additional points. First, the observed kappa statistic of 0.16 suggests great difference in individual classification of individual patients by the revised Geneva score and Wells rule. Explanations for this are the different criteria on which both scores are based and the subjective item of the Wells rule. We found that 97% of the cases in which individual patients were classified differently could be explained by this subjective item. Although implicit clinical judgement may improve the accuracy of a prediction rule, as was shown using the original Geneva score, and the subjective item of the Wells rule has been shown to be of high predictive value for PE in comparison to other items, the Wells rule did not perform better than the completely objective revised Geneva score.[9,10] Second, although the patients were prospectively followed, the revised Geneva score was assessed retrospectively. Nonetheless, inclusion bias was not present since we included consecutive patients and their medical charts were abstracted by researchers blinded to the final diagnosis. Third, D-dimer measurements were only performed in patients classified as PE unlikely according to the Wells rule. Therefore, D-dimer results were available for only 80% (233/293) of all patients classified into the low or intermediate clinical probability groups by the revised Geneva score.

In summary, this study suggests that the performance of the revised Geneva score is equivalent to that of the Wells rule in a cohort largely dominated by outpatients. It seems safe to withhold oral anticoagulation therapy in patients with suspected PE, a low or intermediate clinical probability by the revised Geneva score and a normal D-dimer level. Prospective clinical outcome studies with larger numbers of patients are needed to confirm these latter findings.

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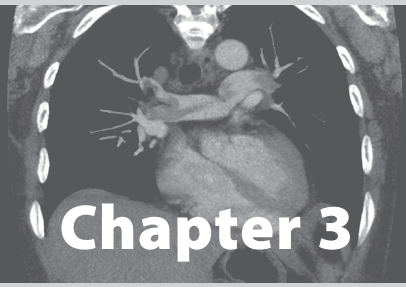


Chapter 3

Simplification of the revised Geneva score for assessing clinical probability of pulmonary embolism

F.A. Klok, I.C.M. Mos, M. Nijkeuter, M. Righini, A. Perrier, G. Le Gal and M.V. Huisman

Arch Intern Med 2008; 168:2131-6

ABSTRACT

Background

We have evaluated a simplified version of the revised Geneva score, which is a fully standardized clinical decision rule (CDR) in the diagnostic work-up of suspected pulmonary embolism (PE).

Methods

Data regarding 1049 patients from 2 prospective diagnostic trials that included patients with suspected PE were combined. We constructed the simplified CDR by attributing 1 point to each item of the original CDR and compared the diagnostic accuracy of the 2 versions by receiver operating characteristic (ROC) analyses. We also assessed the safety of ruling out PE on the basis of the combination of either a low- or intermediate clinical probability (using a 3-level scheme) or a "PE unlikely" assessment (using a dichotomized rule) with the simplified rule in combination with a normal highly sensitive D-dimer test result.

Results

Area under the curve for the original revised Geneva score was comparable to that of the simplified score (0.75, 95% confidence interval [CI] 0.71-0.78 vs. 0.74, 95% CI 0.70-0.77). During a three months follow-up period, no patient with a combination of either a low (0%; 95% CI 0.0%-1.7%) or intermediate (0%; 95% CI 0.0%-2.8%) clinical probability, or a "PE unlikely" assessment (0%; 95% CI 0.0%-1.2%) with the simplified score and a normal D-dimer test result was diagnosed with symptomatic venous thromboembolism.

Conclusion

This study suggests that simplification of the revised Geneva score does not lead to a decrease in diagnostic accuracy or clinical utility of the score, which should be confirmed in a prospective study.

INTRODUCTION

A clinical decision rule (CDR) can be defined as an instrument containing variables obtained from history, physical examination and simple diagnostic tests quantifying the likelihood of a diagnosis, prognosis, or likely response to treatment in an individual patient.[1] CDRs are especially utilized in clinical circumstances involving common problems to simplify and increase the accuracy of the clinicians' diagnostic and prognostic assessments. Because of the nonspecific nature of the presenting signs and symptoms of acute pulmonary embolism (PE), this diagnosis is clinically suspected in many patients who report respiratory or chest distress. As a result of this, the prevalence of PE in this population is relatively low. Several CDRs have been developed to assist the clinician in diagnostic decision making of suspected PE.[2] Correct implementation of CDRs in diagnostic strategies has been proven to decrease the need for expensive, time-consuming and invasive diagnostic imaging procedures. Moreover, the venous thromboembolism (VTE) failure rate is acceptably low when anticoagulant treatment is withheld in patients in whom PE is ruled out by various non-invasive diagnostic criteria including a CDR.[3-5]

Although 2 CDRs for the pretest probability of PE have been extensively validated, i.e. the Wells rule and the Geneva score, both have practical limitations.[6-10] A fully standardized rule exclusively based on objective clinical items, the revised Geneva score, has been developed and validated recently.[9,10] The revised Geneva score is independent of physicians' implicit judgement, which makes this CDR objective and easily reproducible.[10] The score consists of 8 variables with different individual weights (Table 1), which might lead to miscalculations in acute patient care. Also, a more complicated score may be less likely to be used by clinicians or remembered correctly.[11] Therefore, we evaluated whether a simplified version of the revised Geneva score in which each variable is attributed 1 point (Table 1), would retain its diagnostic

Table 1. Simplification of the revised Geneva score.

Variable	Original	Simplified
Age >65 years	1	1
Previous DVT or PE	3	1
Surgery or fracture within 1 month	2	1
Active malignancy	2	1
Unilateral lower limb pain	3	1
Hemoptysis	2	1
Heart rate 74-94 beats/min	3	1
Heart rate ≥95 beats/min*	5	1
Pain on lower limb deep vein palpation and unilateral edema	4	1

*By the original score, patients are awarded 0 points (heart beat <74 beats/min), 3 points (heart rate 74-94 beats/min) or 5 points (heart rate ≥95 beats/min); by the simplified score, patients are awarded 1 point if the heart rate exceeds 73 beats/min and one additional point (2 points in total) if the heart rate exceeds 94 beats/min. DVT=deep vein thrombosis, PE=pulmonary embolism.

accuracy and clinical usefulness. To test this hypothesis, we compared the performance of the original and the simplified revised Geneva scores in 2 large patient cohorts.

METHODS

Patients

Data from 2 large prospective diagnostic trials that included patients with suspected PE were used and combined for the validation of the simplified revised Geneva score.[3,4] In the first trial (study A), consecutive patients with suspected PE admitted to the emergency department of 3 teaching hospitals (Geneva University Hospital, Geneva, Switzerland; Angers University Hospital, Angers, France; and Hôpital Européen Georges-Pompidou, Paris, France) between August 1st 2002 and November 30th 2003 were eligible for inclusion.[3] The Geneva score was assessed in all patients before further diagnostic testing.[7] In patients with either a low or intermediate probability, plasma D-dimer levels were measured using a quantitative assay (VIDAS D-Dimer Exclusion Test; BioMerieux, Marcy L'Etoile, France). Pulmonary embolism was ruled out in patients with a level below the cut-off value of 500 ng/mL. Patients with a D-dimer level greater than 500 ng/mL as well as patients with high clinical probability underwent proximal venous-compression ultrasonography of the lower limbs and multi-detector row computed tomography (CT). Patients with CT findings indicating PE or patients with respiratory distress in combination with ultrasonography that showed deep venous thrombosis received anticoagulant treatment, whereas such therapy was withheld in patients in whom both test results were normal.

In the second study (study B), the clinical effectiveness of a simplified algorithm using the dichotomized Wells rule, D-dimer tests and CT in patients with suspected PE was evaluated.[4] Only patients from the Leiden University Medical Center who participated in that study were included in the present analysis. Pulmonary embolism was considered to be excluded if the diagnosis of PE was unlikely (Wells score ≤4 points) in combination with a normal quantitative D-dimer test result. When the Wells score was 4 or less in combination with an increased D-dimer value or when the diagnosis of PE was likely (Wells score >4), the diagnosis of PE was established by CT. Patients in both studies were followed for three months. Patients with confirmed venous thromboembolism (VTE) were brought back for reexamination. All other patients were instructed to report any new signs of VTE to their general practitioner or to the emergency department of the participating hospitals. At the end of the three months follow-up period, all patients were interviewed by telephone and were asked to disclose all health-related events since their hospital discharge. The family physician was contacted whenever a possible event was disclosed by the interim history, and charts were reviewed if a patient was readmitted to the hospital for any cause or died during the follow-up period. Recurrent VTE was diagnosed according to standardized criteria.[3,4] Both studies were approved by the Institutional Review

Board of all participating hospitals, and all patients provided written informed consent before they were enrolled.

In study A, D-dimer testing was part of the diagnostic work-up of all patients with either a low or intermediate probability according to the Geneva score. In study B, D-dimer tests were performed only in patients with a Wells score of 4 points or less. This resulted in missing D-dimer data for 69 patients in the low- and intermediate probability group and for 29 patients in the unlikely clinical probability group as assessed by the simplified revised Geneva score.

Assessment of the revised Geneva score

In study A, the data collection form was identical to that used in the derivation study of the original revised Geneva score, allowing retrospective calculation of the simplified revised Geneva score for each patient. In study B, the Wells rule was used for assessing clinical probability. The revised Geneva score comprises 4 variables not included in the Wells rule: age, unilateral lower limb pain, heart rate, and signs of deep venous thrombosis (pain on lower limb deep venous palpation and unilateral edema). The 4 variables absent from the original database were extracted from the medical charts in a prespecified standard way by 2 independent observers after blinding of the diagnosis (PE or no PE) by a third person not involved in the data extraction. Lower limb pain and signs of deep venous thrombosis were routinely recorded in patient charts in the setting of a clinically suspected PE. Therefore, there were no missing data.[10]

In the simplified revised Geneva score, all variables were given 1 point if present (Table 1). Because of the different weights of increasing heart rate in the original score, we attributed 1 point to a heart rate between 75 and 94 beats/min and an additional point for a heart rate of 95 beats/min or more.

Data analysis

Patient characteristics and outcomes of both studies were combined in a single database. Optimal cut-off points for the simplified Geneva score were determined by receiver operating characteristic (ROC) analysis. To account for the existence of both 3-level (low, intermediate, or high clinical probability) and 2-level (PE unlikely or likely) schemes in clinical practice, we set cut-off points for both schemes. Diagnostic accuracy of the simplified revised Geneva score and the revised Geneva score was compared by means of the area under the curve (AUC) in ROC analyses. Contrasting the AUC for the continuous scores was designed to compare the original and simplified rule precisely, using all possible point scores. However, the continuous score is not meant for clinical use. Hence, we additionally compared the 3-level classification scheme of both scores. Lastly, we studied the clinical course of patients with a normal D-dimer result in different clinical probability categories using the simplified revised Geneva score. Statistical analysis was performed by using SPSS software (SPSS for Windows 14.0.2; SPSS Inc, Chicago, Illinois). P-values <0.05 were considered statistically significant.

RESULTS

Patients

Study A included 756 outpatients. They had a mean (± standard deviation) age of 60 (±19) years, 454 were female (60%) and 194 patients (26%) were diagnosed with acute PE. However, owing to missing values mainly for heart rate, the revised Geneva score could not be computed for 7 patients, leaving 749 for the present analysis, including 192 patients with PE (26%). Three hundred patients in study B with suspected PE were included in the present study. These patients were 47 (±16) years old at time of diagnosis, 181 were female (60%) and 289 were outpatients (96%). The overall prevalence of PE in this cohort was 16% (49 patients). Taken as a whole, the complete study population consisted of 1049 patients with a PE prevalence of 23% (241 patients).

Predictive accuracy of the simplified score

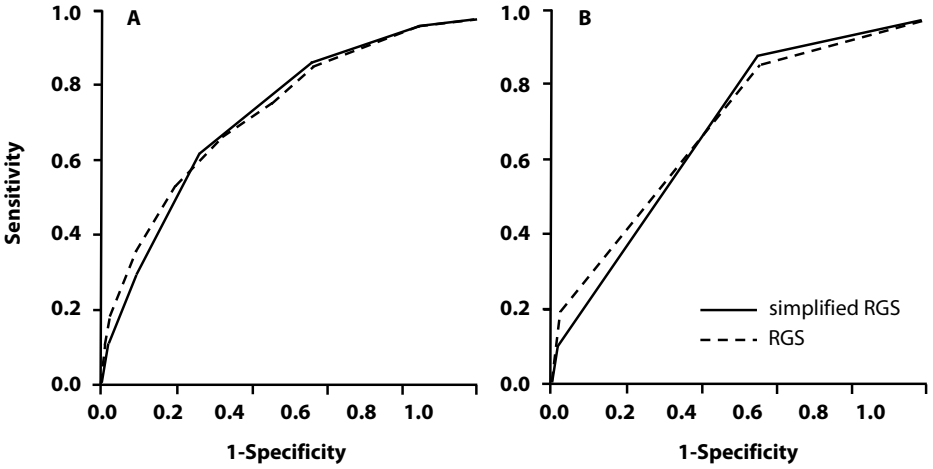
After selecting the optimal cut-off points for the 3-level scheme, a low clinical probability was defined as a score of 0 or 1 point, an intermediate probability as 2 to 4 points, and a high probability as 5 points or more. With the use of these cut-off points, 378 patients (36%) were assigned to the low clinical probability category (prevalence of PE 7.7%, 95% confidence interval [CI] 5.2-11%), 629 patients (60%) to the intermediate clinical probability category (prevalence of PE 29%, 95% CI 26-33%), and 42 patients (4.0%) to the high clinical probability category (prevalence of PE 64%, 95% CI 48-79%; Table 2). The optimal cut-off point for the 2-level scheme was 3 points. Patients with a score of 0 to 2 were categorized as being unlikely to have PE and those with a score of 3 or more as likely to have PE (Table 2); 681 patients (65%) were designated unlikely to have PE (prevalence of PE, 13%, 95% CI 11-16%) and 368 patients (35%) were designated likely to have PE (prevalence of PE 42%, 95% CI 37-47%).

Table 2. Score application in the study population, percentage with PE, and proportions of the population in the 3-level and 2-level clinical probability categories.

	Three-level scheme			Two-level scheme	
	Low	Intermediate	High	PE unlikely	PE likely
Number	378	629	42	681	368
% population	36	60	4.0	65	35
% PE	7.7	29	64	13	42

PE=pulmonary embolism.

We compared the AUC for the revised Geneva score and simplified revised Geneva score (Figures 1A and 1B). The AUC of the continuous score was 0.75 (95% CI 0.71-0.78) for the revised Geneva rule and 0.74 (95% CI 0.70-0.77) for the simplified revised Geneva rule. The AUC of the 3-level classification scheme was 0.70 (95% CI 0.66-0.74) for the revised Geneva score and 0.68 (95% CI 0.64-0.72) for the simplified revised Geneva score.



Figures 1A and 1B. Receiver operating characteristic curves of the continuous revised Geneva score (RGS) and simplified RGS (A) and 3-level categorized RGS and simplified RGS (B).

Utility of the simplified score

Finally, we studied the clinical utility of the simplified revised Geneva score. Flowcharts for both dichotomized and trichotomized rules are shown in Figures 2 and 3. Of all patients in the combined patient population with a normal result of the D-dimer test, in whom PE was excluded (n=361), 2 patients were lost during follow-up and an additional 10 received anticoagulant therapy for reasons other than PE. These patients were excluded from the following analysis. During three months of follow-up, no patient with a low (0/219, 0%; 95% CI 0.0-1.7%) or intermediate (0/130, 0%; 95% CI 0.0-2.8%) clinical probability score by the simplified revised Geneva score and a normal D-dimer result at inclusion was subsequently diagnosed as having VTE (Figure 2). When the 2-level rule was used, no patient with an unlikely clinical probability

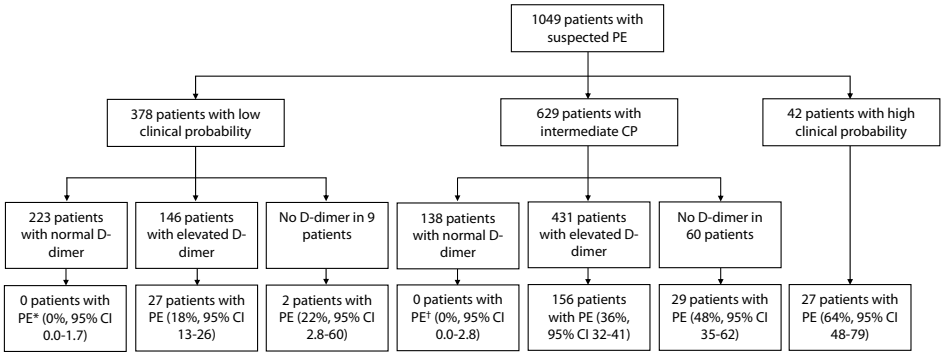


Figure 2. Flowchart of patients showing outcomes by 3-level simplified revised Geneva score. *One patient was lost to follow-up and 3 patients were treated with anticoagulant therapy for reasons other than pulmonary embolism (PE); †One patient was lost to follow-up and 7 patients were treated with anticoagulant therapy for reasons other than PE. CI=confidence interval, CP=clinical probability.

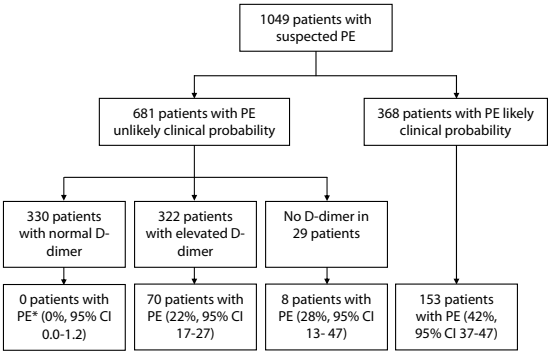


Figure 3. Flowchart of patients showing outcomes with dichotomous use of the simplified revised Geneva score. *Two patients were lost to follow-up and 10 patients were treated with anticoagulant therapy for reasons other than pulmonary embolism (PE). CI indicates confidence interval.

(0/318, 0%; 95% CI 0.0-1.2%) was subsequently diagnosed with venous thromboembolism after the three months follow-up period (Figure 3).

DISCUSSION

This study shows that it is possible to simplify the revised Geneva score without decreasing the diagnostic accuracy of the rule. The distribution of the patient proportions by the simplified revised Geneva score in both trichotomized and dichotomized categories and the prevalence of PE in these categories were comparable to those of the original revised Geneva score as well as to 3 other validated CDRs: the Wells rule, the Geneva score and the rule suggested by Kline and colleagues.[6,7,9,12] The simplified revised Geneva score is clinically useful and might safely rule out PE when combined with a normal D-dimer result using a highly sensitive assay. Indeed, in this cohort, the VTE failure rates were extremely low in patients with normal D-dimer results and a low or intermediate clinical probability (3-level scheme) or a "PE unlikely" assessment (2-level score). Furthermore, the simplified score would likely be easier to compute and may reduce computational errors in clinical practice in busy environments with a heavy workload.

Several studies have shown D-dimer assays to have a high negative predictive value and to be a sensitive but nonspecific marker of PE.[13] However, different sensitivity for several D-dimer assays has been described in the literature.[2,13-15] Less sensitive tests yield a lower negative predictive value for the same pretest probability of PE. Also, the negative predictive value of a normal D-dimer test result diminishes as disease prevalence rises.[16] As a consequence, the proportion of patients with suspected PE in whom D-dimer testing can safely be used to exclude PE depends on both the prevalence of the disease and the sensitivity of the D-dimer assay. This is why we adopted 2 different schemes. Table 3 shows the post-test probability for PE in various combinations of clinical probability categories and D-dimer assays. The upper

Table 3. Post-test probability for acute PE according to the sensitivity of D-dimer assays and clinical probability category as assigned by simplified revised Geneva score.

	Three-level scheme			Two-level scheme	
	Low	Intermediate	High	PE unlikely	PE likely
Prevalence of PE	8%	29%	64%	13%	42%
Posttest PE					
Highly sensitive DD*	1%	3%	12%	1%	5%
Less sensitive DD†	1%	6%	23%	2%	11%
Low sensitivity DD¶	2%	9%	29%	3%	14%

Figures for sensitivity and specificity are extracted from Di Nisio et al.[16] *Sensitivity 97%, specificity 40%; †Sensitivity 90%, specificity 60%; ¶Sensitivity 85%, specificity 65%. PE=pulmonary embolism, DD=D-dimer assay.

limit of the 95% confidence interval of the three months thromboembolic rate after negative pulmonary angiography is 2.7%.[17] Using this percentage as the upper posttest probability limit above which it is no longer safe to rule out PE by the combination of clinical probability and a negative D-dimer result, Table 3 shows that, with a 3-level score, a less sensitive D-dimer assay would exclude PE safely only in low-probability patients, whereas the same assay would still be safe in the patients in whom PE was unlikely by using the 2-level score. For this reason, a less sensitive assay would rule out PE in more patients and therefore be more useful in combination with the dichotomized rule because there are more patients categorized as PE unlikely than in the low clinical probability category. Conversely, the 3-level score would be more useful when a highly sensitive assay is used because it would safely rule out PE in both the low and intermediate probability groups, which would regroup a higher number of patients than the PE unlikely category. In the present study, a highly sensitive quantitative D-dimer assay with a reported sensitivity of 95% to 98% was used, and the outcome of three months follow-up was good in either low- or intermediate probability as well as in the PE unlikely category.[2] However, a physician using the simplified revised Geneva score in combination with a D-dimer assay with a lower sensitivity should probably restrict its use to the low clinical probability category of the 3-level score to exclude PE. The AUC of ROC analysis of the simplified score was similar to that of the original score. Given that the original score assigned very different weights to the individual variables, at least some loss of predictive accuracy would have been expected, and this might therefore seem surprising. Because this is also true for the ROC curve using all the score values and not only 2 cut-off values, this observation is not due to cut-off selection in this particular population.

This study has limitations. We performed a retrospective analysis, which can be subject to various biases. We acknowledge that prospectively studying the clinical utility and outcomes in a new sample would be the best way of testing our hypothesis. Nevertheless, the revised Geneva score could be calculated in more than 99% of patients. Also, the original cohorts prospectively included consecutive patients with minimal loss to follow-up (0.5% in study A and 0.1% in study B). There were some differences in general characteristics between the 2

study populations, i.e. mean age and prevalence of PE. However, the prevalence of PE according to the number of points in the simplified revised Geneva score was similar in the 2 groups (data not shown), which actually adds validity to the simplified score. Finally, by study design, D-dimer results were not available for all patients. Data were missing in 9 patients (2.4%) with low clinical probability, in 60 patients (9.5%) with intermediate clinical probability, and in 29 patients (4.3%) designated as PE unlikely.

In summary, our data indicate that simplification of the revised Geneva score does not decrease the score's diagnostic accuracy or clinical utility. Prospective outcome studies are needed, however, to confirm our findings.

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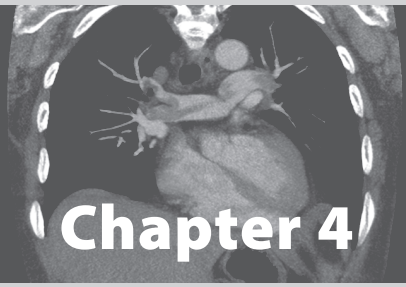

Chapter 4

Safety of ruling out acute pulmonary embolism by normal CT pulmonary angiography in patients with an indication for CT: systematic review and meta-analysis

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ABSTRACT

Introduction

Several outcome studies have ruled out acute pulmonary embolism (PE) by normal computed tomography pulmonary angiography (CTPA). We performed a meta-analysis in order to determine the safety of this strategy in a specific group of patients with a strict indication for CTPA, i.e. 'likely' or 'high' clinical probability for PE, an elevated D-dimer concentration, or both.

Methods

Studies that ruled out PE in patients with a strict indication for CTPA by normal CTPA were searched for in Medline, EMBASE, Web of Science and the Cochrane dataset. Primary endpoint was the occurrence of (fatal) thromboembolic events (VTE) in a three months follow-up period.

Results

Three studies were identified that excluded PE by CTPA alone (2020 patients) and three studies that performed additional bilateral compression ultrasonography (CUS) of the legs after normal CTPA (1069 patients). The pooled incidence of VTE at three months was 1.2% (95% CI 0.8-1.8%) based on a normal CTPA as a sole test and 1.1% (95% CI 0.6-2.0%) based on normal CTPA and negative CUS, resulting in NPVs of 98.8% (95% CI 98.2-99.2%) and 98.9% (95% CI 98.0-99.4%) respectively. Risk of fatal PE did not differ between both diagnostic strategies (0.6% vs. 0.5%).

Conclusion

A normal CTPA alone safely excludes PE in all patients in whom CTPA is required to rule out this disease. There is no need for additional ultrasonography to rule out VTE in these patients.

INTRODUCTION

Computed tomography pulmonary angiography (CTPA) is currently the preferred thoracic imaging test for patients suspected of having acute pulmonary embolism (PE).[1] This is the result of the high negative predictive value (NPV) of CTPA that was shown to range from 98.7 to 99.9%.[2,3] In addition, it has been demonstrated that it is unnecessary to perform additional imaging tests after a normal multi-detector row CTPA before excluding venous thromboembolic disease and withholding anticoagulant therapy.[2,3] However, in these reports, patients with low, intermediate as well as patients with high clinical pretest probability for having PE were selected for CTPA. In several recent studies, it has been reported that acute PE can be ruled without the need for radiological imaging tests in a specific patient population with 'low' or 'unlikely' clinical probability for PE in combination with a normal highly sensitive D-dimer test result.[4-6] Since the NPV of a test is dependent on the incidence of the disease in the tested population, the NPV of CTPA in patients in whom PE can not be ruled out by a clinical decision rule and a D-dimer test, i.e. with 'likely' or 'high' pretest probability for PE or an abnormal D-dimer test result (incidence of PE 37-47%[7]), is likely to be less favorable than the NPV of CTPA in the overall population suspected of having PE (incidence of PE 20-26%[7]). Furthermore, several studies have shown that despite of a negative CTPA, non-symptomatic deep venous thrombosis (DVT) can be identified by compression ultrasonography (CUS) in a small proportion of patients with suspected PE.[4,8,9] Our objective was to perform a systematic review and meta-analysis to determine the safety of excluding acute PE on the basis of a normal CTPA alone for all patients with clinically suspected acute PE and a strict indication for CTPA. In addition, we studied the additional value of CUS after a normal CTPA in this specific patient cohort.

METHODS

Data sources

A literature search was performed to identify all published prospective outcome studies that excluded PE on the basis of a normal CTPA result. Medline, Embase, Web of Science and the Cochrane dataset were searched using predefined search terms. Search criteria included "pulmonary embolism" or "venous thromboembolism" or "venous thrombosis" and "computed tomography" or "spiral CT". Articles published from January 1990 till September 2008 were eligible for this analysis. Papers were not limited to the English language. All references of the included studies were reviewed for potential relevant articles.

Study outcome

Outcome of this meta-analysis was the NPV of CTPA and the safety of withholding anticoagulant therapy based on a normal CTPA result in patients with a strict indication for CTPA, i.e. a

clinical decision rule indicating 'likely' or 'high' probability, an elevated D-dimer concentration, or both. Endpoints were objectively confirmed adverse thrombotic events subsequent to a normal CTPA including all occurrences of venous thromboembolism (VTE), i.e. both DVT and PE, and mortality attributable to PE.

Study selection and inclusion criteria

Mandatory for inclusion was a diagnostic strategy based on a clinical decision rule and a D-dimer test without additional imaging tests prior to CT scanning. In addition to studies that used CTPA as only imaging test, we also included studies that had used CUS of the legs following a normal CTPA to study the additional value of CUS for ruling out VTE. Further criteria for selection were a prospective design, consecutive patient selection, predefined endpoints, clear description of inclusion and exclusion criteria, and a clinical follow-up of more than one month. Two reviewers independently reviewed all identified studies. In case of disagreement, a third reviewer was consulted.

Data abstraction

Data regarding study design, patient characteristics, diagnostic algorithm (clinical decision rule, D-dimer assay and CT modality), follow-up period, completeness of follow-up and endpoints were abstracted by two independent researchers. Guidelines proposed by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group were followed to extract and present the data.[10] Individual study quality was assessed by the following items: patient enrollment, outcome assessment, duration of follow-up, loss to follow-up and funding source.

Statistical analysis

We identified the reported number of objectively confirmed cases of VTE and in addition all deaths attributed to PE for each study. Patients who received anticoagulants for reasons other than VTE and patients who were lost to follow-up were excluded from the analysis. A meta-analysis was performed by pooling the proportions in a fixed effects as well as in a random effects model. Because the criteria for the performance of CTPA in the included studies were comparable, the disease incidence was expected to be similar between the studies. For this reason pooling of the NPV was reasonable. The proportions were weighted according to the inverse of the squared standard error. Shown proportions and confidence intervals (CI) in the text represent a fixed effects model calculated proportion. Studies with CTPA alone and with additional CUS following a normal CTPA were pooled separately. For assessment of heterogeneity, I^2 was calculated for all comparisons.[11] We defined the upper limit of the 95% CI of the fatal and non-fatal three months thromboembolic rate after a normal invasive pulmonary angiography as the cut-off point for the safe exclusion of PE by CTPA, thereby comparing CTPA with the reference standard. For assessment of the effect of the additive use of CUS following a normal CTPA on mortality, the weighted relative risk of fatal PE was calculated. Finally the

sensitivity for both diagnostic strategies was calculated. For statistical analysis SPSS version 16.0 and Comprehensive Meta-Analysis (version 2.0, Biostat, Englewood, New Jersey, USA) were used.

RESULTS

Study selection

The literature search revealed 1075 studies; 1052 studies were excluded after review of title and abstract and 23 studies were identified for more detailed evaluation. After full review, an additional 18 studies were excluded due to a diagnostic algorithm that did not meet our predefined criteria, i.e. no clinical decision rule, D-dimer or CTPA performed, or performance of supplementary imaging tests before the CTPA. Three studies using CTPA without further imaging[5,12,13] and three studies that incorporated CUS after CTPA[4,8,9] were left for inclusion in this meta-analysis. No new articles were identified by reviewing the references of these six studies.

Quality and characteristics of the included studies

All six included studies were of a prospective design with consecutive patient enrolment. The duration of follow-up was three months in all studies and loss to follow-up varied between 0.0% and 1.3% (Table 1). The demographic characteristics of patients in the studies were comparable (Table 2). Mean age varied from 50 to 60 years, the proportion of male gender ranged between 35% and 47% and the majority of patients were outpatients. Different clinical decision rules were used, i.e. the Geneva score, the revised Geneva score, the Wells rule or the Hyers criteria, in two or three level schemes.[14-18] Also, different quantitative D-dimer tests were used: VIDAS D-dimer assay (BioMérieux, Marcy- l'Etoile, France), STA Liatest (Diagnostica Stago, Asnières, France, SimpliRED (Agen Biomedical Limited, Acaccia Ridge, Australia), Tinaquant assay (Roche Diagnostica, Mannheim, Germany) and an immunoturbimetric latex agglutination assay (IL-Test, Instrumentation Laboratory, Lexington, MA). Furthermore, the use of single- or multi-detector row CT modalities varied between the studies. In two studies, patients were randomized between two diagnostic strategies, i.e. CTPA or ventilation perfusion scintigraphy and CTPA or CUS preceding CTPA.[4,12] Only the patients randomized to CTPA were included in this analysis. Overall, the fraction of patients who had an indication for CTPA was 70% (range 35-93%; Table 3). The overall proportion of inconclusive CT scan results was reported to be 1.8% (range 0.9-4.6%). The overall incidence of PE by positive CTPA in these cohorts was 28% (range 18-36%).

Table 1. Study quality assessment.

Study	Study design	Patient enrollment	Outcome assessment	Duration of follow-up (months)	Lost to follow-up (n, %)	Funding source
van Belle[5]	Multicenter	Prospective, consecutive	Radiologist and adjudication committee; blinded	3	4 (0.1)	Unrestricted grants from the participating hospitals
Righini[12]	Multicenter, RCT	Prospective, consecutive	Independent and adjudication committee; blinded	3	1 (0.1)	Grant from the Swiss National Research Foundation, from the Projects Hospitaliers de Recherche Clinique and from Pneumonlogie Développement
Ghanima[13]	Single center	Prospective, consecutive	Independent adjudication committee	3	0 (0)	Grant from the Eastern Norway Regional Health Authory
Anderson 2005[9]	Multicenter	Prospective, consecutive	Laboratory, radiologist and adjudication committee ; blinded	3	11 (1.3)	Grant from Heart and stroke foundation of Nova Scotia
Anderson 2007[4]	Multicenter, RCT	Prospective, consecutive	Radiologists and adjudication committee; blinded	3	7 (1.0)	Grant from the Canadian Institutes of Health Research
Perrier[8]	Multicenter	Prospective, consecutive	Independent adjudication committee	3	4 (1.2)	Grant from the Hirsch Fund of the University of Geneva

RCT=randomized controlled trial, n=number.

Meta-analysis

Three studies were identified that excluded PE in symptomatic patients with an indication for CT-scanning based on a normal CTPA without additional imaging tests. Of all 2020 patients with an initial normal CTPA result, 25 (1.2%, 95% CI 0.80-1.8) were diagnosed with VTE in a three months follow-up period (Tables 3 and 4, Figure 1). Of these, 12 (12/2020; 0.60%, 95% CI 0.40-1.1) were classified as fatal PE. Markedly, only in two of these 12 patients, an autopsy was performed and PE was objectively identified as cause of death. The NPV for symptomatic VTE in three months following a negative CTPA in patients with an indication for CTPA was 98.8% (95% CI 98.2-99.2). In the three studies that included CUS of the legs subsequent to a normal CTPA, 1069 symptomatic patients with an indication for CTPA and eventually a normal CTPA were identified. Twenty-one cases of DVT (21/1069; 2.4%, 95% CI 1.6-3.7) were identified by CUS performed shortly after the CTPA (Tables 3 and 4). During three months follow-up, nine additional patients (9/1048; 1.1%, 95% CI 0.60-2.0) with initially normal CTPA and CUS results were diagnosed with symptomatic VTE. Four of these 1048 patients in whom VTE was excluded and who were not treated with anticoagulants, died (4/1048; 0.50%, 95% CI 0.20-1.1) possibly as a consequence of PE. The NPV for symptomatic VTE in three months after a normal CTPA

Table 2. Patient characteristics of included studies.

Study	Number	Mean age (year ±SD)	Male (n, %)	History of VTE (n, %)	Cancer (n, %)	Surgery, immobilization or trauma (n, %)	Outpatient (n, %)	CDR (2- or 3- level scheme)[¶]	Single/ multi slice CT	D-Dimer assay
van Belle[5]	3306	53 ±18	1409 (43)	480 (15)	476 (14)	610 (19)	2701 (82)	Wells (2)	Single / MSCT	VIDAS / Tinaquant
Righini[12]	901*	60 ±19	410 (46)	121 (14)	72 (8.0)	59 (6.5)[#]	901 (100)	RGS (3)	MSCT	VIDAS
Ghanima[13]	432	58	201 (47)	43 (10)	31 (7.2)	38 (8.8)	432 (100)	Hyers criteria (3)	MSCT	STA-Lia
Anderson 2005[9]	858	50 ±18	300 (35)	77 (9.0)	58 (6.8)	160 (19)	858 (100)	Wells (3)	Single	SimpliRED/IL test[+]
Anderson 2007[4]	694*	53 ±19	259 (37)	64 (9.2)	67 (9.7)	161 (23)[#]	619 (90)	Wells (2)	Single / MSCT	Local practice
Perrier[8]	756	60 ±19	302 (40)	142 (19)	75 (9.9)	146 (19)	756 (100)	GS (3)	MSCT	VIDAS

*Only patients included in the CT-group after randomization; [#]number of patients with recent immobilization not mentioned; [¶]two level scheme: likely/less likely; three level scheme: low, intermediate and high clinical probability; [+]immunoturbimetric latex agglutination assay. CDR=clinical decision rule, VTE=venous thromboembolism, RGS=revised Geneva score, GS=Geneva score, MSCT=multi-detector row computed tomography, n=number, SD=standard deviation.

Table 3. Outcome of negative CT scans of the included studies.

Study	Patients (n)	CTPA performed (n, %)	Inconclusive CTPA result (n, %)	CTPA positive for PE (n, %)	CTPA negative for PE (n, %)	Resulting study population† (n)	VTE in follow-up (by immediate CUS according to protocol/ symptomatic)	Fatal PE (certain/ possible) (n/n)
CTPA alone								
van Belle[5]	3306	2249 (68)	20 (0.9)	647 (30)	1505 (67)	1435	-/18	2/5
Righini[12]	838#	558 (67)	15 (2.7)	179 (32)	364 (65)	364*	-/5	0/3
Ghanima[13]	432#	329 (76)	15 (4.6)	93 (28)	221 (67)	221	-/2	0/2
CTPA followed by CUS								
Anderson 2005[9]	858	300 (35)+	8¥ (1.7)	59 (20)	241 (80)	241‡	11/0	0/0
Anderson 2007[4]	694	646 (93)	10 (1.5)	115 (18)	531 (82)	531	7/4	0/2
Perrier[8]	756#	524 (69)	13 (2.5)	187 (36)	324 (62)	297	3/5	0/2

*In the follow-up of the complete study population without PE, one patient was lost to follow-up and 30 patients used anticoagulant therapy for other reasons than PE (the fraction of the latter patients in the normal CTPA cohort was not reported); #this number does not include study patients in case of protocol violation, lost to follow-up or use of oral anticoagulants for other reasons than VTE; +only CT scans performed in case of either 'high' clinical probability or elevated D-dimer test in combination with 'low' or 'intermediate' clinical probability; ¥number of inconclusive CTPA results for all performed CT scans in this study (n=467); †total number of patients with normal CTPA, complete follow-up and without anticoagulant therapy; ‡of the total study population, PE was ruled out by other means than by CTPA in 26 patients (CT indicated but not performed or inconclusive CTPA result followed by additional imaging; the fraction of the latter patients in the normal CTPA cohort was not reported). PE=pulmonary embolism, VTE=venous thromboembolism, CUS=compression ultrasonography.

		Event rate	Lower limit	Upper limit	0.0 5.0	Relative weight
CTPA alone	van Belle[5]	1.3	0.8	2.0		72.00
	Righini[12]	1.4	0.6	3.3		19.98
	Ghanima[13]	0.9	0.2	3.5		8.03
	Fixed	**1.2**	**0.8**	**1.8**		
	Random	**1.2**	**0.8**	**1.8**		
CTPA followed by CUS	Anderson 2005[9]	0.2	0.0	3.4		25.00
	Anderson 2007[4]	0.8	0.3	2.0		33.51
	Perrier[8]	1.7	0.7	4.0		41.49
	Fixed	**1.1**	**0.6**	**2.1**		
	Random	**1.0**	**0.4**	**2.3**		

Figure 1. Pooled proportions (fixed as well as random effects model) of the confirmed venous thromboembolism event rate after a normal CTPA and after a normal computed tomography pulmonary angiography (CTPA) followed by a negative compression ultrasonography (CUS) of the legs.

followed by CUS was 98.9% (95% CI 98.0-99.4). Therefore, the NPV of CTPA alone was equal to the NPV of CTPA followed by CUS (98.8% vs. 98.9%). The pooled proportions of fatal PE in follow-up were comparable as well (0.6% and 0.5%, Table 4), indicating a relative risk of 1.2. The use of a random effects model did not materially influences the study results (Table 4). The pooled sensitivity for detecting PE by CTPA alone was 97.3% (95% CI 96.1-98.2), the sensitivity for detecting PE of CTPA combined with additional CUS was 97.4% (95% CI 95.1-98.6).

Table 4. Random and fixed model proportions of study endpoints.

Model	VTE in FU after normal CTPA without CUS	Fatal PE in FU after normal CTPA without CUS	Positive echo directly subsequent to normal CTPA followed by CUS	VTE in FU after normal CTPA and negative CUS	Fatal PE in FU after normal CTPA and negative CUS
Fixed	1.2	0.6	2.4	1.1	0.5
95% CI	0.8-1.8	0.4-1.1	1.6-3.7	0.6-2.0	0.2-1.1
Random	1.2	0.6	2.0	1.0	0.5
95% CI	0.8-1.8	0.4-1.1	0.7-5.2	0.4-2.3	0.2-1.1
I^2	0.000	0.000	78.98	29.35	0.000

PE=pulmonary embolism, VTE=venous thromboembolism, FU=follow-up, CI=confidence interval, CTPA=computed tomography pulmonary angiography, CUS=compression ultrasonography.

DISCUSSION

The main finding of this study is that the NVP of CTPA to rule out PE in a patient population with an indication for CT scanning is 98.8% (95% CI 98.2-99.2). Furthermore, the three months fatal recurrent risk after a normal CTPA in this particular patient population is very low (0.6%, 95% CI 0.40-1.1). An invasive pulmonary angiography is the reference standard for the diagnosis of PE.[1] The upper limit of the 95% confidence interval of the three months VTE rate after normal

pulmonary angiography is 2.7%.[19] Using this fraction as the upper posttest probability limit above which it is no longer safe to rule out PE by a diagnostic test, our data show that a normal CTPA alone is a valid criterion for the safe exclusion of acute PE, even in this specific population. Furthermore, the three months PE associated mortality rate after a normal invasive pulmonary angiography is 0.3% (95% CI 0.02-0.7%) which is comparable with the pooled mortality rate observed in our study (0.6%, 95% CI 0.40-1.1).[19] Our analysis of the three studies that included CUS after a normal CTPA allowed us to test the additional value of CUS for ruling out VTE. In these three studies, the proportion of patients with CUS proved DVT in spite of a normal CTPA result was low (2.4%). Furthermore, the NPV for symptomatic VTE in three months of follow-up of CTPA alone was comparable to the NPV of CTPA followed by CUS (98.8% versus 98.9%). In accordance with this finding, the VTE-related mortality risk was not different between both diagnostic strategies.

Some additional observations require comment. We intended to study the performance of CTPA in all patients in whom this imaging modality is required to rule out PE. For this reason, our study patients had an overall moderate probability for having PE (28%). It could be reasoned that the NPV of the CTPA is lower in more selected patients with a higher clinical probability than in the population that we studied in this report. Of note, in the recent guidelines of the European Society of Cardiology on the diagnosis of acute PE, the safe exclusion of PE in a high clinical probability population by a normal CTPA result alone is being debated because of possible false negative CTPA results.[1] Nonetheless, no current evidence exists that additional imaging, e.g. CUS or ventilation perfusion scintigraphy, would prevent VTE in a three months follow-up period in this small selected group of patients. In our analysis it was not possible to study this issue in more detail, since none of the included studies had reported the incidence of symptomatic VTE after normal CTPA result alone in a selection of high probability patients only. In addition, the distinction of patients with a high clinical probability for PE is clinically unpractical since this would imply a different diagnostic strategy for the same (normal) CTPA result, as it would be unpractical and unnecessary to distinguish patients with a 'low' from patients with a 'less likely' clinical probability for the interpretation of a normal D-dimer test result. Furthermore, the best threshold, i.e. clinical decision rule or D-dimer concentration cut-off points, for defining a high risk population in whom negative CTPA does not safely rule out PE is unknown.

We consider our results to be representative because our findings are based on a pooled analysis of a large cohort of over 3000 patients. Second, the analyzed studies were of high quality with a prospective design, including consecutive patients and using standardized diagnostic tests. Third, follow-up time was consistent in all studies (three months) and all endpoints were well defined and confirmed by objective tests by predefined criteria. Finally, demographic characteristics of the patients were comparable between all included studies. Even so, this meta-analysis has some limitations. Inherent to the design of a meta-analysis, pooling observational or non-randomized data could lead to biases. Specifically for our analysis, different clinical decision rules, D-dimer assays and CT-scanners were used between the included studies.

The distinct use of the clinical decision rules, with either 2- (PE 'likely' or 'unlikely') or 3-level schemes ('low', 'intermediate' or 'high' probability of PE), resulted in differences in the fraction of patients who were eligible for CTPA without the need for D-dimer testing. Nevertheless, quantitative, highly sensitive D-dimer tests were used in all 6 included studies and all patients with an abnormal D-dime test result underwent CTPA. Thus, the different use of clinical decision rules did not affect the overall proportion of patients that was finally selected for CTPA. Also, we could not correct for differences between the performances of single- and multi-detector row CT scanners. In addition, all included studies reported a low number of inconclusive CTPA results (1.8%). We excluded these cases from our analysis. Finally, by study design, we could not objectively assess whether the reported VTE related mortality was actually caused by acute PE. Definite cause of death was only determined by autopsy in 11% of the fatal cases. As a consequence, our mortality rates are likely to be overestimated.

In summary, the NPV and safety of excluding acute PE in patients with an indication for CTPA, i.e. 'likely' or 'high' clinical probability, an elevated D-dimer concentration or both, by a normal CTPA without further imaging tests is comparable to the NPV and safety of a normal invasive pulmonary angiography. Furthermore, a strategy including CUS of the legs following a normal CTPA did not improve its diagnostic performance. The clinical implication of our findings is that anticoagulant therapy can safely be withheld in all patients with suspected PE after using CDR and D-dimer testing, and a normal CTPA. In our view, there is no need for additional CUS of the legs to rule out VTE in these patients.

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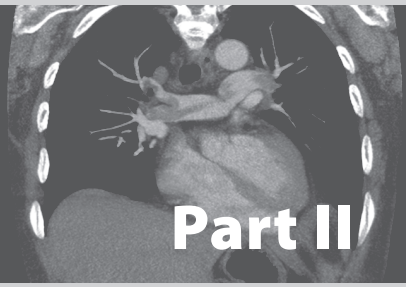
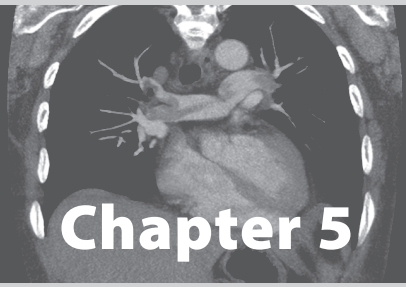


Part II

Short term clinical outcome after acute pulmonary embolism



Chapter 5

Brain-type natriuretic peptide levels in the prediction of adverse outcome in patients with pulmonary embolism: systematic review and meta-analysis

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ABSTRACT

Background

The potential role of elevated brain-type natriuretic peptides (BNP) in the differentiation of patients suffering from acute pulmonary embolism (PE) at risk for adverse clinical outcome has not been fully established.

Methods

Articles reporting on studies that evaluated the risk of adverse outcome in patients with PE and elevated BNP or N-terminal-pro-BNP (NT-pro-BNP) levels were abstracted from Medline and EMBASE. Information on study design, patient and assay characteristics as well as clinical outcome was extracted. Primary endpoints were overall mortality and a predefined composite outcome of adverse clinical events.

Results

Data from 13 studies were included. In 51% (576/1132) of the patients, BNP or NT–pro-BNP levels were increased. Elevated levels of BNP or NT-pro-BNP were significantly associated with right ventricular dysfunction (odds ratio [OR] 39; 95% confidence interval [CI] 17-89). Patients with high BNP or NT–pro-BNP concentration were at higher risk of complicated in-hospital course (OR 6.8; 95% CI 4.4-10) and 30-day mortality (OR 7.6; 95% CI 3.4-17). Patients with a high BNP or NT-pro-BNP had a 10% risk of dying (68/671; 95% CI 8.0-13%), whereas 23% (209/909; 95% CI 20-26%) had an adverse clinical outcome.

Conclusions

High concentrations of BNP or NT-pro-BNP distinguish patients with PE at higher risk of complicated in-hospital course and death from those with low BNP levels. Increased BNP or NT–pro-BNP concentrations alone, however, do not justify more invasive treatment regimens.

INTRODUCTION

Right ventricular dysfunction on echocardiography is a common clinical finding in patients with acute pulmonary embolism (PE) and predicts poor outcome.[1-3] Prognostic stratification after measuring right ventricular function in hemodynamically stable patients with acute PE can potentially be used for making treatment decisions: patients identified with a low risk of complicated outcome may be eligible for outpatient management whereas high risk patients may benefit from more aggressive treatment.[1,2]

Several cardiac biomarkers have emerged as indicator of right ventricular dysfunction and predictor of clinical outcome in patients with acute PE. A recent meta-analysis demonstrated that elevated Troponin levels identify patients with PE at high risk of short-term death and adverse outcome.[4] Brain-type natriuretic peptide (BNP) is also a marker of ventricular dysfunction. This hormone is released in response to myocyte stretch. It is synthesized as an inactive prohormone (pro-BNP) that is split into the active hormone BNP and the inactive N-terminal fragment (NT–pro-BNP).[5] Several prospective studies have been performed to identify the potential role of either BNP or NT–pro-BNP in the risk stratification of patients with PE.[6-18] However, reported studies have limited patient numbers, used different cut-off points and involved different clinical endpoints. Therefore, we performed a meta-analysis of studies in patients with acute PE with the aim of evaluating the predictive value of elevated levels of BNP or NT–pro-BNP for clinical outcome after PE.

METHODS

Data sources

A literature search was performed to identify all published prospective studies on BNP or NT–pro-BNP levels and clinical outcome in patients with acute PE. Medline and EMBASE were searched using predefined search terms between January 1980 and October 2007. Search criteria included "pulmonary embolism" and "pro–brain natriuretic peptide" or "brain natriuretic peptide" or "natriuretic peptide." Also, by searching the reference lists of all established studies, the researchers aimed to identify additional relevant articles. Articles were not limited to the English language. Only complete articles were applicable for this analysis.

Study outcome

Objectively adjudicated short-term adverse clinical events were used as a primary outcome of this meta-analysis. Adverse clinical outcome was defined as the occurrence of any of the following: death, cardiopulmonary resuscitation, mechanical ventilation, use of vasopressors, thrombolysis, thrombosuction, open surgical embolectomy or admission to the intensive care unit. Right ventricular dysfunction was used as secondary endpoint.

Study selection and data extraction

Two independent researchers performed the study selection. In case of disagreements, a third researcher was consulted. Criteria for selection were as follows: prospective design, consecutive inclusion of patients, clear description of inclusion and exclusion criteria, objective criteria for diagnosis of PE, predefined endpoints, standardized treatment and the possibility of creating a 2 by 2 table based on BNP or NT–pro-BNP levels and clinical endpoints. Study sample size was not an eligibility criterion. Objective criteria for PE were positive findings on computed tomography (CT) or conventional pulmonary angiography, high-probability ventilation perfusion scintigraphy, or clinical suspicion of PE in combination with ultrasonography proven deep venous thrombosis. This latter criterion is supported by the findings of Le Gal and colleagues who recently described that a positive compression ultrasonography of the lower limb veins is highly predictive of PE on CT in suspected patients.[19] Data regarding patient characteristics, exclusion criteria, diagnostic criteria for PE, severity of PE (inclusion of hemodynamically unstable patients and use of thrombolytic therapy), completeness of follow-up, immunoassay, timing of sampling, cut-off level, follow-up period and endpoints were abstracted.

Statistical Analysis

Data were entered in Review Manager (version 4.2 for Windows; The Nordic Cochrane Center, 7 2003, Copenhagen, Denmark). Individual and pooled odds ratios (OR) were calculated to assess the relation between elevated BNP or NT–pro-BNP levels and clinical outcome. Mantel-Haenszel methods for combining trials were used for weighting the studies. Cochran's Chi-Square test and the I^2 test for heterogeneity were used to assess interstudy heterogeneity. The Chi-Square test assesses whether observed differences in results are compatible with chance alone. The I^2 describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error. Statistically significant heterogeneity was considered present at Chi-Square $p<0.10$ and $I^2>50\%$.

RESULTS

Study selection

After the literature search, 124 potentially relevant studies were identified. Articles were excluded by review of title and abstract in case of review articles (48), animal studies (2), case reports (5), editorials, letters or author replies (13), studies not covering the clinical course of PE (6) and if the article concerned studies on other diseases than PE (17). After full review, an additional 20 studies were excluded because our predefined endpoints were not reported (17) or cut-off points were not mentioned (3). The remaining 13 studies met our criteria and were included in this meta-analysis.[6-18]

Characteristics of included studies

Demographic characteristics of the patients were comparable between all included studies (Table 1). Mean age of the patients varied between 53 and 75 years; the proportion of females ranged from 36 to 74%. In most patients, the diagnosis of PE was confirmed by CT, high-probability ventilation perfusion scintigraphy or pulmonary angiography. In three studies, hemodynamically unstable patients were excluded.[7,11,17] Noticeably, in two of these latter studies, some patients received thrombolytic therapy during their hospital stay.[7,11] Two included studies reported on partially overlapping patient cohorts.[16,18] Because one of these studies used BNP[16] and the other NT-pro-BNP[18] levels as an outcome parameter, both studies could be incorporated into subgroup analyses based on type of BNP testing.

Assays and cut-off points

As shown in Table 1, all studies reporting NT-pro-BNP levels used a Roche analyzer (two types: Elecsys 2010 analyzer, Meylan France; electro-chemiluminescence method-ECLIA, Roche Diagnostics GmbH, Mannheim, Germany), with three different cut-off levels, varying from 500 to 1000 pg/mL. In the BNP studies, two assays with four different cut-off levels varying between 75 and 100 pg/mL were used. In all included studies, the timing of sampling was comparable. Cut-off levels were not predefined in 10 studies. In these articles, receiver operating characteristic (ROC) analyses were performed to retrospectively determine optimal cut-off values with regard to complicated PE. Normal levels are defined as levels beneath or equal to the cut-off point.

Clinical outcome

Overall, in 51% (576/1132) of the patients, the assays showed elevated plasma concentrations of BNP or NT-pro-BNP. Data on overall mortality were reported in four studies using BNP[10,11,14,17] and four studies using NT–pro-BNP.[8,12,13,15] In the BNP cohort, 17 of 123 patients (14%; 95% confidence interval [CI] 8.3–21%) with elevated BNP levels died compared with 3 of 138 (2.2%; 95% CI 0.45–6.2%) of those with normal BNP levels. This resulted in an overall OR for death of 6.5 (95% CI 2.0–21; Figure 1). One study had a follow-up of three months[17], as compared with the other three, which had only in-hospital follow-up. If this single study was left out of the analysis, overall OR decreased to 3.3 (95% CI 0.6–18). In the NT-pro-BNP cohort, 46 of 250 patients (18%; 95% CI 14-24%) with elevated NT–pro-BNP levels died in comparison with 2 of 160 (1.3%; 95% CI 0.15–4.4%) of those with normal NT–pro-BNP levels; OR for death was 8.7 (95% CI 2.8–27%; Figure 1). Numbers on PE-related mortality were only available in three studies.[11,13,17] Because follow-up time was dissimilar between these studies and not all mortality cases were adjudicated by an independent, blinded committee to determine the cause of death, we could not include PE-related mortality as an outcome of this meta-analysis.

Ten studies provided data on adverse clinical outcome[6,8-13,15,16,18] of which six had NT-pro-BNP levels as an outcome parameter.[6,8,12,13,15,18] Overall, criteria for adverse clinical outcome were comparable throughout all studies. In the BNP study group, 47 of 128 (37%; 95% CI

Table 1. Characteristics of included studies.

Marker	Ref	n	Female (%)	Age*	Assay†	Timing of sampling	Cut-off	Follow-up	PE diagnosis	Hemodynamic instability¥	Thrombolysis (n, %)
NT-pro-BNP	6	60	60	72 ±15	Roche, Elecsys 2010 analyzer	Admission	1000pg/mL§	In hospital	PA, V/Q, ultrasonography∂	Yes	1 (1.7)
	8	107	63	61 ±6	Roche, Elecsys 2010 analyzer	Admission, 4h, 8h, 24h	1000pg/mL	30 days	PA, V/Q, ultrasonography∂	Yes	–¤
	12	124	60	60 ±18	Roche, Elecsys 2010 analyzer	Admission, 4h, 8h, 24h	1000pg/mL	In hospital	PA, V/Q, ultrasonography∂	Yes	12 (11)
	13	100	65	63 ±18	Roche, ECLIA	Admission	600pg/mL	40 days	PA, V/Q	Yes	7 (7.0)
	15	79	63	63 ±17	Roche, Elecsys 2010 analyzer	Admission	600pg/mL	In hospital	PA, V/Q	Yes	8 (10)
	18	73	41	61 ±18	Roche, Elecsys 2010 analyzer	Admission	500pg/mL	In hospital	PA, V/Q	Yes	10 (14)
BNP	7	67	41	64 ±17	Biosite Diagnostics, Triage	Admission	100 pg/mL	NA‡	CT, V/Q	No	6 (9.0)
	9	181	58	53 ±17	Biosite Diagnostics, Triage	Admission	90pg/mL§	6 months	PA, V/Q	Yes	13 (22)
	10	51	65	79 ±9	Biosite Diagnostics, Triage	Admission	100 pg/mL	In hospital	PA, V/Q, ultrasonography∂	Yes	0 (0)
	11	61	74	75 ±14	Biosite Diagnostics, Triage	Admission	89 pg/mL	In hospital	PA, pulmonary angiography	No	7 (11)
	14	46	36	57 ±19	Biosite Diagnostics, Triage	Admission	90 pg/mL	In hospital	PA, V/Q, echocardiography∆	Yes	22 (48)
	16	73	41	61 ±18	Biosite Diagnostics, Triage	Within 4 hours	90pg/mL§	In hospital	PA, V/Q, embolectomy	Yes	6 (8.2)
	17	110	-¶	58 ±18	Immuno radiometric assay, Shionoria	Admission	75 pg/mL	3 months	PA, V/Q, ultrasonography	No	0 (0)

*Mean ±SD; †manufacturer and kind of assay (all were quantitative assays); ‡not applicable: endpoint was right ventricular dysfunction at time of diagnosis; ¶information was not provided; §predefined cut-off point; ∂typical clinical presentation and positive ultrasonography of lower limbs; ∆typical presentation and suggestive echocardiography; ¤specific information was not provided; ¥patients with hemodynamic instability were eligible for the study. PA=computed tomography or conventional pulmonary angiography, V/Q=ventilation perfusion scintigraphy, PE=pulmonary embolism, SD=standard deviation, n=number.

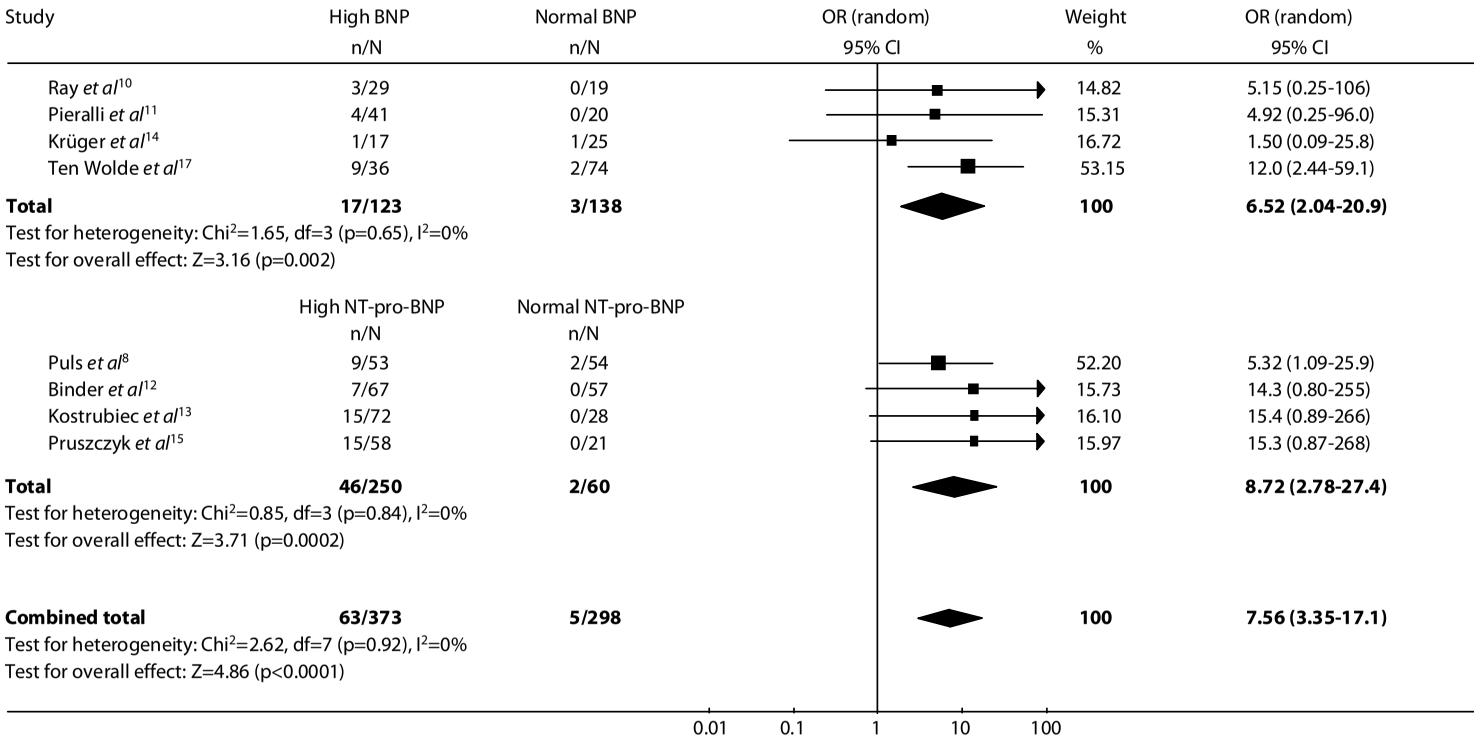

Figure 1. Odds ratio (OR) for overall mortality based on elevated BNP or NT–pro-BNP levels. Different cut-off points were used for different studies; Mantel-Haenszel methods for combining trials were used for weighting the studies. CI indicates confidence interval.

28-46%) patients with elevated BNP levels had adverse advents during follow-up in comparison with 28 of 208 (13%; 95% CI 9.1-19%) patients with normal plasma concentrations. High BNP levels were associated with a higher risk of occurrence of adverse clinical events (OR 6.3; 95% CI 3.6–11; Figure 2). This OR was even higher (9.5; 95% CI 3.5-25) after exclusion of one study with six months of follow-up[9], thereby limiting the outcome to in-hospital clinical course. Of the 318 patients with elevated NT-pro-BNP levels, 102 experienced short-term adverse events (32%; 95% CI 27-38%) as compared with 12 of 225 (5.3%; 95% CI 2.8-9.1%) patients with normal NT-pro-BNP levels. Patients with high NT-pro-BNP serum concentration were at higher risk of complicated in-hospital course compared with patients with normal levels (OR 7.5; 95% CI 3.8-15; Figure 2). Pooled data of all assays showed elevated BNP or NT-pro-BNP levels in 52% of the patients with a risk of 23% (209/909; 95% CI 20–26%) and an OR of 6.8 (95% CI 4.4-10) toward complicated clinical course.

Right ventricular dysfunction

Data on right ventricular dysfunction were reported in six studies (Figure 3). Four studies were evaluating BNP (243 patients)[7,11,14,16] and two studies evaluated NT–pro-BNP levels (197 patients).[12,18] The incidence of right ventricular dysfunction was 85% (116/137; 95% CI 78-90%) and 12% (13/106; 95% CI 6.7-20%) in patients with and without elevated BNP levels respectively. A positive association was found between increased concentration of BNP and the presence of right ventricular dysfunction (OR 81; 95% CI 27-238). In the NT-pro-BNP studies, the incidence of right ventricular dysfunction was 45% (49/109; 95% CI 35-55%) in patients with elevated NT-pro-BNP levels compared with 4.5% (4/88; 95% CI 1.3-11%) in patients with normal NT-pro-BNP levels. Elevated NT-pro-BNP levels were associated with the presence of right ventricular dysfunction (OR 17; 95% CI 5.7–49). Pooled data of all assays revealed a combined OR of 39 (95% CI 17-89).

DISCUSSION

This meta-analysis demonstrates a significant relation between high levels of BNP or NT-pro-BNP and deterioration of clinical condition in patients with acute PE. This is physiologically plausible because BNP is released in reaction to right ventricular stress, which has been shown to predict a non-benign course in patients with PE.[1-3] This latter relation is also demonstrated in this analysis: we found a very strong correlation between increased levels of BNP or NT-pro-BNP and right ventricular dysfunction on echocardiography (Figure 3).

There are some points for discussion if BNP or NT-pro-BNP levels would be incorporated in clinical risk stratification and treatment strategies for patients with acute PE. First, timing of blood sampling has consequences for the established BNP concentration. The BNP pro-hormone (pro-BNP) in normal ventricular myocytes is not stored to a significant amount. As a consequence, it takes several hours for the plasma natriuretic peptide levels to increase after

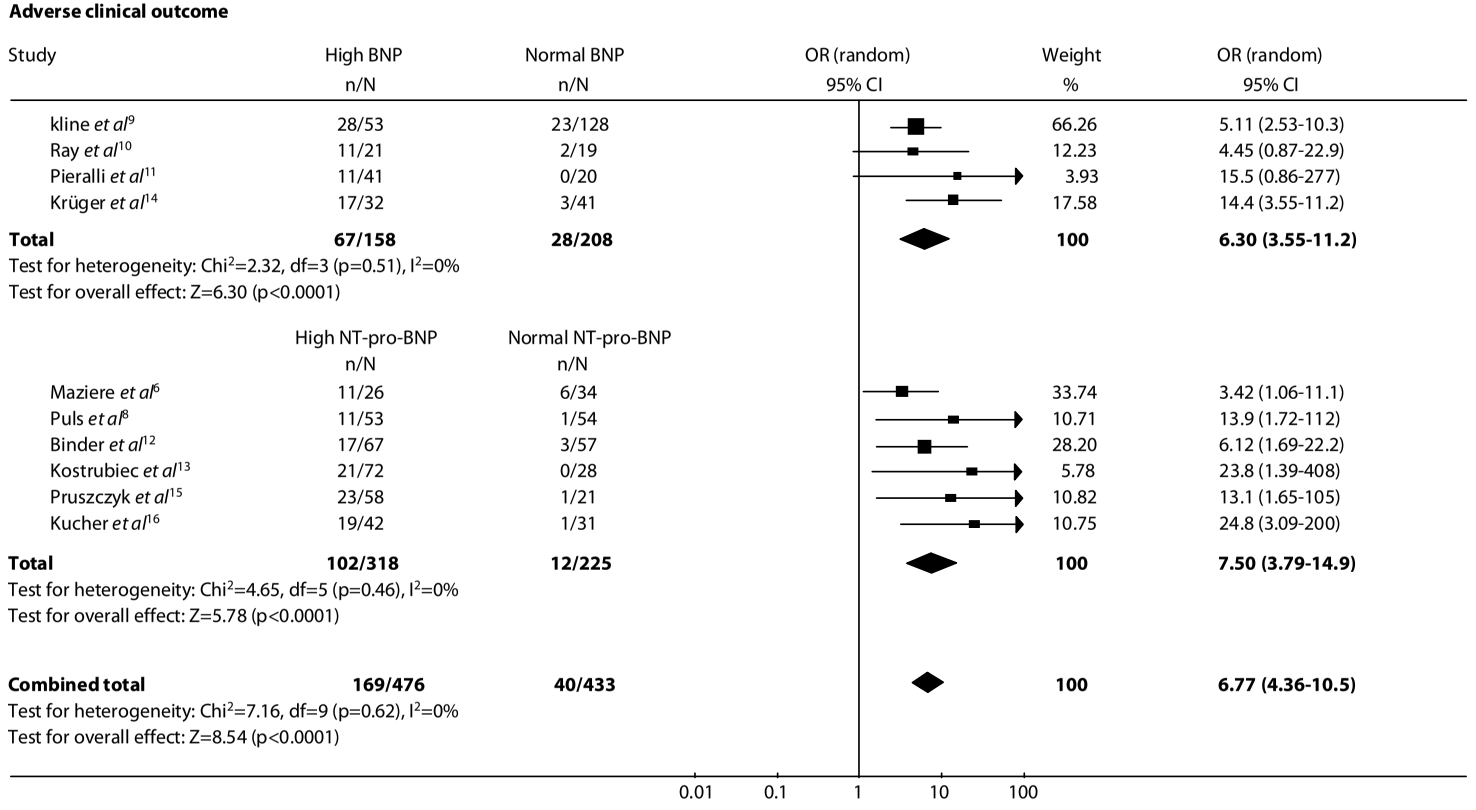

Figure 2. Odds ratio (OR) for adverse clinical outcome based on elevated BNP or NT–pro-BNP levels. Different cut-off points were used for different studies; Mantel-Haenszel methods for combining trials were used for weighting the studies. CI indicates confidence interval.

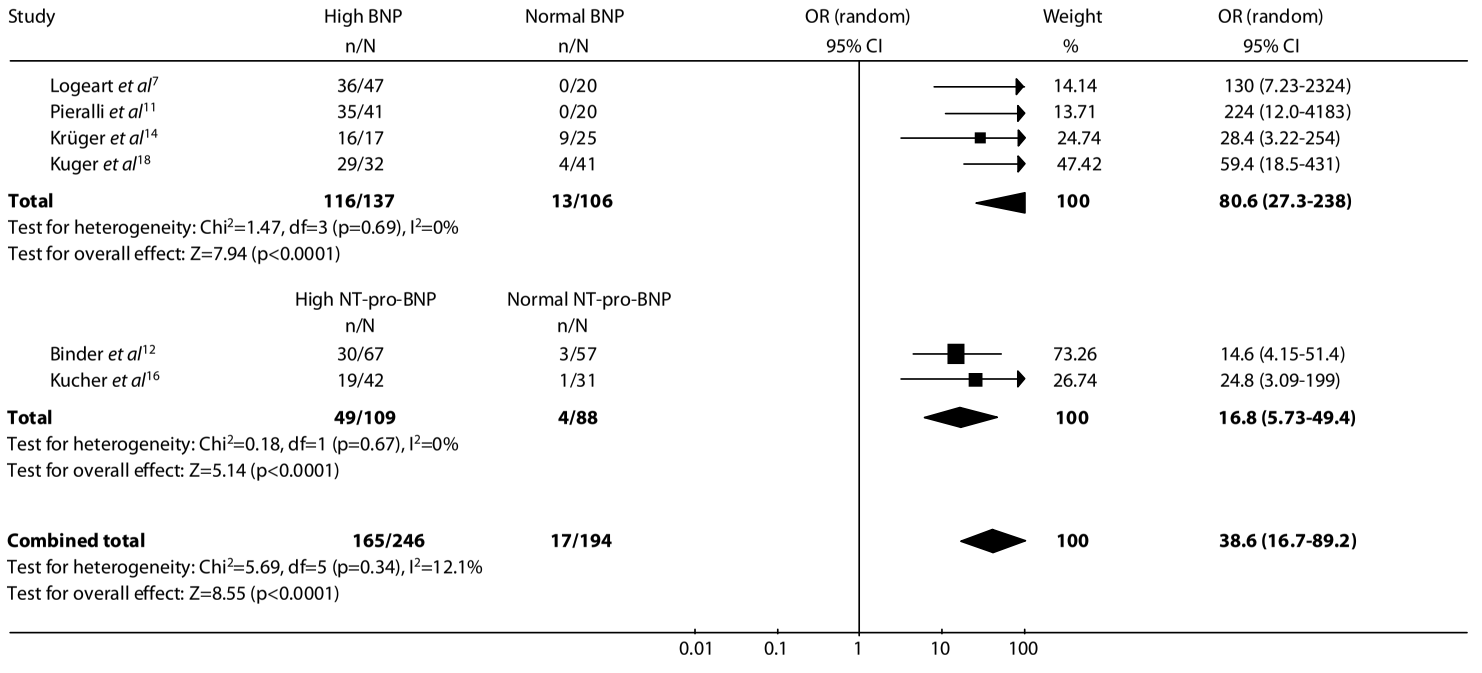

Figure 3. Odds ratio (OR) for right ventricular dysfunction on echocardiography based on elevated BNP or NT–pro-BNP levels. Different cut-off points were used for different studies; Mantel-Haenszel methods for combining trials were used for weighting the studies. CI indicates confidence interval.

the onset of acute myocardial stretch.[20] A very recent onset of complaints could therefore result in false-negative BNP or NT–pro-BNP test results. Second, many different cut-off levels for BNP or NT–pro-BNP are proposed in the literature.[21,22] The variation may be related to patient selection, sex, and age.[22] Nonetheless, despite the different cut-off levels and different assays, the prognostic value of both NT–pro-BNP and BNP was consistent in all included studies.

What are the potential implications of our findings? First, normal levels of BNP have a high negative predictive value for unfavorable clinical outcome. Therefore, patients with normal levels of BNP or NT-pro-BNP have low risks for death as well as for hemodynamic deterioration resulting in any adverse events. Conversely, elevated concentrations of B-type natriuretic peptides are a non-specific finding occurring in more than half of the patients. An explanation for this phenomenon is the elevation of natriuretic peptides in a multitude of other conditions, including preexisting left ventricular dysfunction, older age, renal impairment and chronic lung disease.[23] The combination of BNP with other clinical risk factors for adverse outcome may improve sensitivity and positive predictive value for clinical deterioration. Such algorithms for risk stratification would be clinically useful if they were able to identify patients eligible for outpatient management or for standard or intensive in-hospital treatment. Proposals for such algorithms including markers or biomarkers of right ventricular function (e.g. BNP or NT–pro-BNP, Troponin, Growth Differentiation Factor-15 or heart-type fatty acid-binding protein) have been made but not yet validated prospectively in clinical outcome studies.[4,8,12,13,24,25] Future studies are required to determine the clinical benefits of more aggressive treatments in patients with adverse prognosis as identified by these risk stratifications and less intensive treatment, including out of hospital treatment, in patients with normal values of BNP.

This meta-analysis has limitations. First, included studies used different assays with different retrospectively calculated cut-off points. Second, duration of follow-up and definitions of endpoints varied among the studies. In addition, most studies did not mention completeness of follow-up. Nonetheless, we have included a large cohort of prospectively followed patients and our analysis showed no evidence of heterogeneity between the outcomes of the incorporated studies. Third, the relative risk for mortality is not adjusted for confounding factors, thus part of the effect ascribed to high BNP values may be related to clinical conditions associated with PE. Fourth, we could not determine the ideal cut-off for the two BNP tests because we did not retrieve the raw data of the included studies to perform ROC and other analyses. Finally, in the included studies, it is not stated whether thrombolytic therapy or intensive care unit admission was the result of the clinical condition or a high BNP or NT-pro-BNP value.

In summary, elevated levels of BNP or NT-pro-BNP are indicators of right ventricular dysfunction in patients with acute PE and strong risk factors for short term mortality as well as for overall short term complicated clinical outcome. It remains to be demonstrated whether it could play a role in risk stratification algorithms identifying patients who could benefit from differentiated forms of therapy, of which thrombolytic therapy and home treatment are two poles of the spectrum.

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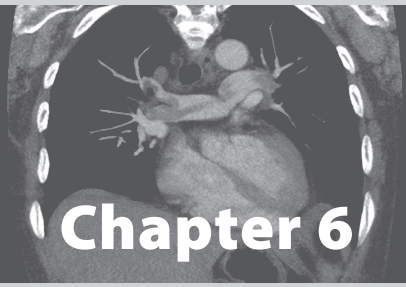

Chapter 6

Comparison of CT assessed right ventricular size and cardiac biomarkers for predicting short term clinical outcome in normotensive patients suspected for having acute pulmonary embolism

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†Equally contributed

J Thromb Haemost; in revision

ABSTRACT

Purpose

To compare the clinical utility of right ventricular enlargement assessed by multi-detector row computed tomography (CT) and elevation of cardiac biomarkers for predicting adverse outcome after acute pulmonary embolism (PE).

Methods

We included 113 consecutive normotensive patients with CT pulmonary angiography (CTPA) proven PE and 226 consecutive patients in whom PE was suspected but ruled out. The following predictors of complicated clinical course were studied: right/left ventricular ratios (RV/LV-ratios) on axial and reconstructed 4-chamber (4-CH) CT-views >1.0, D-dimer >3000 pg/mL FEU, Troponin-T >0.09 ng/mL and NT-pro-BNP >600 pg/mL.

Results

All predictors were associated with adverse outcome in patients with and without PE, with odds ratios of 3.7 (axial), 9.0 (4-CH), 3.5 (D-dimer), 6.3 (Troponin-T) and 31 (NT-pro-BNP) for patients with PE. Area under the receiver operator characteristic curve for PE patients of NT-pro-BNP was higher (0.85; 95% CI 0.73-0.97) than that of axial RV/LV-ratio (0.64, 95% CI 0.47-0.81; p=0.14), 4-CH RV/LV-ratio (0.64, 95% CI 0.48-0.81; p=0.15), D-dimer (0.64, 95% CI 0.46-0.82; p=0.048) and Troponin-T (0.62, 95% CI 0.41-0.82; p=0.037). 72% of patients had a NT-pro-BNP ≤600 pg/mL with a negative predictive value (NPV) of 99%. 4-CH RV/LV-ratio <1 had equally excellent NPV (98%), but less patients were categorized as having low risk for complications (43%; p<0.001).

Conclusion

NT-pro-BNP had the highest discriminative power and clinical utility as predictor of adverse events after PE in our study population. Future studies should confirm these findings and evaluate the safety of home-treatment based on low NT-pro-BNP levels or RV/LV-ratios.

INTRODUCTION

Mortality rates in hemodynamically stable patients with acute pulmonary embolism (PE) range from 2% to 6% and increase considerably to 30% or more in patients presenting with hemodynamic instability or shock.[1] For this latter patient category, invasive treatment regimes including thrombolysis, thrombosuction or surgical embolectomy might be life saving.[2,3] In contrast, outpatient treatment may be considered for hemodynamically stable patients with relatively mild disease.[2,4] It is however challenging to identify those patients who present in a hemodynamically stable state but who are at high risk for clinical deterioration and death in the first period after the diagnosis of PE and start of anticoagulation therapy. These patients might benefit from more intensive clinical surveillance or even thrombolysis, whereas outpatient treatment is contraindicated.[2,5-7]

One of the main causes of early death after PE is right ventricular failure.[1] Hence, it seems very plausible to use indicators of right ventricular function as predictors of short term clinical outcome after acute PE. Especially tests for the evaluation of ventricular function that are easy to obtain and widely available are of particular interest for clinical use, since these are likely to aid the physicians in performing rapid risk stratification and determining treatment strategy. Retrospective studies have previously shown that right ventricular enlargement on computed tomography pulmonary angiography (CTPA; Odds Ratio [OR] 4.0) and elevated levels of cardiac biomarkers such as NT-pro-BNP (OR 6.8) and Troponin (OR 7.0) are predictive for the occurrence of adverse events and early mortality after acute PE.[8-11] This is also true for highly elevated D-dimer levels as indicator of high embolus load (OR 7.3), which is associated with increased risk of right ventricular impairment.[12-14] Importantly, the ability of these different predictors to identify patients at risk for adverse clinical outcome has not yet been directly compared in a prospective outcome study. Furthermore, a recent paper demonstrated that results from previous studies should be interpreted and compared with caution because of the clinical and methodological diversity of these studies.[15]

Therefore, the purpose of this prospective cohort study was to compare the predictive accuracy and clinical utility of easy right ventricular function tests, i.e. CT-derived right-to-left ventricular diameter ratios (RV/LV-ratio) and NT-pro-BNP and Troponin-T, as well as D-dimer levels, for predicting adverse events in the short term clinical course of acute PE.

METHODS

Patients

Consecutive, hemodynamically stable in- and outpatients who presented to our hospital with suspected acute PE between September 1st 2005 and December 1st 2008, and with a strict indication for CTPA were included. This CTPA indication comprised patients with either a likely

clinical probability by the Wells Rule (>4 points total) or an abnormal D-dimer blood test (>500 ng/mL FEU).[16] Only patients with an unlikely probability in combination with a normal D-dimer test result did not undergo CTPA since PE can be safely ruled out in that patient category.[16] These latter patients could therefore not be included in this study. Patients diagnosed with acute PE by CTPA were initially treated with therapeutic unfractionated or low-molecular-weight heparin for at least 5 days, followed by vitamin K antagonists for a period of at least three months aiming at an INR of 2.0-3.0.[2] In case of severe PE or clinical deterioration, admission to the intensive care unit and/or administration of thrombolytic drugs was considered, according to the judgment of the attending clinician. Exclusion criteria for the study were: impossibility of follow-up, age younger than 18 years, pregnancy, known allergy to intravenous application of iodine contrast media or hemodynamic instability at initial presentation. This study was approved by the Institutional Review Board of our hospital and all patients provided written informed consent.

Endpoints

All patients were followed for 6 weeks. Follow-up consisted of a scheduled visit to our vascular medicine outpatient clinic for the patients with confirmed acute PE and a telephone interview for all patients in whom PE was ruled out by CTPA. The primary study outcome was the occurrence of one or more adverse clinical events in the first 6 weeks following study inclusion. Adverse events were defined as the occurrence of any of the following: all cause mortality, resuscitation after respiratory or cardiac arrest, admittance to intensive care unit, need for mechanical ventilation or use of inotropic agents, and administration of thrombolytic drugs.

Procedures

All patients underwent multi-detector row CTPA (Aquilion 64; Toshiba Medical Systems, Otawara, Japan) of the chest during breath-hold at inspiration. CTPA was performed after bolus injection of iodinated contrast agent (80-100 mL Xenetix 300, Guerbet, Aulnay-sous-Bois, France, or 60-80 mL Iomeron 400 mg/mL, Bracco, Milan, Italy) via antecubital vein injection with a flow rate of 4.0 mL/sec using an automatic injector (Stellant CT, MedRad, Pittsburgh, USA). Bolus tracking was performed by placing a region of interest in the pulmonary trunk. Image acquisition was automatically started 5 seconds after reaching a predefined threshold difference of 100 HU using SureStart (Toshiba Medical Systems, Otawara, Japan). Scan parameters were: rotation time 0.5 sec, pitch factor 53.0, tube voltage 100 kV and tube current depending on patient size and shape. Images were reconstructed with a slice thickness of 1.0 or 0.5 mm.

Analysis of RV/LV-ratios was performed on a post-processing workstation (Vitrea, version 2, Vital Images, Minnetonka, USA) in standard axial views and in reconstructed 4-chamber (4-CH) views (Figure 1) by one observer with two years of experience and supervised by a radiologist with 10 years of experience in thoracic CT imaging. The 4-CH view was reconstructed by using 2-dimensional multiplanar reformats of the original axial source data as was suggested by

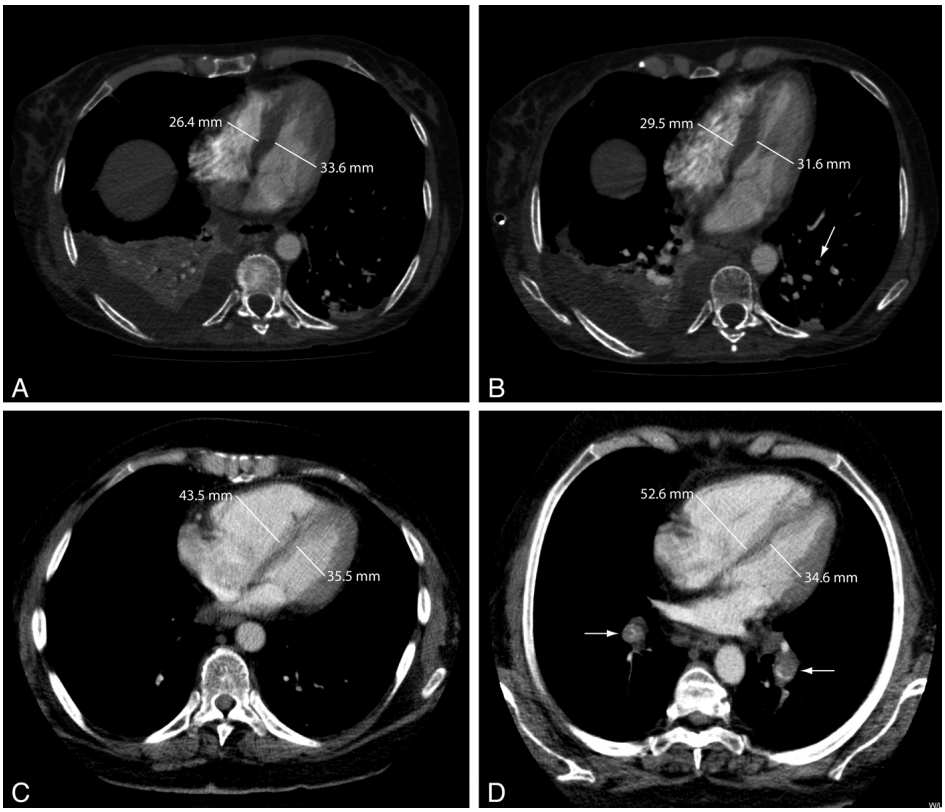

Figure 1. Measurement of right ventricular (RV) and left ventricular (LV) dimensions in axial (A, C) and reconstructed computed tomography 4-chamber views (B, D). A and B represent the same patient with acute pulmonary embolism (PE) and RV/LV-ratio ≤1.0. Note the right sided pleural effusion, bilateral atelectasis, and diaphragmatic hernia (A, B). Panels C and D represent a patient with acute PE and RV/LV-ratio >1.0. Large bilateral pulmonary artery emboli are present (D). Pulmonary emboli are marked by arrows (A-D).

Quiroz et al.[11] Right and left ventricular dimensions were measured by identifying the maximal distance between the ventricular endocardium and the interventricular septum, perpendicular to the long axis.[10,11] The RV/LV-ratio was then calculated. Right ventricular enlargement was considered present when the RV/LV-ratio was greater than 1.0.[10]

Venous plasma and serum samples were obtained on admission and were immediately stored at –80°C. After all patients were included, samples were analyzed in batches after a single thaw. Troponin-T and NT-pro-BNP levels were determined with the use of quantitative immunoassays (Elecsys 2010 analyzer, Roche Diagnostics, Mannheim, Germany). For Troponin-T, a reference value of 0.09 ng/mL was used to distinguish between normal and elevated levels as proposed by the manufacturer. For NT-pro-BNP, the prognostically relevant cut-off level was set at 600 pg/mL.[17] D-dimer levels were determined using a quantitative, automated immunoassay (STA LIA D-dimeer assay; Roche, Mannheim, Germany). D-dimer levels exceeding 3000 ng/mL FEU were defined to be a poor prognostic sign.[13]

The study was performed in blinded fashion: since both the CT measurements of ventricular function as well as the biomarker blood levels were assessed post-hoc, the treating physicians were unaware of these results, precluding information bias. Also, the researchers who measured the ventricular ratios and the biomarker levels were blinded for the clinical course of the study patients.

Statistics

The sample size calculation was primarily based on RV/LV-ratios with the following assumptions: a 20% risk on the primary study outcome in case of a RV/LV-ratio >1.0, a <3% risk in case of a RV/LV-ratio ≤1 and a 50% prevalence of RV/LV-ratio >1.0 in patients with acute PE.[1,8,10,11,18] To detect this risk difference with a power of 80% and a two-tailed alpha of 0.05, we needed 110 included subjects with PE.

For logistic and financial reasons, we determined before the start of the study that the measurements of ventricular function and biomarkers were to be performed in all patients with acute PE diagnosed within the study period, and in twice that number of patients in whom PE was ruled out by CTPA, but not in all of these latter patients. The cohort of patients without PE that was included in the following analyses consisted of consecutive patients from the start of the study until this double number was achieved.

First, we studied the association of right ventricular enlargement, biomarkers and acute PE by calculating ORs by logistic regression for elevated RV/LV-ratios and biomarker levels between patients with and without acute PE, adjusted for age, gender, active malignancy and presence of cardiopulmonary comorbidity. Second, we studied the association between RV/LV-ratios, biomarkers and adverse clinical outcome in patients with established PE as well as in those without PE separately. Also, we weighed the discriminatory ability of the predefined cut-off levels of the RV/LV-ratio and biomarkers for adverse clinical outcome by comparing the area under the curve (AUC) in receiver operator characteristic (ROC) analyses for patients with established acute PE only.[19] In addition, we used these ROC curves to evaluate whether the predefined cut-off points of our predictors were chosen optimally for predicting adverse outcome. Furthermore, we evaluated the clinical utility of RV/LV-ratios and biomarkers by assessing and comparing the specific test characteristics for predicting adverse clinical outcome for each predictor individually. These analyses were performed for all patients and for a selected cohort of outpatients only. Finally, we studied whether combing different tests would have additional predictive value and clinical applicability compared to the individual tests. Differences between categorical variables were studied using the Chi-Square test en continuous variables using an independent samples T-test. SPSS version 14.02 (SPSS Inc, Chicago, IL) was used for all analysis. A two-sided p-value <0.05 was considered to indicate a significant difference.

RESULTS

Patients

Within the study period, 113 of the included 439 patients were diagnosed with acute PE. All 113 patients with PE and the first 226 patients in whom PE was ruled out by CTPA were selected for further analysis. The baseline characteristics of these patients are depicted in Table 1. The mean age in the overall study population was 56 years. Patients with PE had a higher proportion of males (53% vs. 42%) and had more often previous venous thromboembolism (22% vs. 19%) and recent immobility, surgery, trauma or were in postpartum period (31% vs. 13%) than the patients without PE. The patients without PE had a higher prevalence of chronic obstructive pulmonary disease (COPD; 6.2% vs. 16%), left sided hart failure (4.4% vs. 7.5%) and were more often inpatients (18% vs. 25%).

Table 1. General characteristics of the study population.

	Patients with PE (n=113)	Patients without PE (n=226)
Age (years ±SD)	56 ±17	56 ±21
Male sex (n, %)	60 (53)	95 (42)
Previous PE or DVT (n, %)	25 (22)	43 (19)
Immobility, surgery, trauma, postpartum (n, %)	35 (31)*	29 (13)*
Known thrombophilia† (n, %)	3 (2.7)	10 (4.4)
Active malignancy (n, %)	24 (21)	56 (25)
COPD (n, %)	7 (6.2)*	36 (16)*
Left sided heart failure (n, %)	5 (4.4)	17 (7.5)
Inpatient (n, %)	20 (18)	57 (25)

†In our hospital, patients are not routinely screened for thrombophilia; *p<0.05 on Chi-Square test.
PE=pulmonary embolism, DVT=deep vein thrombosis, COPD=chronic obstructive pulmonary disease, SD=standard deviation, n=number.

Adverse events

Of the 113 patients with established acute PE, 10 had a complicated clinical course (8.9%; 95% CI 4.3-16%; Table 2). Four patients experienced clinical deterioration necessitating cardiopulmonary resuscitation within 12 days after diagnosis: of those, 2 died immediately, 1 died after 9 days of acute PE and severe cerebral hemorrhage, and one was successfully resuscitated and completed the follow-up period without further complications. One patient received thrombolytic therapy because of a large saddle embolus and one patient died after 10 days of hospital acquired pneumonia and PE. Three patients died of progressive cancer on days 15, 21 and 39 respectively. Finally, one patient suffered from acute PE after major abdominal surgery. After 10 days a large hepatic hematoma was discovered. Following this, this patient underwent new surgery and was admitted to the intensive care unit. She recovered completely without further complications. Overall, death was attributed to acute PE in 4 patients. None of the patients with acute PE was lost to follow-up.

Table 2. Characteristics of patients with adverse clinical events in the course of established acute pulmonary embolism.

Gender	Age (years)	In/out patient	Adverse event	RV/LV-ratio (axial view)	RV/LV-ratio (4-CH view)	D-dimer level (ng/mL FEU)	Troponin-T (ng/mL)	NT-pro-BNP (pg/mL)
Female	80	Out	day 1: unsuccessful resuscitation after saddle embolus, pulmonary embolism attributable death	3.1	3.2	>5000	<0.01	1964
Female	55	Out	day 1: thrombolysis because of large saddle embolus	1.5	1.5	>5000	0.03	5059
Female	83	Out	day 2: successful resuscitation followed by thrombolysis, mechanical ventilation and admittance to the ICU. Patient died at day 9 of pulmonary embolism and cerebral bleeding.	1.7	2.0	>5000	<0.01	6540
Male	70	Out	day 2: successful resuscitation	1.2	1.1	>5000	0.11	4245
Male	80	Out	day 10: patient died of severe pneumonia and pulmonary embolism	0.87	1.0	976	0.11	2979
Female	50	In	day 10: (PE occurred 1 day post major abdominal-surgery) re-operation and admittance to the ICU because of major bleeding.	1.2	1.3	4736	<0.01	2520
Female	80	Out	day 12: unsuccessful resuscitation, autopsy proven pulmonary embolism attributable death	1.4	1.5	1281	0.21	5026
Female	59	Out	day 15: patient died of progressive malignancy of unknown origin	0.94	1.04	>5000	0.10	1619
Male	47	In	day 21: patient died of progressive non-Hodgkin lymphoma	1.3	1.2	1332	<0.01	623
Male	68	Out	day 39: patient died of progressive prostate cancer	1.2	1.3	>5000	<0.01	151

Overall, death was attributed to pulmonary embolism in 4 patients. RV/LV-ratio=ventricular volume ratio, 4-CH=four chamber, PE=pulmonary embolism, ICU=intensive care unit.

Fifteen of the 226 patients without PE died during the follow-up period. Cause of death was malignancy in 11 patients and renal failure, pulmonary fibrosis, pneumonia and heart failure in the other patients respectively. In addition, 3 patients were admitted to the intensive care unit after heart surgery and one patient was lost to follow-up. Two patients in whom PE was initially ruled out had recurrent complaints and underwent a second CTPA. PE was established in one of these 2 patients. Patients with established PE were at slightly higher risk for complicated clinical course then patients in whom PE was ruled out: OR adjusted for age, gender, active malignancy and presence of cardiopulmonary comorbidity was 1.5 (95% CI 0.63-3.6).

RV/LV-ratios and biomarkers in patients with and without PE

RV/LV-ratio was higher in patient with PE than in patients without PE for both axial (1.1 vs. 0.89; p<0.001) as well as reconstructed 4-CH views (1.1 vs. 0.86; p<0.001). In addition, adjusted ORs for increased RV/LV-ratio were increased for patients with established acute PE for axial (OR 6.6, 95% CI 3.8-11) along with 4-CH views (OR 14, 95% CI 7.3-25). Adjusted OR for elevated levels of Troponin-T (3.6, 95% CI 1.3-10), NT-pro-BNP (1.5, 95% CI 0.87-2.7) and D-dimer (5.6, 95 %CI 3.1-9.9) were also increased for patients with PE. Thus, acute PE was independently associated with increased right ventricular dimensions and elevated biomarker levels.

RV/LV-ratio and biomarkers as predictors for adverse events

Blood levels of Troponin-T, D-dimer, NT-pro-BNP and RV/LV-ratios in both views were higher in the patients with acute PE who suffered adverse clinical events than in those with uncomplicated clinical course (Table 3). Following this, right ventricular enlargement and elevated biomarkers increased the risk of adverse events with adjusted ORs of 3.7 (95% CI 0.74-19), 9.0 (95% CI 1.1-79), 3.5 (95% CI 0.86-15), 6.3 (95% CI 1.3-31) and 31 (95% CI 3.6-257) for axial RV/LV-ratios, 4-CH RV/LV-ratios, D-dimer, Troponin-T and NT-pro-BNP respectively. Furthermore, we identified an increased risk for adverse events associated with right ventricular enlargement and elevated biomarkers in the patients in whom PE was ruled out, although less pronounced than in patients with PE, with adjusted ORs ranging from 2.0 to 3.8 (Table 3).

Table 3. Medians and interquartile range for ventricular volume ratio and biomarkers in patients with and without acute PE and with and without adverse clinical outcome.

	RV/LV-ratio (axial)	RV/LV-ratio (4-CH)	D-dimer level (ng/mL FEU)	Troponin-T (ng/mL)	NT-pro-BNP (pg/mL)
PE, uncomplicated clinical course (median, IQR)	1.0 (0.92-1.1)*	1.0 (0.90-1.1)**	2232 (1201-4656)*	0.0 (<0.01-<0.01)*	180 (45-387)**
PE, adverse clinical outcome (median, IQR)	1.3 (1.1-1.6)*	1.2 (1.1-1.4)**	>5000 (1319->5000)*	0.0 (<0.01-0.16)*	2068 (78-4400)**
Adjusted OR for adverse events†	3.7 (0.74-19)	9.0 (1.1-79)	3.5 (0.86-15)	6.3 (1.3-31)	31 (3.6-257)
PE ruled out by CT, uncomplicated clinical course (median, IQR)	0.90 (0.80-0.97)	0.85 (0.76-0.93)*	874 (595-1991)*	0.0 (<0.01-<0.01)	153 (54-522)*
PE ruled out by CT, adverse clinical outcome (median, IQR)	0.95 (0.82-1.1)	0.95 (0.79-1.0)*	2377 (1565-3194)*	0.0 <0.01-<0.01)	715 (76-5794)*
Adjusted OR for adverse events†	3.2 (1.1-9.4)	3.3 (1.1-9.8)	2.3 (0.74-7.4)	2.0 (0.22-18)	3.8 (1.4-10)

Mann-Whitney-U tests were performed between uncomplicated and complicated clinical course for patients with PE and without PE separately: *p<0.05, **p<0.01; †from predefined cut-off values. RV/LV-ratio=ventricular volume ratio, 4-CH=four chamber, CT=computed tomography, IQR=interquartile range.

Discriminatory ability and clinical utility of RV/LV-ratio and biomarkers for predicating adverse clinical outcome in patients with acute PE

ROC analyses revealed that from the 5 predictors of adverse events, NT-pro-BNP had higher AUC (0.85, 95% CI 0.73-0.97) compared to axial RV/LV-dimensions (0.64, 95% CI 0.47-0.81; p=0.014),

Table 4. Test characteristics of CT measured right ventricular enlargement and elevated biomarkers for predicting adverse clinical outcome in patients with acute PE.

	Increased RV/LV-ratio (>1.0, axial view)	Increased RV/LV-ratio (>1.0, 4-CH view)	Elevated D-dimer (>3000 ng/mL FEU)	Elevated Troponin-T (>0.09 ng/mL)	Elevated NT-pro-BNP (>600 pg/mL)
Sensitivity (%, 95% CI)	80 (44-96)	90 (56-99.8)	70 (35-93)	40 (12-74)	90 (56-99.8)
Specificity (%, 95% CI)	48 (38-58)	46 (36-57)	60 (50-70)	93 (86-97)	78 (70-84)
Proportion identified as high risk (%, 95% CI)	56 (46-66)	57 (47-67)	42 (33-52)	8.9 (4.4-16)	28 (20-38)
Proportion identified as low risk (%, 95% CI)	44 (34-54)	43 (33-53)	58 (48-67)	91 (84-97)	72 (62-80)
Negative predictive value (%, 95% CI)	96 (86-99.5)	98 (86-99.8)	95 (86-99)	93 (86-97)	99 (92-99.9)
Positive predictive value (%, 95% CI)	13 (5.7-24)	16 (7.8-28)	15 (6.5-28)	30 (8.1-65)	29 (15-48)

RV/LV-ratio=ventricular volume ratio, 4-CH=four chamber, CT=computed tomography, CI=confidence interval.

4-CH RV/LV-ratios (0.64, 95% CI 0.48-0.81; p=0.15), D-dimer (0.64, 95% CI 0.47-0.81; p=0.048) and Troponin-T (0.62, 95% CI 0.41-0.82; p=0.037). Of note, changing the thresholds of these 5 predictors did not improve the prognostic performance of any of them (data not shown).

The high discriminative power of NT-pro-BNP levels exceeding 600 pg/mL was underlined by a high sensitivity (90%, 95% CI 56-99.8) and specificity (78%, 95% CI 70-84) for adverse clinical outcome compared to the remaining 4 predictors (Table 4). RV/LV-ratio >1.0 on 4-CH view had equally high sensitivity (90%, 95% CI 56-99.8) but lower specificity (46%, 95% CI 36-57, p<0.001). Furthermore, although the specificity of elevated Troponin-T levels was higher (93%, 95% CI 86-97; p=0.004), this was accompanied by a significantly lower sensitivity (40%, 95% CI 12-74) than that of NT-pro-BNP (p=0.022).

None of the 5 predictors was able to identify patients at very high risk for adverse events, with low positive predictive values in the range of 14% to 30% (Table 4). On the other hand, negative predictive values were over 90% for all predictors and highest for NT-pro-BNP (99%, 95% CI 92-99.9) and RV/LV-ratio on 4-CH view (98%, 95% CI 86-99.8). Low Troponin-T (91%) and NT-pro-BNP levels (72%) categorized more patients as having a low risk on complications than normal RV/LV-ratio on axial (44%) and 4-CH view (43%; p<0.001 compared to low Troponin-T and NT-pro-BNP levels) and D-Dimer levels under 3000 ng/mL FEU (58%; p<0.01 compared to low Troponin-T levels and p=0.041 compared to low NT-pro-BNP levels). Elevated NT-pro-BNP levels in combination with LV/RV-ratio >1.0 on 4-CH views had a sensitivity of 80% (95% CI 44-96), a specificity of 88% (95% CI 0.78-93), a positive predicting value of 42% (95% CI 21-67) and a negative predicative value of 97% (95% CI 90-99.6), resulting in an AUC of 0.84 (95% CI 0.69-0.99). These test performances were not different from that of NT-pro-BNP alone.

Finally, we calculated the test characteristics of all 5 predictors of adverse clinical outcome for outpatients only. D-dimer levels below 3000 ng/mL FEU were found in 55% of the outpatients

with a negative predictive value of 96% (95% CI 90-99.5), low Troponin-T levels in 91% (negative predictive value 94%, 95% CI 87-98), low NT-pro-BNP levels in 77% (negative predictive value 99%, 95% CI 90-99.9), RV/LV-ratio <1.0 on axial view in 45% (negative predicative value 95%; 95% CI 82-99) and RV/LV-ratio <1.0 on 4-CH view in 44% of the out-patients (negative predictive value 97%, 95% CI 85-99.9).

DISCUSSION

This prospective cohort study has three important findings. First, acute PE is associated with an increased incidence of right ventricular enlargement and higher levels of cardiac biomarkers compared to patients in whom PE is ruled out by CTPA. Second, right ventricular enlargement and elevated levels of cardiac biomarkers predict adverse clinical events in both patients with PE as well as in those without PE. Finally, easy obtainable markers for right ventricular dysfunction such as RV/LV-ratios and cardiac biomarkers can be used for risk stratification, that is for identification of patients with PE who are at low risk for complications. Although all studied predictors had high negative predictive values for adverse events after acute PE, low levels of NT-pro-BNP were found to have superior clinical discriminatory ability and clinical utility compared to the other 4 predictors in our study population.

This clinical utility of the tests under study is determined by the ability of accurately distinguishing PE patients at high or low risk of early complications, thereby identifying a specific patient group that profits from customized, more aggressive treatment, i.e. more intensive clinical surveillance or thrombolysis, or less stringent treatment, i.e. outpatient treatment. ROC analysis showed that NT-pro-BNP levels over 600 pg/mL were found to have the highest AUC. Moreover, its negative predictive value was 99%, indicating a risk for adverse events lower than 1.0% for 72% of the patients with PE. The results from NT-pro-BNP analysis are usually available within the hour and since NT-pro-BNP has evolved to be an increasingly important diagnostic and prognostic tool for patients with heart failure, the assays are widely available. Increased RV/LV-ratio on 4-CH view had comparable excellent sensitivity and negative predictive value compared to elevated NT-pro-BNP levels. In addition, this is presumably the easiest and cheapest test of the two, since this can be performed in all standard CTPA scans, which have become the imaging test of choice for establishing the diagnosis of acute PE in recent years.[10,11,16] Measuring RV/LV-ratios does not require additional administration of contrast material or increased radiation dose, and takes only a few minutes of time. Nonetheless, RV/LV-ratios had significantly lower specificity than elevated levels of NT-pro-BNP and classified only 43% and 44% of the patients in the low risk category. Therefore, the accuracy and clinical utility of NT-pro-BNP for identification of PE patients with low risk of adverse events was superior to that of RV/LV-ratios. Markedly, risk stratification based on the combination of NT-pro-BNP levels as well as RV/LV-ratio on 4-CH views did not show better prognosis than NT-pro-BNP levels

alone. Finally, although high Troponin-T levels categorized 91% of the patients in the low-risk category, its negative predictive value was only 93% due to a lower sensitivity of 40%.

The underlying mechanism for increased right ventricular dimensions, decreased right ventricular function and acute PE has been well established.[1] Even so, to our knowledge this is the first prospective study describing the association of right ventricular enlargement and elevated cardiac biomarkers in patients with acute PE in contrast to patients in whom this diagnosis was suspected but ruled out. Furthermore, this is the first report directly comparing various cardiac biomarkers and RV/LV-ratios for predicting adverse outcome after acute PE.

What is the clinical applicability of our results? A recent meta-analysis[20] has shown that treatment with low molecular weight heparin is at least as effective and safe as treatment with unfractionated heparin for the initial treatment of non-massive PE, enabling start of treatment at an outpatient basis of these patients. This approach may imply great benefits such as saving costs and increasing patient satisfaction.[21] Reduction in iatrogenic problems might be a third beneficial effect.[22] Relatively small prospective outcome studies have demonstrated that outpatient treatment might be feasible, although these patients were selected for outpatient treatment based on clinical intuition, and not on explicit predefined criteria.[4,21] Identification of patients accessible for outpatient treatment based on well-defined, standardized selection criteria may help improving safety and more widespread acceptance of outpatient management. Our study demonstrates that from 5 easily obtainable tests of adverse clinical outcome, NT-pro-BNP is the best tool for selecting patients with a low risk for adverse outcome, who can be considered for outpatient treatment.

The main limitation of this study is that since the sample size of this study was primarily based on RV/LV-ratio on CTPA, the results observed for the other parameters might be underpowered, leading to wide confidence intervals. Furthermore, the fraction of males and the mean age of the patients with acute PE was slightly different compared to previous studies.[11,14,17,23,24] This could affect the generalizability of our study results and therefore, these should be accordingly interpreted. Nonetheless, we consider our data representative for several reasons. First, our study was of prospective design including consecutive patients with suspected acute PE, and by blinding both the attending physicians as well as the researchers, there was no information bias. Second, we had very low lost to follow-up rates: 0 of 113 patients with PE and 1 of 226 of the patients without PE. Third, we used predefined cut-off points for our predictors that were established by previous studies. Furthermore, post-hoc analyses in our data confirmed these thresholds to have the highest discriminatory ability (data not shown). Fourth, the ORs for adverse events regarding the 5 studied predictors calculated from our data are in accordance with the confidence intervals of those reported in previous studies.

Finally, although signs of right ventricular dysfunction on echocardiography are clearly associated with adverse events after PE[1,11,23,24], we have not incorporated echocardiography in our study design. The main reason for this decision was that in our hospital, as well as in many other hospitals, it is not possible to perform echocardiography as a clinical routine in all

patients diagnosed with acute PE. Additionally, the performance of RV/LV-ratios on 4-CH views has been demonstrated to be comparable to that of echocardiography.[11]

In summary, right ventricular enlargement and elevated cardiac biomarkers, that are independently associated with acute PE, are predictive for a complicated clinical course in patients with acute PE and also in patients who were suspected of this disease but in whom PE was ruled out by CTPA. These tests are especially valuable in identifying patients with low risk of adverse events after acute PE is diagnosed. NT-pro-BNP levels below 600 pg/mL have the highest clinical discriminatory ability and clinical utility as compared to D-dimer levels below 3000 ng/mL FEU, Troponin-T levels below 0.09 ng/mL and RV/LV-ratios less than 1.0 for both axial as well as 4-CH views in our study population. Future outcome studies should confirm these results and the safety of home-treatment based on low NT-pro-BNP levels and/or RV/LV-ratios.

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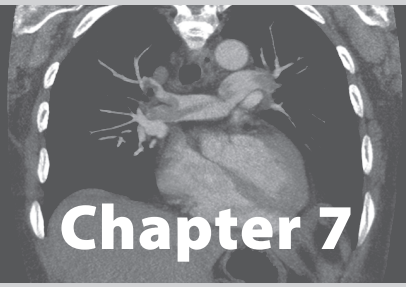

Chapter 7

Usefulness of ECG-synchronized MDCT assessed right and left ventricular function for predicting short term clinical outcome in patients with clinically suspected acute pulmonary embolism

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Submitted

ABSTRACT

Purpose

To assess whether right and left ventricular (RV and LV) ejection fraction (EF) by electrocardiography (ECG)-synchronized multi-detector row computed tomography (CT) predict the short term clinical outcome after acute pulmonary embolism (PE).

Methods

In addition to standard CT pulmonary angiography, 439 consecutive patients presenting with clinically suspected acute PE underwent ECG-synchronized dynamic cardiac CT to assess RV and LV function. Predefined thresholds for decreased RV and LV function were used to predict adverse events.

Results

113 patients were diagnosed with PE. RVEF was decreased and RV/LV volume as well as dimension ratios were increased in patients with versus patients without PE ($p<0.001$ for all). RVEF <47% had a very high odds ratio (36, 95% confidence interval [CI] 2.2-590) and a higher area under the receiver operator characteristic curve (0.75, 95% CI 0.56-0.88) for predicting adverse outcome after PE than LVEF <57% (difference 0.11, 95% CI 0.04-0.18), end-diastolic RV/LV >1.2 (difference 0.08, 95% CI -0.7-0.23), end-systolic RV/LV ratio >1.4 (difference 0.14, 95% CI 0.07-0.21) and axial RV/LV ratio >1 (difference 0.11, 95% CI 0.02-0.21). All studied CT measured markers of ventricular function had comparable high negative predictive values (94-98%) and limited positive predictive values (9.6-18%) for adverse outcome after PE. Importantly, cardiac CT was associated with increased exposure to radiation and contrast dye.

Conclusion

CT assessed RVEF has a high predictive value as well as a high sensitivity for adverse clinical outcome after PE although the potential benefit of ECG-synchronized cardiac CT compared to standard CT-imaging is low and may not outweigh its disadvantages.

INTRODUCTION

Acute pulmonary embolism (PE) is a common and potentially fatal condition. The mortality rate in hemodynamically stable patients with acute PE is 2-6%.[1,2] Right ventricle (RV) failure is the main cause of death within the first period after the acute event.[3-5] Early echocardiographic evaluation of RV function has been shown predictive for adverse clinical outcome.[6-10] Nowadays, computed tomography (CT) pulmonary angiography is the diagnostic test of first choice in the work-up of patients with suspected acute PE by direct visualization of the pulmonary emboli.[11] From the same CT scan, information concerning possible RV dilatation can be easily obtained by measuring right-to-left ventricular dimension ratios in transverse and/or reconstructed four chamber views. Several studies have shown the prognostic value of RV dilatation on clinical outcome identified with standard CT pulmonary angiography.[3,12,13] However, these dimension ratios obtained from standard non-electrocardiographic (ECG)-synchronized scans are no direct measure of RV function. It has been shown that with ECG-synchronized cardiac CT, RV function can be assessed with high accuracy and reproducibility as compared to echocardiography and magnetic resonance imaging, the latter being the current reference standard for ventricular volume measurements.[14,15] Only two studies have investigated the use of ECG-synchronized CT in small patient groups with suspected acute PE. One study showed that assessing ventricular function with ECG-synchronized CT was of additional value in stratifying patients with PE.[16] In the other study, ECG-synchronized cardiac CT showed minimal improvement in predicting 30-day mortality.[17] Larger prospective outcome studies are however needed to definitively establish the clinical usefulness of ECG-synchronized cardiac CT with functional analysis in patients with clinically suspected acute PE. Accordingly, the purpose of the present study was to assess to what extent the assessment of ventricular function with ECG-synchronized cardiac CT has additional clinical value to standard CT pulmonary angiography in patients with clinically suspected acute PE.

METHODS

Study population

For this prospective cohort study, 430 consecutive hemodynamically stable in- and outpatients presenting with suspected acute PE between September 2005 and December 2008 were included for analysis. All patients underwent standard CT pulmonary angiography and ECG-synchronized dynamic cardiac multi-detector row CT under strict indications: Wells rule >4 points or an abnormal D-dimer blood test of >500 ng/mL FEU.[11] Inclusion criteria for the study were: clinically suspected acute PE, age ≥18 years and willingness to participate. Exclusion criteria were: impossibility to follow-up, known allergy to intravenous application of iodinated contrast media, renal dysfunction with a glomerular filtration rate <30 mL/min, pregnancy,

hemodynamic instability at presentation with setting of cardiopulmonary resuscitation, life expectancy less than three months and failure to obtain written informed consent. Under these conditions, 439 patients were eligible for the study. In nine patients, the dynamic cardiac CT scan had failed due to technical problems, arrhythmia or insufficient contrast. These patients were excluded. The study was approved by the Institutional Review Board of our hospital and all patients provided written informed consent.

Image acquisition

All patients underwent standard contrast-enhanced CT pulmonary angiography to confirm or exclude the diagnosis of acute PE followed within the same session by dynamic cardiac CT for the assessment of biventricular function using a 16-, 64- or 320-slice multi-detector row CT scanner (Aquilion 16CFX; Aquilion 64; Aquilion ONE, all scanners: Toshiba Medical Systems, Otawara, Japan). CT pulmonary angiography was performed during breath-hold at inspiration after administration of iodinated contrast agent (80-100 mL Xenetix 300, Guerbet, Aulnay-sous-Bois, France, or 60-80 mL Iomeron 400 mg/mL, Bracco, Milan, Italy) into an antecubital vein with a flow rate of 4.0 mL/sec. An automatic power injector was used (Stellant CT, MedRad, Pittsburgh, USA) for contrast administration. A region of interest was placed in the main pulmonary artery for bolus tracking and after reaching a predefined threshold difference of 100 HU with use of SureStart (Toshiba Medical Systems), image acquisition was started automatically after a fixed delay of 5 seconds. Scan parameters were: rotation time 0.5 sec, pitch factor 53.0, tube voltage 100 kV. Tube current was dependent on patient size and shape. Estimated radiation dose was 3.3 mSv for CT pulmonary angiography. Images were reconstructed with 1.0 or 0.5 mm slice thickness and sent to the PACS system.

Then, ECG-synchronized dynamic cardiac CT was performed after administration of 35-40 mL contrast agent with a flow rate of 2.5-3.0 mL/sec, followed by a 30 mL saline bolus chaser and a fixed delay of 15 seconds. Scan parameters were: tube voltage 120 kV and tube current 200 mA. Depending on heart rate, the optimal rotation time and pitch factor were automatically determined to obtain optimal temporal resolution for helical scanning. Estimated radiation dose was 3.6 mSv for ECG-synchronized cardiac CT. Images for cardiac functional analysis were reconstructed in twenty cardiac phases (every 5% of the RR-interval, ranging from 0-95%) by using a segmental reconstruction algorithm. Adjacent 2 mm thick sections were retrospectively reconstructed in a 512x512 matrix by using a 200-240 mm field-of-view. The entire heart from aortic root to cardiac apex was covered within the reconstructed sections per cardiac phase point. The reconstructed volumes were transferred to a dedicated workstation running on Linux software.

Diagnosis of PE

CT pulmonary angiography scans were evaluated on a PACS workstation. The presence of PE was defined as at least one filling defect in the pulmonary artery tree. The degree of pulmonary

arterial obstruction was quantified by the method of Qanadli et al.[18] An obstruction index of 40% or greater was used as cut-off value for the identification of patients at risk for adverse clinical outcome.[18]

Cardiac function

Analysis of ventricular function by volumetric measures on ECG-synchronized cardiac CT was performed by using dedicated cardiac function analysis software (CT-MASS; Medical Imaging Systems, Leiden, The Netherlands). First, the phases with the largest and smallest RV volumes were selected by inspecting running cine movies on midventricular level and represented the end-diastolic and end-systolic phase, respectively. Endocardial borders for the RV as well as for the left ventricle (LV) were drawn on every other transverse section in end-diastolic and end-systolic phases. The entire volume of the ventricles from the apex to the level of the pulmonary outflow tract was covered for both phases. End-diastolic and end-systolic volumes, stroke volume and ejection fraction were calculated. Thresholds for RV (<47%) and LV dysfunction (<57%), as well as increased end-diastolic RV/LV (>1.2) and end-systolic RV/LV volume ratios (>1.4) were set at the lower respectively higher borders of the 95% confidence interval of these values determined in healthy persons.[19] Assessment of ventricular ratios by diameter measures on standard CT pulmonary angiography was performed on a post-processing workstation (Vitrea, version 2, Vital Images, Minnetonka, USA). RV and LV diameters (i.e. the maximum diameter between the ventricular endocardium and interventricular septum for the RV and the LV) were measured in standard axial views as previously described.[12] RV dysfunction was defined as a RV/LV dimension ratio of greater than 1.0.[13] All contours were drawn after the patients had completed their follow-up and by researchers who were blinded for the final diagnosis and clinical outcome of the study patients.

Clinical outcome

Follow-up consisted of a scheduled visit to the vascular medicine outpatient clinic in patients with confirmed diagnosis of acute PE. A follow-up telephone interview was performed in all patients where acute PE was ruled out. Adverse clinical outcome was defined as the occurrence of one or more of the following: death, cardiopulmonary resuscitation, admittance to intensive care unit, need for mechanical ventilation and/or administration of inotropic or anticoagulant agents. A 6 week follow-up period was chosen since we considered this to reflect the acute consequences of the acute PE best.

Statistical analysis

Statistical analysis was performed using SPSS version 16.0 for windows (SPSS, Chicago, Illinois, USA). Dependent on normal or skewed distribution, mean and standard deviations or medians and interquartile ranges (IQR) were calculated for RV and LV ejection fraction, end-diastolic volume, end-systolic volume, RV/LV volumes ratios, RV/LV dimension ratios and vascular

obstruction index. For the comparison of cardiac function between the patients with and without PE, logarithmic transformation was applied for skewed distributed variables to allow use of an independent samples T-test. A Chi-Square test was applied to evaluate differences between patients with and without the occurrence of adverse clinical outcome, using our predefined thresholds. Receiver operator characteristic (ROC) analysis was applied to assess and compare the discriminatory ability of the predefined cut-off values for RV ejection fraction, RV/LV-ratios and vascular obstruction index in predicting clinical outcome by comparing the area under the curve (AUC).[20] Furthermore, sensitivity, specificity, positive predictive value and negative predictive values were calculated. A p-value of <0.05 was considered to indicate a statistically significant difference.

RESULTS

Study population

In total, 430 patients with suspected acute PE were included. Mean age was 55 ±17 years and 45% were males (Table 1). Pulmonary embolism was confirmed in 113 patients (26%) on CT pulmonary angiography. The median degree of pulmonary artery obstruction was 25% (IQR 10%-50%). The patient cohort with PE was 56 ±17 years and included 60 male patients. Furthermore, 22% had a history of venous thromboembolism (VTE), 31% of immobility, recent surgery or trauma, and 21% suffered from active malignancy. Finally, 6.2% of the patients were previously diagnosed with COPD and 4.4% with left sided heart failure. The patients without acute PE were less often male (42%), had less frequently previous VTE (13%) and a history of immobility, trauma or recent surgery (21%). Preexisting COPD was more frequent in the patients without PE (16%, Table 1).

Table 1. Demographic findings and clinical characteristics.

	Patients with PE (n=113)	Patients without PE (n=317)	Total population (n=330)
Age (years ±SD)	56 ±17	55 ±17	55 ±17
Male sex (n, %)	60 (53)*	133 (42)*	193 (45)
Previous PE or DVT (n, %)	25 (22)*	42 (13)*	67 (16)
Immobility, surgery, trauma (n, %)	35 (31)*	67 (21)*	102 (24)
Active malignancy (n, %)	24 (21)	77 (24)	101 (24)
COPD (n, %)	7 (6.2)*	51 (16)*	58 (14)
Left sided heart failure (n, %)	5 (4.4)	28 (8.8)	33 (8)

*p<0.05 on Chi-Square test. PE=pulmonary embolism, n=number, DVT=deep vein thrombosis, COPD=chronic obstructive pulmonary disease, SD=standard deviation.

Cardiac function

Table 2 shows the results of the ECG-synchronized volumetric dynamic CT and non-synchronized CT pulmonary angiography diameter ratios. Patients diagnosed with acute PE had significantly lower RV ejection fraction than patients without PE (49.1% vs. 51.8%, p<0.001). End-diastolic and end-systolic RV/LV volume ratios were higher in patients with PE as well. For the LV function measurements, no significant differences were found between patients with and without PE (Table 2). Finally, the RV/LV dimension ratios measured on standard CT pulmonary angiography were significantly higher in patients with PE than in patients without PE (1.0 vs. 0.86, p<0.001).

Table 2. Ventricular ejection fraction and RV/LV volume as well as diameter ratios in patients with and without acute pulmonary embolism.

	Patients with PE	Patients without PE	p-value*
ECG-synchronized CT			
RV ejection fraction (median, IQR)	49.1 (39-54)	51.8 (47-57)	<0.001
LV ejection fraction (median, IQR)	54.8 (49-59)	55.4 (48-61)	0.64
End-diastolic RV/LV volume ratio (median, IQR)	1.1 (1.0-1.4)	1.1 (0.97-1.2)	0.001
End-systolic RV/LV volume ratio (median, IQR)	1.3 (1.0-1.7)	1.1 (0.98-1.4)	<0.001
Non-synchronized CT pulmonary angiography			
RV/LV diameter ratio on axial view (median, IQR)	1.0 (0.92-1.2)	0.86 (0.77-0.94)	<0.001

*Independent samples T-test after logarithmic transformation of the skewed distributed variables.
PE=pulmonary embolism, RV=right ventricle, LV=left ventricle, SD=standard deviation, IQR=interquartile range.

Clinical outcome

Follow-up after six weeks was completed in all 113 patients with PE. Two of the 317 without PE were lost to follow-up (0.63%). Adverse clinical outcome was reported in 10 of 113 patients (8.9%) with acute PE. Seven patients died: four deaths were attributed to acute PE and three patients died of progressive cancer. Furthermore, one patient received thrombolytic therapy because of a saddle embolus, one patient was successfully resuscitated and one patient was admitted to the intensive care unit due to complicated post-surgical course. Of the 317 patients without PE, 22 died during follow-up. Causes of death were malignancy (n=15), pneumonia (n=2), heart failure (n=2), renal failure (n=1), pulmonary fibrosis (n=1) and hemorrhage (n=1).

Table 3 and Figure 1 show the results for ventricular volume ratios and diameter ratios in patients with PE based on clinical outcome. In patients with PE, RV ejection fraction (38.9% vs. 49.7%, p=0.008) and LV ejection fraction (45.7% vs. 55.0%, p<0.05) were both significantly lower in patients who experienced adverse clinical outcome than in patients with an uncomplicated clinical course. Furthermore, axial RV/LV dimension ratios (1.3 vs. 1.0, p=0.007) and end-diastolic and end-systolic RV/LV dimension ratios were both significantly higher in patients with PE and adverse clinical outcome than in those with uncomplicated course (Table 3).

Table 3. Overview of cardiac function in patients with acute pulmonary embolism, with and without adverse clinical outcome.

	Uncomplicated course (n=103)	Adverse outcome (n=10)	p-value*
ECG-synchronized CT			
RV ejection fraction (median, IQR)	49.7 (41-55)	38.9 (28-46)	0.005
LV ejection fraction (median, IQR)	55.0 (50-59)	45.7 (33-55)	0.041
End-diastolic RV/LV volume ratio (median, IQR)	1.1 (1.0-1.3)	1.4 (1.4-2.5)	0.047
End-systolic RV/LV volume ratio (median, IQR)	1.3 (1.0-1.6)	1.8 (1.2-2.6)	0.040
Non-synchronized CT pulmonary angiography			
RV/LV diameter ratio on axial view (median, IQR)	1.0 (0.92-1.1)	1.3 (1.1-1.6)	0.007
Obstruction index (median, IQR)	25 (10-50)	35 (8-63)	0.93

*Chi-Square test based on predefined endpoints. RV=right ventricle, LV=left ventricle, IQR=interquartile range, n=number.

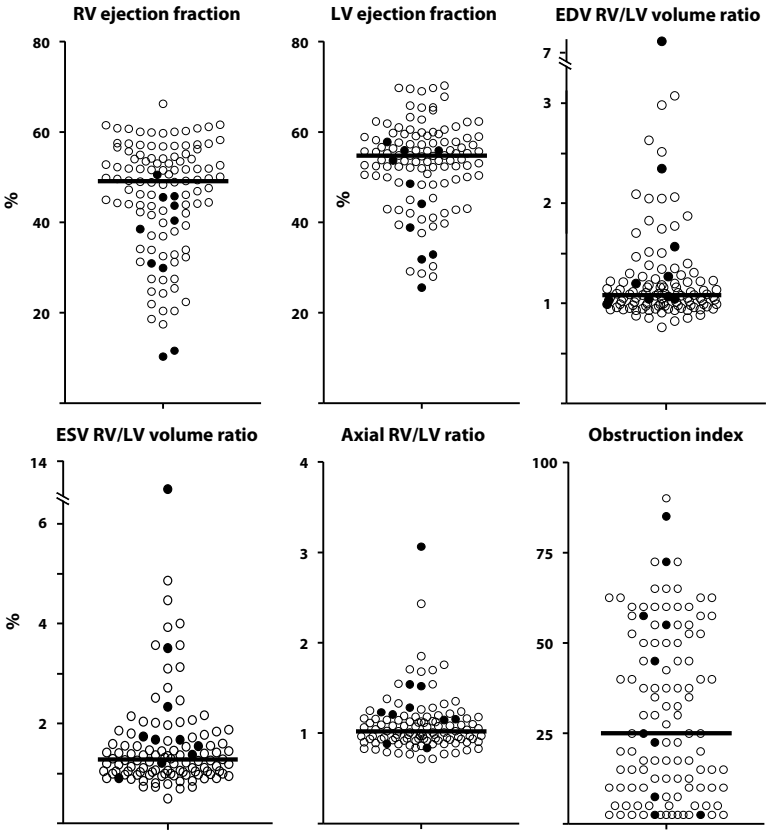

Figure 1. Distribution of the left and right ventricular (LV and RV) ejection fractions, ventricular ratios and obstruction index in the patients with acute pulmonary embolism. Horizontal bars represent medians, black circles represent patients with adverse clinical outcome. ESV=end-systolic volume, EDV=end-systolic volume.

Table 4 shows the predictive values for clinical outcome for the ventricular ejection fractions and RV/LV ratios. The sensitivity of the studied predictors ranged between 50% and 90%, with the highest for RV and LV ejection fraction. Overall, the specificity was lower than the sensitivity, ranging from 37%-69% and was best for the pulmonary obstruction index. The best predictor for adverse clinical events in our population was RV ejection fraction <47% with an adjusted odds ratio of 36 (95% confidence interval [CI] 2.2-590), an AUC of 0.75 (95% CI 0.62-0.88), a positive predictive value of 18% (95% CI 8.6-31%) and a negative predictive value of 98% (95% CI 91- >99.9%). AUCs of LV ejection fraction <57% (difference 0.11; 95% CI 0.04-0.18), end-diastolic RV/LV >1.2 (difference 0.8; 95% CI -0.7-0.23), end-systolic RV/LV ratio >1.4 (difference 0.14; 95% CI 0.07-0.21), axial RV/LV ratio >1 (difference 0.11; 95% CI 0.02-0.21) and pulmonary artery obstruction index >40% (0.16; 95% CI 0.05-0.26) were lower. The AUCs of the ventricular volume and dimension ratios were comparable. Altering the thresholds of our predictors (decrease for RV and LV ejection fraction and increase for the ventricular ratio's and obstruction index) changed the sensitivity/specificity ratio in favor of the specificity, but did not result in significant increase in AUC of ROC analysis for any of the parameters. Finally, ROC analysis of the parameters of RV and LV function in the patients without PE resulted in poor overall predictive accuracy with AUCs ranging from 0.49-0.64.

Table 4. Predictive value of different parameters for adverse clinical outcome in patients with acute pulmonary embolism.

	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	PPV (%, 95% CI)	NPV (%, 95% CI)	AUC (%, 95% CI)
RV ejection fraction <47%	90 (56-99.8)	60 (50-69)	18 (8.6-31)	98 (91- >99.9)	0.75 (0.62-0.88)
LV ejection fraction <57%	90 (56-99.8)	37 (28-47)	9.6 (3.6-19)	97 (88-99.9)	0.64 (0.48-0.79)
ED RV/LV volume ratio >1.2	70 (35-39)	64 (54-73)	16 (6.6-30)	96 (88-99)	0.67 (0.50-0.84)
ES RV/LV volume ratio >1.4	60 (26-88)	62 (52-71)	13 (5.1-27)	94 (85-98)	0.61 (0.42-0.79)
Axial RV/LV dimension ratio >1.0	80 (44-96)	48 (38-58)	13 (5.7-24)	96 (86-99.5)	0.64 (0.47-0.81)
Obstruction index >40%	50 (19-81)	69 (59-77)	13 (4.4-28)	93 (85-98)	0.59 (0.40-0.78)

AUC=area under the curve, PPV=positive predictive value, NPV=negative predictive value, RV=right ventricle, LV=left ventricle, ED=end-diastolic, ES=end-systolic.

DISCUSSION

The main findings of this study were that RV ejection fraction assessed by ECG-synchronized cardiac CT is an important predictor for clinical outcome in patients with acute PE. Furthermore, RV ejection fraction had a superior predictive accuracy compared to LV ejection fraction in this context. Also, ECG-synchronized RV/LV volumes were not better predictors of adverse outcome than static CT assessed RV/LV dimension ratios. Finally, all studied CT measured markers of ventricular function, i.e. both ECG-triggered as well as standard measurements, had comparable

high negative predictive values (94-98%) and limited positive predictive values (9.6-18%) for adverse outcome after PE

Two earlier studies investigated the additional value of ECG-synchronized cardiac CT in patients with acute PE. In one study, cardiac ventricular measurements obtained with standard CT pulmonary angiography and ECG-synchronized cardiac CT were compared in 30 patients with PE, and a statistical model was developed to evaluate the potential improvement in predicting mortality.[17] The mean difference between ECG-synchronized measurements and the non-ECG-gated axial RV/LV ratios was 8%, suggesting an improvement in specificity. Another study that evaluated 29 patients with acute PE found that RV ejection fraction measured by ECG-synchronized CT scans was correlated to the location of the pulmonary emboli and therefore possibly of clinical use in predicting prognosis of patients with acute PE.[16] Both studies had low sample sizes and did not have follow-up data. Our prospective outcome study adds to these findings that RV ejection fraction lower than 47% was indeed associated with poor prognosis (adjusted odds ratio 36) and predicted adverse outcome with high sensitivity (90%) and negative predictive value (98%). Therefore, our results indicate that the risk of adverse events is very low in normotensive patients diagnosed with acute PE but with a RV ejection fraction of 47% or higher. However, although the overall accuracy assessed with ROC analyses showed that RV ejection fraction had a higher ability to correctly classify patients at risk for adverse events than simple RV/LV dimension ratios, the negative predictive values of both tests were similarly high, confirming previous studies that earlier reported a high negative predictive value of ventricular dimension ratios for adverse outcome in patients suffering from PE.[3,12,13] Consequently, the potential additional clinical value achieved by cardiac CT on top of the routine CT-scan in patients with PE was mainly derived from gained specificity. Even so, its positive predictive value (18%) was still insufficient to justify more invasive treatment measures. Notably, in patients without PE, which comprised 74% of our population, no substantial additional value was obtained by ECG-synchronized cardiac CT as well.

As RV/LV dimension ratios, end-diastolic and end-systolic RV/LV volume ratios were also found predictive for clinical outcome. Although volumetric measurements may have been expected to represent a more accurate estimation of RV/LV dimensions, the diagnostic performance of simple RV/LV diameter ratios derived from CT pulmonary angiography was equivalent to that of the RV/LV volume ratios in this study. Apparently, end-diastolic or end-systolic volume ratios alone did not have additional value in representing RV systolic function to ventricular dimension ratios. Remarkably, in our patients with PE, each of the cardiac parameters had better discriminatory value in predicting adverse clinical outcome than the pulmonary artery obstruction index, emphasizing the importance of ventricular evaluation in patients with PE.

Some important clinical issues regarding ECG-synchronized cardiac CT need to be addressed. Radiation exposure was increased by acquiring extra ECG-synchronized CT as compared to CT pulmonary angiography alone (increase of 3-4 mSv), which should be justified when applying the technique. In addition, a small but extra amount of contrast agent was needed for the

cardiac scan (35-40 mL). This might imply a contraindication for patients with renal function impairment. Furthermore, although acquisition of ECG-synchronized data is a fast technique, advanced post-processing is needed for obtaining dynamic volumetric ventricular function by ejection fraction. That process is much more time-consuming than obtaining simple RV/LV diameter ratios from CT pulmonary angiography scans. Therefore, we suggest that with the current techniques and based on this study, the potential benefit of ECG-synchronized cardiac CT for obtaining ventricular function may not outweigh its disadvantages. It remains to be studied whether this technique might be beneficial for selected patient groups with PE and otherwise poor prognosis due to older age or comorbid conditions. Due to the relatively limited study sample, we could not further evaluate this latter hypothesis.

Although previous studies have shown the prognostic value of RV dysfunction on clinical outcome in patients with acute PE[3,5,8], this is to our knowledge the first large prospective study that investigated the predictive value for short term clinical outcome of ECG-gated cardiac CT in patients with and without acute PE. Still, one study limitations remains. Although the lost to follow-up rate was very low (0% and 0.63% for patients with and without PE respectively), the total sample size and the number of adverse events reported in this study were relatively limited, contributing to the high negative predictive values with broad confidence intervals.

In conclusion, RV ejection fraction, obtained with ECG-synchronized cardiac CT was found the best predictor for clinical outcome in patients with acute PE, although only of weak additional value to axial RV/LV diameter ratios obtained with standard CT pulmonary angiography.

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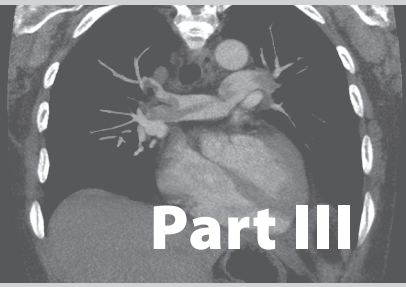
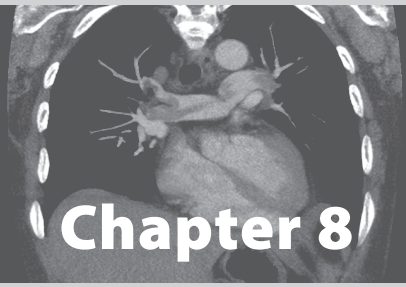


Part III

Long term clinical course of acute pulmonary embolism



Chapter 8

Prospective cardiopulmonary screening program to detect chronic thromboembolic pulmonary hypertension in patients after acute pulmonary embolism

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ABSTRACT

Rationale

Chronic thromboembolic pulmonary hypertension (CTEPH) after pulmonary embolism (PE) is associated with high morbidity and mortality. Understanding the incidence of CTEPH after PE is important for evaluating the need for screening but also debated as a result of different inclusion criteria among previous studies. We determined the incidence of CTEPH after acute PE in an unselected patient cohort, and the utility of a screening program for this disease.

Methods

A cohort screening study in an unselected series of consecutive patients (n=866) diagnosed with acute PE between January 2001 and July 2007 was conducted. All patients who were not previously diagnosed with pulmonary hypertension (PH) and had survived until study inclusion were invited for echocardiography. Patients with echocardiographic suspicion of PH underwent complete work-up for CTEPH, including ventilation-perfusion scintigraphy and right heart catheterization.

Results

After an average follow-up of 34 months and from all 866 patients, PH was diagnosed in 19 patients by routine clinical care and in 10 by our screening program; 4 patients had CTEPH, who were all diagnosed by routine clinical care. The cumulative incidence of CTEPH after all cause PE was 0.57% (95% confidence interval [CI] 0.02-1.2%) and after unprovoked PE 1.5% (95% CI 0.08-3.1%).

Conclusion

The incidence of CTEPH after PE in our large and unselected patient cohort was 0.57%. Because of this low incidence and the very low yield of the echocardiography based screening program, wide scale implementation of prolonged follow-up including echocardiography of all patients with PE to detect CTEPH seems not warranted.

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a life-threatening condition characterized by intraluminal thrombus organization and fibrous stenosis or complete obliteration of the pulmonary arteries.[1] CTEPH has commonly been associated with acute pulmonary embolism (PE), although the pathogenesis of impaired clearance of acute thrombi and the resulting vascular remodeling is unknown, and a history of symptomatic venous thromboembolism (VTE) is lacking in 31–42% of the patients diagnosed with CTEPH.[1-3]

The incidence of CTEPH has been reported to be between 0.1% and 8.8% in patients after acute PE.[1,4-7] This wide range can be explained by important differences in the inclusion and diagnostic criteria between these previous studies: selection of patients was often based on the etiology of the acute PE, patients with other comorbid conditions associated with pulmonary hypertension were frequently excluded and the diagnosis of CTEPH was not always confirmed by right heart catheterization.[1,4-7]

Since CTEPH is a very serious but potentially treatable disease, the exact incidence of CTEPH in the clinical course of acute PE is of particular interest. High frequencies of 3.8 to 8.8%[4,6] would suggest the need for prolonged follow-up after discontinuation of anticoagulant therapy including specific screening programs for CTEPH by echocardiography, whereas lower frequencies would not.

The purpose of this study was to evaluate the efficacy of a screening program for CTEPH in patients after acute PE. This evaluation was based on the overall incidence of CTEPH and the additional utility of this screening program on top of standard clinical care. Accordingly, we performed a prospective cohort screening study evaluating the occurrence of CTEPH in an unselected large series of patients diagnosed with acute PE.

METHODS

Patients

Consecutive patients diagnosed with a first or recurrent episode of acute PE in the period between January 1st 2001 and July 1st 2007 of an academic (Leiden University Medical Center, Leiden, the Netherlands) and affiliated teaching hospital (Medical Center Haaglanden, The Hague, the Netherlands) were eligible for study inclusion, irrespective of age, medical history or comorbid conditions. Neither of these 2 hospitals serves as a tertiary referral center for CTEPH. All patients diagnosed and treated for acute PE are registered in a database by physicians of all clinical specialties of both hospitals. For the purpose of this study, we have crosschecked this database with data from the radiology department to ensure no patients were missing. The diagnosis of acute PE was verified for all registered patients according to predefined criteria which were intraluminal filling defects on pulmonary angiography or computed tomography

pulmonary angiography (CTPA), high probability ventilation perfusion scintigraphy (VQ-scan) or intermediate probability VQ-scan in combination with objectively diagnosed deep venous thrombosis (DVT).[8] All patients fulfilling these criteria were included in this analysis. Unprovoked PE was defined as PE occurring in the absence of the following risk factors: active malignancy, immobility more than 3 days or recent long flight, recent surgery or fracture of extremity, pregnancy or peri-partum period, hormone replacement therapy and use of oral contraception. Patients were initially treated with at least 5 days of either unfractioned heparin aiming at a 1.5 to 2.5 prolongation of the activated partial thromboplastin time, or weight based therapeutic doses of LMWH, followed by vitamin K antagonists for a period of at least 6 months with a target international normalized ratio (INR) of 2.0 to 3.0.[9] In patients with severe acute PE, anticoagulant treatment was preceded by administration of thrombolytic drugs, thrombosuction or surgical embolectomy according to the judgment of the attending clinician. Clinical follow-up and treatment monitoring after hospital discharge were performed in the local pulmonary, internal or vascular medicine outpatient clinic as well as in the anticoagulation clinic.

Outcome

Primary outcomes of this study were the incidence of CTEPH and the effectiveness of our screening program. Criteria for the diagnosis of CTEPH were mean pulmonary artery pressures assessed by right heart catheterization exceeding 25 mmHg and normal pulmonary capillary wedge pressure in combination with an abnormal perfusion scintigram and signs for distal or central CTEPH on conventional pulmonary angiography.[10,11] CTEPH was considered excluded in case of a normal perfusion scintigram.[10,11]

Procedures

The original admission and outpatient medical charts of all patients diagnosed with acute PE in the registration period were systematically reviewed using predefined criteria. Only patients with geographical inaccessibility (living outside the Netherlands) precluding follow-up were excluded from study participation. Data regarding diagnostic management, etiology, treatment and documented clinical course of the acute PE at registration as well as recurrent episodes, and established diagnosis of pulmonary hypertension were assembled. For all eligible patients who had died before study inclusion (July 2007), time and cause of death were extracted from the autopsy report or verified with the treating physician or general practitioner. All surviving patients not identified as having pulmonary hypertension were interviewed by telephone to obtain a detailed medical history, presence of clinical symptoms suggestive of pulmonary hypertension and if applicable, results of recent echocardiography. In addition, information on known risk factors for venous thromboembolism (VTE) and CTEPH were noted down. The latter includes large central emboli, unprovoked VTE, splenectomy, presence of lupus anticoagulant or antiphospholipid antibodies, chronic inflammatory conditions and ventriculo-atrial shunts.[12] Furthermore, all these latter patients were invited for a single visit to our vascular medicine

outpatient clinic for a pulmonary hypertension screening by echocardiography. This visit was scheduled between July 1st 2007 and January 1st 2009 and planned at least one year after the index event, or one year after a recurrent thromboembolic episode, to rule out the initial effect of acute PE. All patients who responded to our invitation underwent physical examination and standardized transthoracic echocardiography performed by an experienced technician. This echocardiography was reviewed by an independent expert cardiologist, without knowledge of the patient's medical condition. Echocardiographic criteria for suspected pulmonary hypertension were one or more of the following: 1) maximal tricuspid regurgitation velocity >2.8 m/s, 2) estimated systolic pulmonary artery pressure ≥35 mmHg (maximal pressure gradient across the tricuspid valve calculated by the modified Bernoulli equation plus the estimated right atrium pressure), 3) estimated mean pulmonary artery pressure ≥25 mmHg (estimated systolic pressure plus 2 times enddiastolic pressure as estimated by pulmonary regurgitation enddiastolic velocity divided by 3), 4) borderline value of criterion 1 or 2 in combination with a right ventricular TEI index >0.36 (isovolumic contraction time plus isovolumic relaxation time divided by ejection time), 5) secondary changes associated with pulmonary hypertension, e.g. systolic septal flattening, right ventricular hypertrophy or W-pattern in the right ventricular outflow curve, 6) AcT (acceleration time) <120 or AcT/RVET (right ventricular ejection time) <0.40.[11,13,14] All patients who met one or more of these 6 criteria were suspected of having pulmonary hypertension and underwent further standardized work-up including perfusion lung scintigraphy and right heart catheterization for pressure measurements. The final diagnosis was assessed by an independent expert panel according to our predefined criteria. This study was approved by the Institutional Review Board of both participating hospitals and all patients provided written informed consent.

Statistical analysis

Patients were categorized in 4 sub-groups according to their medical history of single or recurrent and provoked or unprovoked PE. The cumulative incidence of CTEPH after acute PE for all 4 study groups was calculated by the Kaplan-Meier life table method. In addition, we calculated the incidence rates of CTEPH. The number of patient years (py) for both analyses was calculated from the date of the index event until diagnosis of CTEPH was established or ruled out or else until death had occurred, whichever came first. SPSS version 14.02 (SPSS Inc, Chicago, IL) was used for all analysis.

RESULTS

Patients

In 877 patients the diagnosis of acute PE had been established between January 1st 2001 and July 1st 2007. Eleven patients were excluded because of geographical inaccessibility, leaving

866 patients for study inclusion. General characteristics of these patients are shown in Table 1: mean age at registration was 56 years, 410 (47%) were males and 308 patients (36%) had suffered an unprovoked episode of PE. More than 90% of the patients were initially treated with either unfractionated heparin or LMWH alone. A small number of patients additionally received thrombolytic therapy, had a vena cava filter inserted or had surgical embolectomy performed (Table 1). The average follow-up period was 2.8 years.

Table 1. Characteristics of included patients.

	Study patients (n=866)
Age at registration event (years ±SD)	56 ±19
Male sex (n, %)	410 (47)
Unprovoked PE (n, %)	308 (36)
Initial treatment first PE	
Low molecular/unfractioned heparin (n, %)	808 (93)
Thrombolysis (n, %)	38 (4.4)
Surgery, VCF or both (n, %)	20 (2.3)
COPD (n, %)	83 (9.6)
Left sided heart failure (n, %)	42 (4.8)
Overall mortality[§] (n, %)	259 (30)
PE related mortality (n, %)	67 (7.7)
Malignancy related mortality (n, %)	110 (13)
Other (n, %)	82 (9.4)
Number of patient years[‡]	2427

[‡]Number of years from registration date until diagnosis of CTEPH was established or ruled out, or until death had occurred; [§]mortality between registration date and July 1st 2007. PE=Pulmonary embolism, SD=standard deviation, n=number, VCF=vena cava filter, COPD=chronic obstructive pulmonary disease.

Chart review

After reviewing the medical charts of all patients, 19 cases of previously diagnosed pulmonary hypertension were identified (Figure 1) of whom 4 had CTEPH. During the study period 259 patients died, 67 (7.7%) as a direct result of acute (recurrent) PE, 110 (13%) of malignant disease and 82 (9.4%) by other conditions. Of these 259 patients, 185 (71%) had died within the first year after the acute PE, 216 (83%) within 2 years, 238 (92%) within 3 years and 247 (95%) within 4 years. In 69 patients, autopsy reports or echocardiography performed before the patients' death ruled out the presence of pulmonary hypertension. Further, pulmonary hypertension was not adjudicated as cause of death in any of these patients. Therefore, and in accordance with criteria from previous studies[4-7], we assumed that none of these patients had developed CTEPH.

The remaining 588 patients were invited for our screening program. We were able to complete this program in 402 (68%) of them. None of these patients had clinically suspected acute PE at the moment of echocardiography. Echocardiographic criteria for suspected pulmonary

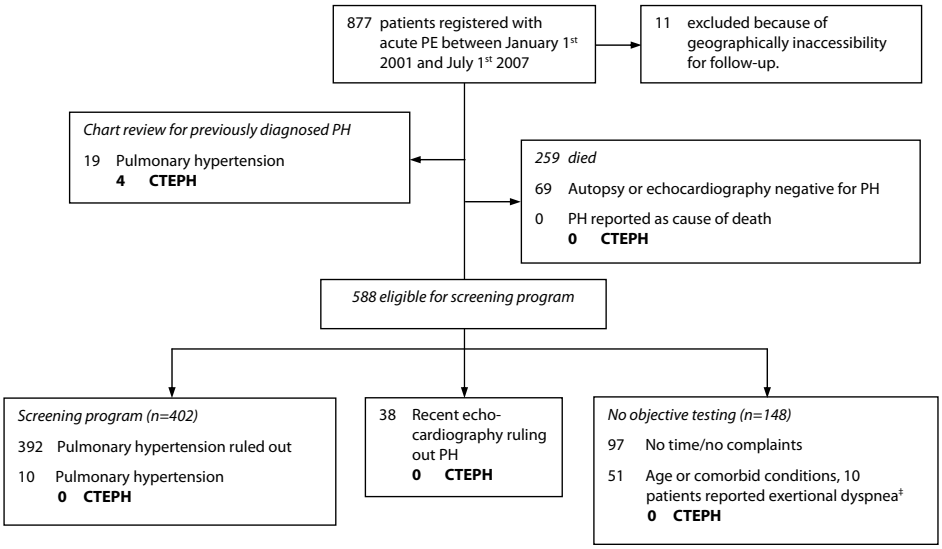

Figure 1. Flowchart of the cohort study. ‡In all 10 patients (100%) with dyspnea, previously diagnosed cardiopulmonary disease reasonably explaining the dyspnea was reported. PE=pulmonary hypertension, PH=pulmonary hypertension, CTEPH=chronic thromboembolic pulmonary hypertension.

hypertension were met by 25 patients. After further clinical work-up and right heart catheterization, pulmonary hypertension was diagnosed in 10 of these patients.

From the 186 patients who did not respond to our invitation, 38 had undergone echocardiography for clinical reasons other than our screening study. None of these patients was diagnosed with pulmonary hypertension. Objective testing for pulmonary hypertension was not performed in the remaining 148 surviving patients. Of these, 97 declared to be in excellent health without any physical complaints and to have no time to be involved in any clinical trials. The final 51 patients were unable to visit our hospital due to old age or comorbid conditions. Most of these patients were over the age of 80 years and suffered from severe cancer. Of these latter 51 patients, 10 reported exertional dyspnea that was reasonably explained by previously diagnosed cardiopulmonary diseases, i.e. chronic obstructive pulmonary disease (COPD), systolic left-sided heart failure, pulmonary cancer, severe anemia or a combination of these conditions. Since none of these patients had unexplained dyspnea[4-6] we assumed that CTEPH was not present in these patients for the purpose of the incidence calculation.

Incidence of CTEPH

Upon study inclusion, 19 patients with a history of PE were already diagnosed with pulmonary hypertension of various causes. Among these, 4 had been diagnosed with CTEPH by routine clinical care, and CTEPH was ruled out by perfusion scintigraphy or pulmonary angiography in the remaining 15 patients. Our screening program identified an additional 10 patients with pulmonary hypertension, but distal or central CTEPH was ruled out in all of these patients after

Table 2. Characteristics of patients with CTEPH.

CTEPH	Sex	Age at first PE (years)	Recurrent PE	Risk factor first PE	Localisation first PE	Thrombolysis, VCF or surgery for first PE	Additional risk factors for CTEPH[§]	Time from first PE to diagnosis CTEPH (days)	Mean PAP at diagnosis CTEPH (mmHg)	NYHA classification at diagnosis CTEPH
1	female	70	Yes	unprovoked	segmental	No	none	118	48	II
2	male	68	No	unprovoked	central	No	none	298	50	III
3	female	59	No	unprovoked	central	No	none	466	48	III
4	female	65	No	unprovoked	segmental	No	none	157	49	III

[§]Additional risk factors for CTEPH to central PE and unprovoked PE, i.e. splenectomy, lupus anticoagulant or antiphospholipid antibodies, chronic inflammatory conditions and ventriculo-atrial shunts.[12] CTEPH=chronic thromboembolic pulmonary hypertension, PE=pulmonary embolism, NYHA=New York Heart Association, PAP=pulmonary artery pressure.

Table 3. Cumulative incidence by the Kaplan-Meier life table method and incidence rates of CTEPH in the study population.

	Number	Cumulative incidence		Incidence rate	
	n CTEPH/n overall	%	95% CI	n/100 py	95% CI
Overall population	4/866	0.57	0.02-1.2	0.16	0.04-0.42
Single event	3/671	0.59	0.02-1.3	0.16	0.03-0.48
Recurrent events	1/195	0.53	0.01-1.6	0.17	0.004-0.93
Unprovoked PE	4/308	1.5	0.08-3.1	0.44	0.12-1.1
Single event	3/220	1.7	0.05-3.7	0.47	0.10-1.4
Recurrent events	1/88	1.2	0.01-3.6	0.37	0.01-2.1
Provoked PE	0/558	0.0	-	0.0	0.0-0.24
Single event	0/451	0.0	-	0.0	0.0-0.31
Recurrent events	0/107	0.0	-	0.0	0.0-1.1

CTEPH=chronic thromboembolic pulmonary hypertension, n=number, CI=confidence interval, PE=pulmonary embolism, py=patient years.

normal perfusion scintigraphy or pulmonary angiography. All 4 patients with CTEPH returned to their physician within 2 years after their first acute PE because of typical symptoms of CTEPH, including exertional dyspnea (Table 2). None of them was found to have additional risk factors for CTEPH or other comorbidity causing pulmonary hypertension. The diagnoses were confirmed by right heart catheterization and measurement of pulmonary artery pressure. Mean time to diagnosis was 260 days. The cumulative incidence of CTEPH in our cohort was 0.57% (4/866, 95% CI 0.02-1.2%) in the overall population, 1.5% (4/308, 95% CI 0.08-3.1%) in the patients with unprovoked PE and 0.0% (0/558) in the patients with provoked PE (Table 3, Figure 2). Incidence rate of CTEPH was 0.16/100 py (95% CI 0.04-0.42/100 py) for the overall population, 0.44/100 py (95% CI 0.12-1.1/100 py) for patients with unprovoked PE and 0.0/100 py (95% CI 0.0-0.24/100 py) for patients with provoked PE (Table 3). Incidences following a single event or recurrent disease were not different between the study groups (Table 3).

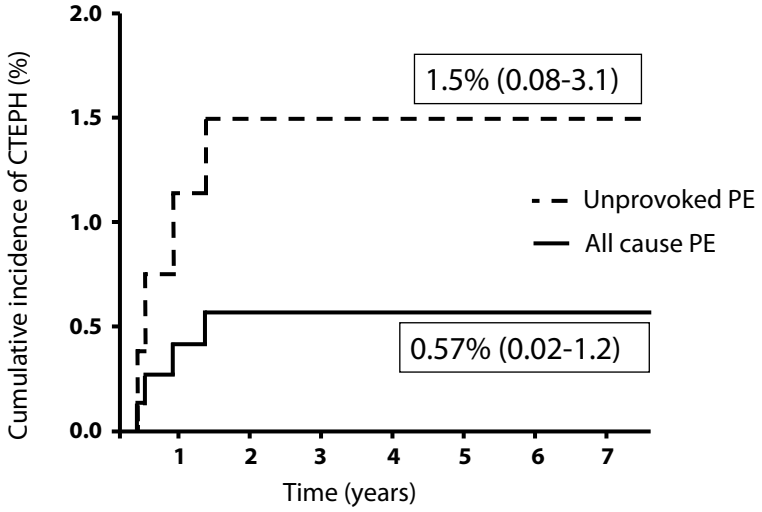

Figure 2. Cumulative incidence of chronic thromboembolic pulmonary hypertension.

Follow-up of patients with CTEPH

Because of distal pulmonary artery involvement, only 1 of the 4 patients with CTEPH was considered suitable for pulmonary endarterectomy. However, this patient refused surgery for personal reasons and was treated with the oral dual endothelin receptor antagonist bosentan.[15] Two additional patients were treated with bosentan of whom one developed severe elevation of transaminases. As a consequence, this treatment was stopped in the latter patient. The final patient did not receive treatment because of the benign clinical presentation of CTEPH (NYHA Class II, satisfactory exercise tolerance without severe desaturation during maximal exercise). At the moment of drafting this paper (April 1st 2009) and after a mean follow-up of 43 months after diagnosis of CTEPH, the clinical condition of all 4 patients was stable.

Efficacy of the screening program

Ten patients with pulmonary hypertension were identified by the screening program in the 402 patients with a history of acute PE but without established pulmonary hypertension, with a mean of 2.8 years after the index thromboembolic event. Pulmonary angiography did not reveal CTEPH in these 10 patients: the pulmonary hypertension was caused by left sided heart disease in 5 patients and by COPD in the remaining 5 patients. All patients with CTEPH from our total study population were previously diagnosed by routine clinical practice.

DISCUSSION

This study has two main findings. First, we observed a 0.57% incidence of CTEPH after acute PE in an unselected large patient series. Second, the yield of a standard screening program to detect CTEPH in patients after acute PE is low, since additional cases of CTEPH to cases identified by routine clinical care, were not detected in our study population.

Understanding of the CTEPH incidence is important to guide the screening and diagnostic strategy in patients after acute PE. The incidence of CTEPH we observed challenges other studies reporting higher incidences ranging from 3.8 to 8.8%.[4-7] There are several reasons for these discrepancies. These previous studies included selected patient cohorts, e.g. excluding patients with transient or permanent risk factors for PE[5] and excluding patients with other conditions associated with pulmonary hypertension.[4-6] In addition, the diagnosis of CTEPH was partly based on results from echocardiography alone without confirmation by right heart catheterization.[6] An incidence of 3.8% was reported in the widely quoted study by Pengo et al, which is considerably higher than the incidence observed in our population.[4] That study and our study mainly differed in inclusion criteria: whereas we only excluded patients who were geographically inaccessible, Pengo additionally excluded all patients with other diseases that could have caused non-thromboembolic pulmonary hypertension (e.g. COPD) or had preexisting exertional dyspnea. Although by design of our study, we are unable to precisely estimate the prevalence of those latter patients in our cohort, they provide a considerable contribution to our sample size. The selection criteria applied by Pengo may have influenced his results, leading to a higher incidence of CTEPH. The duration to diagnosis (within 2 years after diagnosis of PE) on the other hand was well comparable between the 2 studies.

We consider our results to be representative for several reasons. First, we included all patients that presented to the participating hospitals, independently on etiology or severity of the acute PE or presence of comorbid conditions. Our study comprised about 3 times the number of previous reports. All patients received up-to-date anticoagulant treatment regimes with a duration of at least 6 months. Our study involved well over 2400 patient years and only 11 patients (1.3%) were excluded for geographical reasons. Second, we studied all patients with PE, irrespective of persistent symptoms at follow-up and used very sensitive echocardiographic

criteria for establishing the suspicion of pulmonary hypertension.[11,13,14] Third, all cases of CTEPH were diagnosed after invasive hemodynamic measurements and pulmonary artery angiography. Fourth, all patients with CTEPH presented with typical symptoms of pulmonary hypertension and were diagnosed with CTEPH within the first 2 years after their first acute PE. These observations are consistent with the results of earlier studies.[4-7] Finally, the incidence of CTEPH in patients with unprovoked PE in our study was 1.5%. This is in accordance with or within the lower limit of the confidence interval of the incidences described in studies focusing solely on patients with unprovoked PE.[4,5]

It could be reasoned that our estimation of 0.57% represents an underestimation of the incidence of CTEPH since objective testing to confirm or reject this diagnosis was not performed in the complete study population. However, this same issue can be applied to all previous reports on this subject. The vast majority of the non-survivors in our study died within one year after the PE was diagnosed, and a reasonable alternative cause of death was reported in all of them. Furthermore, all cases of CTEPH presented with symptoms of cardiopulmonary impairment. Hence, it is unlikely that we missed cases of CTEPH in the asymptomatic patients who were not able to visit our outpatient clinic or in the patients that had died. Also, plausible alternative diagnoses for dyspnea were confirmed in all 10 patients who reported exertional dyspnea but did not visit our outpatient clinic. Importantly, our estimated incidence of 0.57% is only applicable to patients with a history of acute PE, and not to a more general population.

In this study, a cardiopulmonary screening program to detect CTEPH was evaluated. Although completed by 402 patients, this screening program did not result in any additional patients being detected with a diagnosis of CTEPH beside those patients that were identified by routine clinical practice. In combination with the low frequency of CTEPH, this leads to the conclusion that wide scale implementation of screening programs for CTEPH after acute PE is not warranted and echocardiography to rule out or establish CTEPH should be restricted to patients presenting with characteristic symptoms.

We conclude that CTEPH is a rare complication of acute PE (incidence 0.57%) and that this diagnosis is more frequent in patients with unprovoked acute PE (incidence 1.5%). CTEPH becomes clinically apparent and is diagnosed within the first 2 years following acute PE. Wide scale screening for CTEPH after acute PE results in a very low yield. Although CTEPH occurs infrequently in the clinical course of acute PE, physicians should be aware of this potentially lethal but treatable disease, especially in those patients with unprovoked disease and persistent dyspnea. The direct clinical consequence of our study is that because of the very low incidence of CTEPH after PE, the implementation of extensive follow-up programs for the detection of CTEPH after acute PE seems to be unnecessary.

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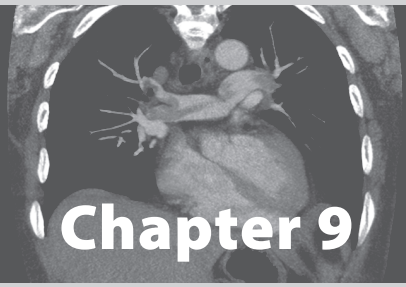

Chapter 9

A simple non-invasive diagnostic algorithm for ruling out chronic thromboembolic pulmonary hypertension in patients after acute pulmonary embolism

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Submitted

ABSTRACT

Background

Our aim was to construct a diagnostic model for ruling out chronic thromboembolic pulmonary hypertension (CTEPH) in symptomatic patients after acute pulmonary embolism (PE) that is based on simple, non-invasive tests.

Methods

Plasma levels of various CTEPH associated biomarkers and conventional ECG criteria for right ventricular hypertrophy were assessed in 82 consecutive patients with confirmed CTEPH and 160 consecutive patients with a history of PE who were suspected to have CTEPH, but in whom this disease was ruled out.

Results

ECG criteria of right ventricular hypertrophy were detected more frequently in the patients with CTEPH (77%) than in the patients without CTEPH (11%, Odds ratio 26, 95% confidence interval [CI] 13-53). Also, clotting factor FVIII activity and the levels of N-terminal-pro-brain-type natriuretic peptide (NT-pro-BNP), Growth Differentiation Factor-15, C-reactive protein and urate, but not D-dimer level, were higher in patients with CTEPH. A diagnostic model including ECG criteria and NT-pro-BNP levels had a sensitivity of 94% (95% CI 86-98%) and a specificity of 65% (95% CI 56-72%). The area under the receiver-operator-characteristic curve was 0.80 (95% CI 0.74-0.85) for the diagnosis of CTEPH. Even with high disease prevalences of up to 10%, the negative predictive value of this model proved to be very high (99%, 95% CI 97- >99.9%).

Conclusions

Ruling out CTEPH in patients after acute PE seems to be safe without additional diagnostic testing in absence of ECG criteria indicative of right ventricular hypertrophy and a normal NT-pro-BNP level.

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) results from chronic obstruction of the pulmonary vascular bed by organized thrombi.[1] The incidence of CTEPH in patients who suffered from acute pulmonary embolism (PE) has been reported to be in the range of 0.5-3.8%, depending on the selection criteria applied in the individual studies.[1-3] The prognosis of patients with CTEPH is poor, unless a successful pulmonary endarterectomy is possible.[1,4] Therefore, early recognition of this disease is crucial for timely referral to a center specialized in the management of pulmonary hypertension, allowing swift and adequate therapeutical intervention.

The clinical presentation of CTEPH is characterized by non-specific symptoms and include exercise intolerance and dyspnea, fatigue, chest pain and syncope (at exercise). These symptoms are also consistent with other, more common cardiopulmonary conditions such as asthma, chronic obstructive pulmonary disease (COPD), interstitial lung disease, coronary artery disease, cardiac arrhythmia or heart failure not caused by chronic pulmonary thrombi.[1,5,6] These non-specific symptoms are commonly reported by patients who suffered from an acute PE and therefore, the possibility of CTEPH can be frequently considered.[7] The diagnostic management of CTEPH is complex. In many patients pulmonary perfusion scintigraphy, transthoracic echocardiography and conventional pulmonary angiography with determination of pulmonary hemodynamics need to be performed before the diagnosis of CTEPH can be refuted. Thus, there is great need for more simple, easily available, less invasive and less expensive tests to safely rule out CTEPH.[1] These tests may include conventional 12-lead electrocardiography (ECG) and biomarkers of heart failure, inflammation or thrombosis that are associated with the pathogenesis or prognosis of CTEPH, and which are widely available for and applicable to outpatient medical care.[8-13] Although the prognostic value of these biomarker levels for CTEPH and/or other entities of pulmonary hypertension are well described, their diagnostic potential has not been systematically studied.[8-13]

In the present study, we examined whether CTEPH can be ruled out in symptomatic patients with a documented history of acute PE by using ECG assessment and measurement of several biomarkers, i.e. N-terminal-pro-B-type natriuretic peptide (NT-pro-BNP), Growth Differentiation Factor-15 (GDF-15), C-reactive protein (CRP), urate, plasma factor VIII coagulant activity (FVIII:C) and D-dimer, or a combination of these tests.

METHODS

Patients

We studied patients from a large follow-up study of patients with acute PE in an academic (Leiden University Medical Center, Leiden, the Netherlands) and affiliated teaching hospital

(Medical Center Haaglanden, The Hague, the Netherlands).[3] This study included all patients who were diagnosed with acute PE between January 2001 and July 2007. The diagnosis of acute PE was based on intraluminal filling defects on pulmonary angiography or computed tomography pulmonary angiography (CTPA), high probability ventilation perfusion scintigraphy (VQ-scan) or intermediate probability VQ-scan in combination with objectively diagnosed deep vein thrombosis (DVT).[14] All patients were treated with at least 5 days of either unfractionated heparin or weight based therapeutic doses of low molecular weight heparin, followed by vitamin K antagonists for a period of at least 6 months. From the 877 consecutive patients diagnosed with PE, 259 had died before the start of the study, 11 were living abroad and therefore were lost to follow-up, 19 were previously diagnosed with pulmonary hypertension and 186 declined participation. For the present analysis, we only studied the remaining patients who reported exertional dyspnea and decreased exercise performance and therefore were suspected of having CTEPH. We additionally included 82 consecutive patients from a CTEPH referral center (Academic Medical Center, Amsterdam, the Netherlands) who were previously diagnosed with CTEPH by regular clinical care. This study was approved by the Institutional Review Board of all participating hospitals and all patients provided informed consent.

Procedures

The routine diagnostic work-up of patients with suspected CTEPH consisted of echocardiography and pulmonary perfusion scintigraphy. If these tests were suggestive of CTEPH, the diagnosis was confirmed or refuted by pulmonary angiography in combination with right heart catheterization. Criteria for the diagnosis of CTEPH were a mean pulmonary artery pressure (mPAP) assessed by right heart catheterization exceeding 25 mmHg and a normal pulmonary capillary wedge pressure in combination with segmental of subsegmental perfusion defects on perfusion scintigram and signs of CTEPH on conventional pulmonary angiography.[1,15] All patients were classified according to the modified New York Heart Association (NYHA) classification of the World Health Organization. Conventional 12-lead ECGs were obtained and blood samples were drawn and stored on the day that the participants of the follow-up study were screened for pulmonary hypertension, or before pulmonary endarterectomy was performed or medical treatment was initiated in the patients with established CTEPH. The ECGs were recorded with the patient in supine position for a 10-second period using the standard 12-lead electrode configuration at a conventional speed (25 mm/s) and sensitivity (1 mV/10 mm). All ECGs were evaluated for the presence of one or more of the following three criteria of right ventricular hypertrophy that have been demonstrated by multivariate logistic regression to predict the presence of pulmonary hypertension optimally: 1) rSR' or rSr' pattern in lead V1, 2) R:S >1 in lead V1 with R >0.5mV and 3) QRS axis >90°.[16]

All blood samples were analyzed in batches after a single thaw. Levels of NT-pro-BNP were measured with the use of quantitative immunoassays (Hitachi Modular E 170 unit, Roche Diagnostics, Mannheim, Germany). GDF-15 serum concentrations were assessed by

immunoradiometric assays using a polyclonal GDF-15 affinity-chromatography-purified, goat anti-human GDF-15 IgG antibody (AF957) from R&D Systems (Minneapolis, MN).[17] CRP and urate measurements were performed using a Hitachi Modular system according the recommendations of the reagent manufacturer (Roche, Diagnostics, Mannheim, Germany). FVIII:C was measured in a one-stage APTT-based clotting assay using immunodepleted FVIII-deficient plasma and automated APTT (BioMerieux, Boxtel, the Netherlands) on an automated coagulation analyzer (STA-R Evolution, Diagnostica Stago, Roche Diagnostics). Results for FVIII:C are expressed as international units (IU) per dL with reference to a normal pooled plasma calibrated against the 4th WHO international standard FVIII/VWF plasma (97/586) (NIBSC, Potters Bar, UK). The D-dimers were measured on the same analyzer using the STA-Liatest D-dimer assay (Diagnostica Stago). The detection range was ≥50 pg/mL for NT-pro-BNP, ≥20 ng/L for GDF-15, ≥1.0 mg/mL for CRP and ≥250 ≤20000 ng/mL for D-dimer. All biomarker measurements were performed by investigators who were blinded to the patients' diagnosis. We used predefined reference values for the biomarkers under study to predict the presence of CTEPH: NT-pro-BNP dependent on age and sex as suggested by the manufacturer, GDF-15 ≥1200 ng/L, CRP ≥3.0 mg/L, urate >0.34 mmol/L for female and >0.42 mmol/L for male patients as suggested by the manufacturer, FVIII:C ≥150 IU/dL, and D-dimer >500 ng/mL FEU being the optimal predictor of thrombosis.[17-19]

Statistics

We calculated the sensitivity and specificity of the conventional ECG criteria of right ventricular hypertrophy and the biomarkers under study for the presence of CTEPH in all patients. Patients from the screening study who were identified as having pulmonary hypertension of other etiology than CTEPH were excluded from further analysis. Differences between the study groups were analyzed using independent samples T-tests for normally distributed continuous variables, Mann-Whitney-U tests for skewed distributed continuous variables and Chi-Square tests for categorical variables. Further, starting with the clinical test with the highest area under the receiver operator characteristic (AUC of ROC) curve and thus with the highest predictive accuracy, we derived 7 additional clinical models by including consecutive diagnostic tests with decreasing AUC in a model to identify the most favorable combination of clinical tests for this purpose. AUC of ROC analyses were compared by the method described by Hanley and McNeil.[20] Our final diagnostic model was based on the combination of diagnostic tests with the optimal combination of sensitivity and thus negative predictive value, and specificity for efficacy reasons. Finally, we used the following formula to calculate the negative predictive value of the newly constructed optimal model according to increasing assumed prevalences of CTEPH: (specificity*(1-prevelence))/{((1-sensitivity)*prevalence) + (specificity*(1-prevalence))}. SPSS version 14.02 (SPSS Inc, Chicago, IL) was used for all analysis. A p-value of <0.05 was considered to indicate a significant difference.

RESULTS

Study patients

We included 170 patients with a history of acute PE and clinically suspected CTEPH. Of these patients, 10 were diagnosed with pulmonary hypertension by right heart catheterization, but none with CTEPH. Therefore, these 10 patients were excluded from further analysis. Pulmonary hypertension was ruled out in the remaining 160 patients. An alternative explanation for the dyspnea was found in the majority of the patients, and was previously established or newly diagnosed heart or lung disease, anemia, morbid obesity or a combination of these conditions. The study population was completed by 82 consecutive patients with established CTEPH. The baseline characteristics of the study patients are presented in Table 1.

Table 1. Patient characteristics.

	Patients with CTEPH (n=82)	**Patients in whom CTEPH was ruled out (n=160)**	**p-value**
Age (years ±SD)	57 ±14	57 ±16	NS
Male sex (n, %)	32 (39)	73 (46)	NS
Active malignancy (n, %)	8 (9.8)	22 (14)	NS
COPD (n, %)	6 (7.3)	35 (22)	0.04
Left sided heart disease (n, %)	6 (7.3)	22 (14)	<0.001
BMI, kg/m^2 (mean, ±SD)	28 ±6.0	29 ±5.2	NS
mPAP, mmHg (mean, ±SD)	44 ±11	-	NA

CTEPH=chronic thromboembolic pulmonary hypertension, n=number, SD=standard deviation, COPD=chronic obstructive pulmonary disease, BMI=body mass index, NS=no statistical significance, NA=not applicable, mPAP=invasively measured mean pulmonary artery pressure.

ECG characteristics and biomarker levels

The typical predefined electrocardiographic signs of pulmonary hypertension were detected significantly more often in patients with CTEPH (77%) than in the symptomatic patients without pulmonary hypertension (11%; Odds ratio 26, 95% confidence interval [CI] 13-53). A closer look at the distribution of the 3 ECG characteristics revealed that right axis was observed most frequently in patients with CTEPH (55%), followed by rSR' or rSr' pattern in lead V1 (45%) and R:S >1 in lead V1 with R >0.5mV (28%); 31 (38%) patients with CTEPH had more than one of the three prespecified ECG characteristics. Circulating levels of NT-pro-BNP, GDF-15, CRP and urate were significantly higher in patients with CTEPH than in the other study group (Table 2 and Figure 1). On the other hand, D-dimer levels were not different between the two study groups, with over 50% of the values beneath the detection level of the used assays (Table 2 and Figure 1).

Table 2. Biomarker levels in the study population.

	Patients with CTEPH (n=82)	Patients in whom CTEPH was ruled out (n=160)	p-value
NT-pro-BNP (pg/mL)	756 (161-2563)	103 (53-214)	<0.001
GDF-15 (ng/L)	1580 (1058-2741)	1200 (813-1789)	<0.001
CRP (mg/L)	4.5 (1.7-8.3)	2.5 (1.3-4.6)	<0.001
Urate (mmol/L)	0.34 (0.24-0.45)	0.31 (0.27-0.38)	<0.001
FVIII:C (IU/dL)	2.0 (1.7-2.5)	1.7 (1.4-2.0)	<0.001
D-dimer (ng/mL FEU)	<250 (<250-432)	<250 (<250-457)	NS

Medians and interquartile range are presented. NS=no statistical significance.

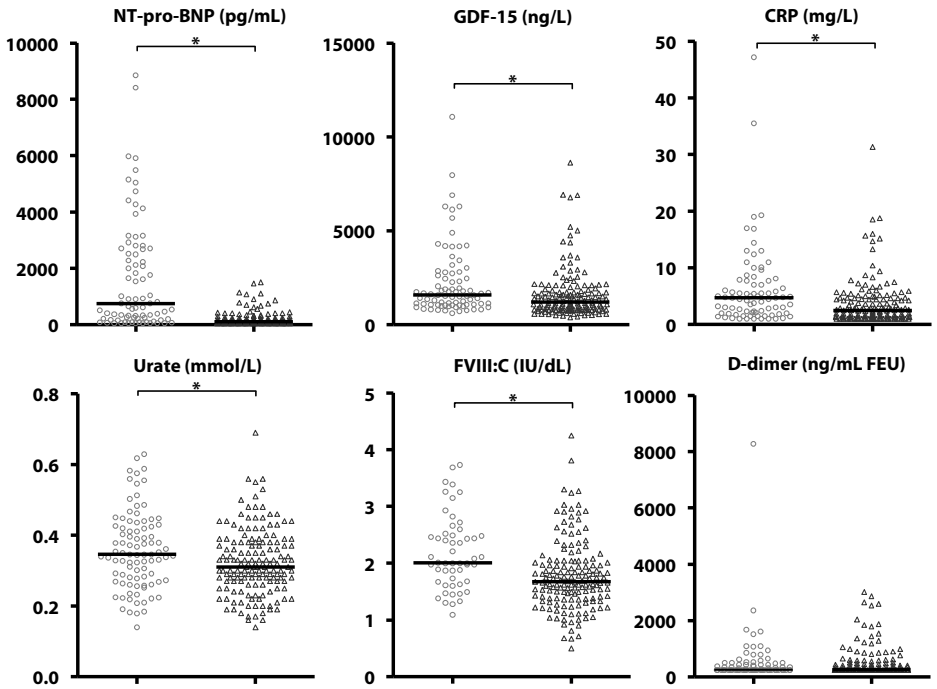

Figure 1. Biomarker levels in the 2 study groups: horizontal bars represent medians, circles patients with CTEPH and triangles patients without pulmonary hypertension. FVIII:C levels were missing for 29 patients with CTEPH; *p<0.001.

Derivation of a diagnostic model

Clear differences between the sensitivity and specificity and AUC of the ROC analyses were observed between the ECG-characteristics and the biomarkers under study using our pre-defined cut-off points (Table 3). The sensitivity of the ECG criteria (77%, 95% CI 67-86), elevated NT-pro-BNP levels (82%, 95% CI 72-89) and high FVIII:C (83%, 95% CI 70-92) were higher than those of elevated GDF-15 (63%, 95% CI 52-74), CRP (64%, 95% CI 53-75), urate (46%, 95% CI 35-57) and D-dimer levels (24%, 95% CI 16-35). On the other hand, specificity was best for the

Table 3. Test characteristics of ECG and biomarkers for the diagnosis of CTEPH in symptomatic patients after acute pulmonary embolism.

	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	AUC (95% CI)
ECG criteria[†]	77 (67-86)	89 (83-93)	0.83 (0.77-0.89)
NT-pro-BNP[¶]	82 (72-89)	70 (62-77)	0.74 (0.66-0.82)
GDF-15[‡]	63 (52-74)	50 (42-58)	0.62 (0.49-0.64)
CRP[¥]	64 (53-75)	61 (52-68)	0.62 (0.53-0.71)
Urate[¶]	46 (35-57)	80 (73-86)	0.62 (0.52-0.71)
FVIII:C[Δ]	83 (70-92)	32 (25-40)	0.57 (0.48-0.66)
D-dimer[§]	24 (16-35)	78 (70-84)	0.48 (0.39-0.57)

[†]Presence of at least 1 of the following criteria: rSR′ or rSr′ pattern in lead V1, R:S >1 in lead V1 with R >0.5mV and QRS axis >90°; [¶]sex and age dependent threshold; [‡]threshold 1200 ng/L; [¥]threshold 3.0 mg/L; [Δ]threshold 150 IU/dL; [§]threshold 500 ng/mL FEU. CI=confidence interval, ECG=electrocardiography, AUC=area under the receiver operator characteristic curve.

ECG-criteria (89%, 95% CI 83-93) and elevated urate levels (80%, 95% CI 73-86). The area under the ROC curve was slightly higher for the ECG-criteria (0.83, 95% CI 0.77-0.89) than for NT-pro-BNP (difference 0.09, 95% CI -0.04-0.17), and significantly higher than GDF-15 (difference 0.21, 95% CI 0.09-0.30), CRP (difference 0.21, 95% CI 0.08-0.32), urate (difference 0.21, 95% CI 0.11-0.21), FVIII:C (difference 0.26, 95% CI 0.12-0.35) and D-dimer levels (difference 0.35, 95% CI 0.18-0.41; Table 3).

We calculated the additional diagnostic value of the biomarkers to ECG assessment, which proved to be the most discriminative test for CTEPH (Table 4). After including NT-pro-BNP to the model (i.e. either one of the 3 ECG criteria positive or NT-pro-BNP levels elevated), the sensitivity increased significantly (+17%, 95% CI 5.4-29), at the cost of specificity (-24%, 95% CI -15 to -33). The AUC of the ROC analysis did not change significantly. By including the remaining tests one after the other to the model, the specificity decreased considerably to 39% and even lower, whereas the sensitivity increased only marginally leading to significantly decreased AUC in model C which consists of ECG assessment, NT-pro-BNP and CRP level measurements (difference 0.17, 95% CI 0.06-0.30), and in all further models. Therefore, we determined that

Table 4. Additional value of biomarkers to ECG assessment for diagnosing CTEPH.

Model		Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	AUC (95% CI)
A	ECG criteria	77 (67-86)	89 (83-93)	0.83 (0.77-0.89)
B	NT-pro-BNP + model A	94 (86-98)	65 (56-72)	0.80 (0.74-0.85)
C	CRP + model B	94 (86-98)	39 (31-47)	0.66 (0.60-0.73)
D	Urate + model C	94 (86-98)	33 (26-41)	0.64 (0.56-0.71)
E	GDF-15 + model D	96 (90-99)	23 (17-30)	0.60 (0.53-0.67)
F	FVIII:C + model E	98 (91-99.7)	13 (7.8-19)	0.55 (0.48-0.63)
G	D-dimer + model F	99 (93- >99.9)	12 (7.3-18)	0.55 (0.48-0.63)

ECG=electrocardiography, AUC=area under the receiver operator characteristic curve, CI=confidence interval.

model B, which includes ECG-assessment as well as NT-pro-BNP testing, was the most optimal diagnostic model for ruling out CTEPH. This model identified all patients with mPAP greater than 30 mmHg. False negative test results only occurred in a small number of the patients with relatively mild disease (mPAP between 26 and 30 mmHg). Interestingly, one of these latter patients even had normal results from all tests.

Effectiveness of the diagnostic model

To test the effectiveness of our diagnostic model, we calculated its negative predictive value for hypothetically increasing disease prevalences (Table 5). In case of a normal NT-pro-BNP level and in the absence of typical ECG characteristics of pulmonary hypertension, it is very unlikely that a dyspnoeic patient with a history of acute PE suffers from CTEPH with negative predictive values of 99% or higher, even in the presence of very high incidences of CTEPH (up to 10%).

Table 5. Negative predictive value of our final algorithm (model B) for increasing assumed prevalences of CTEPH.

Hypothetical incidence of CTEPH	Negative predictive value (%, 95% CI)
0.5%	99.9 (99.9- >99.9)
1.0%	99.9 (99.7- >99.9)
2.0%	99.8 (99.5-99.9)
3.0%	99.7 (99.2-99.9)
4.0%	99.6 (99.0-99.9)
5.0%	99.5 (98.7-99.9)
7.5%	99.3 (98.0-99.8)
10%	99.0 (97.3-99.7)
15%	98.4 (95.8-99.5)

CI=confidence interval.

DISCUSSION

Our results demonstrate that a simple diagnostic model based on ECG-evaluation and NT-pro-BNP measurements can rule out CTEPH with a high level of confidence in patients with a documented history of acute PE and clinically suspected CTEPH. Additional more expensive and invasive tests in these patients to rule out CTEPH seem therefore not necessary.

The sensitivity of the ECG criteria alone was 77%, which confirms earlier studies describing the insufficient diagnostic potential of these ECG criteria for pulmonary hypertension screening purposes.[16,21] The sensitivity, specificity and AUC of the 3 ECG parameters in our cohort were even lower than previously reported.[16] This is likely due to the higher fraction of patients with only mildly elevated mPAP in our study cohort. NT-pro-BNP levels alone showed slightly

higher, but still insufficient sensitivity for CTEPH. Combining the 3 ECG criteria with NT-pro-BNP levels, we obtained a higher sensitivity (94%) with an acceptable specificity.

Although the overall prevalence of CTEPH after acute PE - irrespective of complaints - ranges from 0.5% to 3.8%, this number likely increases 2 or 3 fold in selected patients with prior acute PE who present with clinically suspected CTEPH.[1-3] To facilitate correct interpretation and use of our study results for different clinical settings and patient cohorts, we observed high negative predictive values of our diagnostic model for different hypothetical incidences ranging from 0.5 to 15%, thereby enabling physicians to distinguish the negative predictive value applicable to their specific practice. Importantly, the specificity of our model was not sufficient to confirm CTEPH: patients with suspected CTEPH and one or more ECG characteristics of pulmonary hypertension or elevated blood levels of NT-pro-BNP should therefore be subjected to further diagnostic tests, including echocardiography and right heart catheterization.

Although all biochemical tests under study have been shown to be correlated to the presence and/or prognosis of pulmonary hypertension[8-13], and almost all tests were more increased in patients with CTEPH than in the patients without this disease, their diagnostic value for CTEPH proved to be limited, with the exception of NT-pro-BNP. There are 3 plausible explanations for this observation: 1) the studied biomarkers are especially elevated during acute thrombotic states or during acute heart failure while CTEPH is a chronic disease characterized by relatively slow progression, 2) all studied biomarkers are established prognostic factors for CTEPH and therefore, mostly present in the patients with severe or worsening disease and 3) a considerable proportion of our patient population without CTEPH had co-existing cardiopulmonary and malignant diseases, which are associated with elevation of one or more of the studied biomarkers as well. For instance, GDF-15, a stress-responsive, transforming growth factor-β-related cytokine, is weakly produced under baseline conditions in most tissues but its production increases sharply in response to hemodynamic stress, inflammation, and tissue injury.[22] Elevated circulating levels of GDF-15 have been reported in patients with acute PE and idiopathic pulmonary arterial hypertension and have been shown to provide strong and independent prognostic information in these conditions.[8,23] However, elevated levels of GDF-15 can also be detected in other cardiovascular disease states and in patients with malignant tumors. Therefore, and possibly due to the relatively mildly elevated mPAP in some of our patients, GDF-15 proved to be a poor diagnostic test for CTEPH in our population. CRP is a well-known marker of inflammation and tissue damage that recently has been shown to predict the severity and the outcome in patients with pulmonary hypertension.[9] Also, serum urate or uric acid, the final product of purine degradation, has been proposed to be a prognostic marker for hypoxic states such as chronic heart failure and pulmonary hypertension.[10] Nonetheless, the arguments raised to explain the limited diagnostic accuracy of GDF-15 can also explain the lack of discriminative power of urate and CRP levels for CTEPH. Finally, D-Dimer is a global indicator of coagulation activation and fibrinolysis. D-dimers and FVIII:C are known to be increased during and after acute PE, but also in a wide variety of other

diseases as infection or inflammatory and malignant conditions.[24,25] Both D-dimer and FVIII:C were shown to have very limited diagnostic value for CTEPH in our patient cohort. Altering our predefined thresholds for GDF-15, CRP, urate, FVIII:C or D-dimer did not significantly change our observations (data not shown).

Strengths of this study include the analysis of a large patient cohort with and without CTEPH and the standardized and blinded assessment of ECG characteristics and biomarker levels, thereby increasing the likelihood of generalizability of our results and precluding important biases. Notably, none of the patients with suspected CTEPH from the screening study was diagnosed with CTEPH. One important explanation for this low prevalence is that all patients who were diagnosed with CTEPH prior to the start of our study were included in the CTEPH cohort and consequently, not in the screening study. Our study also had limitations. In spite of the narrow confidence intervals, our conclusions should be confirmed in a future prospective trial since ours was an exploratory but not an outcome study, and therefore, the sensitivity and specificity of the diagnostic tests were calculated retrospectively.

In conclusion, the present study shows that a diagnostic model based on ECG assessment and NT-pro-BNP measurements can be used to rule out CTEPH in patients with a history of acute PE and clinically suspected CTEPH. Therefore, more invasive tests to rule out this disease do not seem necessary in patients without three specific ECG criteria of right ventricular pressure overload and a normal NT-pro-BNP level.

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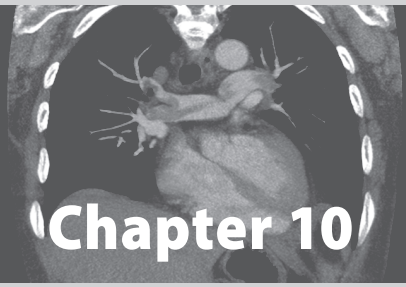

Chapter 10

Prevalence and determinants of exertional dyspnea after acute pulmonary embolism

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Submitted

ABSTRACT

Background

The exact prevalence and etiology of exertional dyspnea in the clinical course of acute pulmonary embolism (PE) have not yet been established.

Methods

A large cohort of consecutive patients diagnosed with acute PE was subjected to a dyspnea questionnaire and invited for cardiopulmonary work-up including the 6-minute walk test, spirometry and echocardiography. The prevalence, severity, determinants and underlying diseases of exertional dyspnea were evaluated.

Results

Of the registered 877 patients, 259 (30%) had died and 11 (1.3%) were excluded for geographical reasons. From the remaining 607 patients, 217 reported exertional dyspnea (36%; 95% CI 32-40%) 3.6 ±1.7 years after the PE. 421 patients completed the cardiopulmonary work-up. After multivariate analysis, cardiopulmonary comorbidity (OR 12; 95% CI 6.5-20), advanced age (OR 1.02 per year; 95% CI 1.01-1.03), higher BMI (OR 1.06 per kg/m^2; 95% CI 1.01-1.1) and a smoking history (OR 1.6; 95% CI 1.02-2.6) were identified as independent predictors of exertional dyspnea. A predefined dyspnea explaining diagnosis could be established in all patients with exertional dyspnea. In only 4 patients, this diagnosis was directly correlated to the acute PE. Increased severity of dyspnea was significantly correlated to decreased exercise performance ($p<0.001$) and the number of dyspnea-related diagnoses ($p<0.001$).

Conclusion

Exertional dyspnea is a frequent symptom in the long term clinical course of acute PE. More severe dyspnea results in decreased exercise capacity and increased burden of cardiopulmonary comorbidity. This dyspnea is not related to the past thromboembolic event in the vast majority of patients.

INTRODUCTION

Dyspnea is a term used to characterize a subjective experience of breathing discomfort that is comprised of qualitatively distinct sensations that vary in intensity.[1] Exertional dyspnea or breathing discomfort is a common and distressing symptom expressed by many patients and its etiology may prove elusive.[1-4] The majority of patients with exertional dyspnea can be diagnosed with one of four diagnoses: asthma, chronic obstructive pulmonary disease (COPD), interstitial lung disease or heart failure.[2-4] Exertional dyspnea after acute pulmonary embolism (PE) represents a particular clinical challenge since this frequent observation requires distinguishing PE related from the above stated causes of dyspnea. In recent studies, exertional dyspnea was observed in 50-60% of the patients after they were diagnosed with acute PE.[5,6] Importantly, 70% of these patients related their symptoms to the acute thromboembolic event suggesting a causal relation between both.[5] PE associated conditions causing exertional dyspnea include ventilation–perfusion mismatch leading to increased dead-space ventilation or chronic thromboembolic pulmonary hypertension (CTEPH) resulting from chronic emboli.[5-9] A third diagnosis could be recurrent PE, although these patients present with more acute or sub-acute worsening symptoms in the majority of cases.[10,11] The relevance of the distinction between PE and non-PE related disease causing dyspnea is underlined by apparent differences in the required diagnostic strategies, treatment and prognosis.

We sought to assess the exact prevalence and etiology of exertional dyspnea in patients with prior acute PE. Therefore, we have interviewed a large cohort of consecutive patients surviving an acute episode of PE and in addition, subjected these patients to a cardiopulmonary work-up.

METHODS

Patients

Consecutive patients who were diagnosed with acute PE in the period between January 1st 2001 and July 1st 2007 in an academic (Leiden University Medical Center, Leiden, the Netherlands) and affiliated teaching hospital (Medical Center Haaglanden, The Hague, The Netherlands) were studied.[12] Eligible patients were identified from the hospital records of the radiology department and the departments of internal, pulmonary and emergency medicine. Acute PE was confirmed by pulmonary angiography, computed tomography pulmonary angiography (CTPA) or ventilation perfusion scintigraphy (VQ-scan).[13] Patients were initially treated with at least 5 days of either unfractionated or weight based therapeutic doses of low molecular weight heparin, followed by oral anticoagulant therapy for a period of at least 6 months. The current survival status and contact information of each eligible patient was retrieved from the hospital administrative database or local municipal registries. All patients who survived until July 1st 2007 were telephonically interviewed for their detailed medical history and the

presence and severity of dyspnea. Furthermore, they were invited for a single visit to our vascular medicine outpatient clinic for cardiopulmonary work-up including the 6-minute walk test, spirometry and echocardiography. This visit was scheduled between July 1st 2007 and January 1st 2009 and planned at least one full year after the index event. Patients who were diagnosed with pulmonary hypertension prior to the start of our study were telephonically interviewed but not invited for a visit, since extensive cardiopulmonary tests were already performed in the diagnostic work-up of these patients. This study was approved by the Institutional Review Board of both participating hospitals and all patients provided informed consent.

Procedures

Patients were telephonically asked to complete a short medical questionnaire that was specifically designed to assess the presence, severity and possible causes of exertional dyspnea in the clinical follow-up of patients with acute PE.[5] In the patients who responded to our invitation for a single visit to our outpatient clinic, the 6-minute walk test was performed in accordance with the ATS guidelines.[14] Results of this 6-minute walk test are presented in percentage of the reference standard.[15] Ventilatory function was measured using a turbine spirometer (Microlab 3300, Sensormedics. Ltd Rochester, UK). Forced vital capacity (FVC), forced expiratory volume in one second (FEV1) and peak expiratory flow (PEF) were measured until three reproducible recordings (with a difference of less than 5%) were obtained. The highest of these 3 values was used for analysis. A VIVID-I portable ultrasound machine (GE Healthcare, Chalfont St. Giles, Bucks, UK) was used for transthoracic echocardiography. Echocardiography included cross sectional, M-mode and Doppler studies, and was performed by an experienced technician according to a standardized protocol. All echocardiographs were reviewed by an independent expert cardiologist. If necessary for establishing a diagnosis in symptomatic patients, further routine clinical work-up consisting of laboratory-, more extensive pulmonary function- or imaging tests was performed under supervision of an independent expert panel. In case of suspected pulmonary hypertension, this further work-up included right heart catheterization at all times.

Outcome

Our primary endpoint was the prevalence of exertional dyspnea as reported by patients surviving an episode of acute PE. Our second endpoint was the assessment of determinants for the presence of exertional dyspnea in the clinical follow-up of acute PE. We studied several variables as possible determinants of exertional dyspnea in the clinical course of acute PE. Length of the follow-up period, centrally located PE, invasive treatment for PE (i.e. administration of thrombolytic drugs, vena cava filter or surgical removal of the embolus) and recurrent PE were included as PE related determinants. Age, gender, body mass index (BMI), smoking status and history of cardiopulmonary disease other than PE were assessed as non-PE related determinants. Our third endpoint included the evaluation of the severity of the reported dyspnea. For the purpose of this analysis, patients were classified according to the criteria of the New

York Heart Association (NYHA) functional classification, although not strictly applicable to a non heart failure population.[16] This classification comprises 4 categories of increasing exercise impairment: no limitation of physical activity by shortness of breath (class I, no symptoms), ordinary physical activity results in dyspnea (class II, mild symptoms), comfortable at rest, but less than ordinary activity causes dyspnea (class III, moderate symptoms) and symptoms of cardiac insufficiency at rest, inability to carry out any physical activity without discomfort (class IV, severe symptoms). In addition to the NYHA classification, the total distance covered during the 6-minute walk test and the modified Borg dyspnea scale were considered to represent the severity of the dyspnea and exercise intolerance.[17] Our final endpoint was the identification of the exact diagnoses causing dyspnea following acute PE. We considered the following diagnoses to be a sufficient justification for the presence of exertional dyspnea: asthma diagnosed according to the NIH guidelines, COPD classified as GOLD II or worse in accordance with the NHLBI/WHO criteria, significant restrictive pulmonary function impairment (FVC <80% and distinct restrictive flow curve), all cause pulmonary hypertension, systolic or diastolic ventricular dysfunction as stated in the ESC guidelines, significant valvular disease according to the ACC/AHA guidelines, anemia (woman <7.4 mmol/l; man < 8.1mmol/l) or obesity (body mass index >30kg/m^2).[18-23] The presence of further, PE-related conditions as explanation for dyspnea was considered unlikely if one or more of the above stated diagnoses could be established.

Statistical analysis

The overall prevalence of exertional dyspnea was assessed for all patients who completed the medical questionnaire. For the analysis of the further endpoints, we included the patients who had completed the cardiopulmonary work-up. Univariate relation between all possible determinants and exertional dyspnea was assessed by calculating odds ratios (OR) with 95% confidence intervals (95% CI). Univariate analysis was followed by multivariate analysis to identify the independent determinants of exertional dyspnea. For this, a conditional logistic regression model was used evaluating all possible determinants. Fisher's analysis of variance (ANOVA) with least significant difference post-hoc tests was used to detect differences among the 4 NYHA classes. A p-value <0.05 was used to define statistical significance. SPSS version 14.02 (SPSS Inc, Chicago, IL) was used for all analysis.

RESULTS

Patients and prevalence of dyspnea

In total, 877 patients were diagnosed with acute PE between January 1st 2001 and July 1st 2007 in the two participating hospitals. Of these, 259 (30%) had died before July 1st 2007 and 11 patients (1.3%) were lost to follow-up. Deaths were attributed to malignancies in 110 patients (13%), (recurrent) PE in 67 patients (7.7%), bleeding from anticoagulant therapy in 6 patients

(0.69%), cardiovascular disease in 30 patients (3.5%), non-malignant pulmonary disease in 11 patients (1.3%) and other causes in 35 patients (4.2%). The remaining 607 patients were successfully contacted after a median period of 3.6 years (interquartile range 2.1-5.1 years). Of those, 30 (4.9%) declared to be in excellent health with no dyspnea, but refused to complete the questionnaire. An additional 156 patients declined visiting our hospital for cardiopulmonary work-up. Finally, 19 patients were diagnosed with pulmonary hypertension prior to the start of our study. Pulmonary function tests, echocardiography and the 6-minute walk test were routinely performed in these patients, and therefore these patients were not invited for further cardiopulmonary work-up. The remaining 402 patients visited our outpatient clinic and completed the cardiopulmonary function tests.

On questioning, 217 of the surviving patients reported dyspnea, resulting in an overall dyspnea prevalence of 36% (217/607; 95% CI 32-40%). From the 217 patients reporting dyspnea, 165 (76%) specified that the dyspnea had developed or worsened after the acute PE.

Predictors of dyspnea

The general characteristics at diagnosis of PE of the 421 patients with complete cardiopulmonary data, i.e. 19 patients previously diagnosed with pulmonary hypertension and 402 who completed the cardiopulmonary work-up, are depicted in Table 1: mean age was 55 years, 225 (53%) were males, 143 (34%) were diagnosed with centrally located PE, 23 (5.5%) patients had received invasive treatment for the PE, recurrent VTE was diagnosed in 64 (15%) patients, 116 (28%) were previously diagnosed with cardiopulmonary disease, mean BMI was 28 kg/m2 and

Table 1. Characteristics of the patients who completed the cardiopulmonary work-up (at diagnosis of PE).

	All patients (n=421)	No dyspnea reported (n=232)	Dyspnea present (n=189)	OR for dyspnea† (95% CI)
Age (years ±SD)	55 ±16	52 ±16	58 ±16	1.02 (1.01-1.04)
Male sex (n, %)	225 (53)	127 (55)	98 (52)	
Central localisation first PE (n, %)	143 (34)	78 (34)	65 (34)	
Thrombolysis, Surgery or VCF for first acute PE (n, %)	23 (5.5)	13 (5.6)	10 (5.3)	
Recurrent VTE (n, %)	64 (15)	30 (13)	34 (18)	
Known history of cardiopulmonary disease (n, %)	116 (28)	22 (9.5)	94 (50)	10.4 (6.1-18)
Body Mass Index (kg/m^2 ±SD)	28 ±5.3	28 ±6.0	29 ±5.1	1.05 (1.01-1.1)
Smoking history				
Current (n, %)	77 (18)	41 (18)	36 (19)	
Former (n, %)	178 (42)	93 (40)	85 (45)	
Never (n, %)	166 (39)	100 (43)	66 (35)	0.64 (0.43-0.96)
Number of pack years (mean ±SD)	14 ±17	10 ±13	18 ±20	1.03 (1.02-1.04)

†Only for significant determinants of dyspnea after univariate analysis (per unit for continuous variables).
PE=Pulmonary embolism, VCF=vena cava filter, VTE=venous thromboembolism, SD=standard deviation, n=number, OR=odds ratio, CI=confidence interval.

255 (61%) patients were current or former smokers. Univariate analysis indicated that none of the PE-related factors was a predictor of dyspnea. In contrast, advanced age, larger BMI, smoking and a history of cardiopulmonary disease were all significantly predictive for dyspnea (Table 1). Importantly, the follow-up period was not different between patients with and without dyspnea (mean 3.4 years [interquartile range 1.9-4.8] vs. 3.8 years [interquartile range 2.1-5.3] respectively). After multivariate analysis, a history of cardiopulmonary disease (OR 12, 95% CI 6.5-20), advanced age (OR 1.02 per year, 95% CI 1.01-1.03), higher BMI (OR 1.06 per kg/m^2, 95% CI 1.01-1.1) and a smoking history (OR 1.6, 95% CI 1.02-2.6) at diagnosis were demonstrated to be independent predictors of exertional dyspnea after acute PE.

Severity and causes of dyspnea

Of the 421 patients with complete cardiopulmonary data, 189 reported dyspnea (45%, 95% CI 40-50%): 151 (80%, 95% CI 73-85%) were classified as NYHA II, 31 (16%, 95% CI 11-22%) as NYHA III and 7 (3.7%, 95% CI 1.5-7.5) as NYHA IV. The mean percentage of predicted walking distance in the 6-minute walk test decreased in subsequent NYHA classes: 99 ±11% in NYHA class I, 96 ±12% in NYHA II class, 77 ±21% in NYHA III class and 35 ±8.4% in NYHA IV class (p=0.017 for the first step, p<0.001 for the last 2 steps). In addition to this observation, the modified Borg dyspnea score after the 6-minute walk test increased in the subsequent NYHA classes: 1.2 ±1.1, 2.5 ±1.5, 4.6 ±1.8 and 6.6 ±1.3 respectively (p<0.001 for the first 2 steps, p=0.002 for the last step). The 6-minute walk test could not be performed in 47 patients because of immobility or other reasons.

The final dyspnea related diagnoses established in the study patients are presented in Table 2. All patients with exertional dyspnea were diagnosed with at least one of the predefined dyspnea explaining conditions. On average, patients in NYHA class II were diagnosed with 1.5, in NYHA class III with 3.0 and patients in NYHA class IV with 3.4 different diagnoses (p<0.001).

Table 2. Causes of dyspnea in the clinical course of acute pulmonary embolism.

	NYHA I (n=232)	NYHA II (n=151)	NYHA III (n=31)	NYHA IV (n=7)
Asthma (n, %)	5 (2.2)	12 (7.9)	3 (9.7)	1 (14)
COPD† (n, %)	6 (2.6)	29 (19)	13 (42)	3 (43)
Restrictive pulmonary function impairment (n, %)	10 (4.3)	9 (6.0)	1 (3.2)	1 (14)
Pulmonary hypertension (n, %)	0 (0)	6 (4.0)	20 (65)	3 (43)
CTEPH (n, %)	0 (0)	1 (0.66)	3 (9.7)	0 (0)
Systolic cardiac dysfunction (n, %)	6 (2.6)	19 (13)	11 (68)	3 (43)
Diastolic cardiac dysfunction (n, %)	66 (28)	59 (39)	19 (35)	5 (71)
Significant valvular heart disease (n, %)	1 (0.43)	3 (2.0)	2 (6.5)	2 (29)
Anemia (n, %)	8 (3.4)	26 (17)	4 (13)	1 (14)
Obesity* (n, %)	65 (28)	50 (33)	18 (58)	3 (43)

Patients can be diagnosed with more than one dyspnea-related disease. †Classification GOLD II or worse; *body mass index >30kg/m^2. COPD=chronic obstructive pulmonary disease, n=number.

Only in 4 patients this diagnosis could be causally related to the past acute PE. These patients were diagnosed with CTEPH after right heart catheterization and pulmonary angiography. CTEPH was ruled out in the remaining 25 patients with pulmonary hypertension after perfusion scintigraphy or pulmonary angiography. Notably, the prevalence of dyspnea related diagnoses in asymptomatic patients was 47%, mainly as a result of 66 cases of diastolic ventricular dysfunction.

DISCUSSION

This study demonstrates that the prevalence of exertional dyspnea in the long term clinical course of acute PE is 36%. This dyspnea was however not related to the past thromboembolic event in the vast majority of the patients. The clinical relevance of the subjective symptom of shortness of breath is underscored by the decreased exercise tolerance and increased prevalence of dyspnea related comorbidity that we found in patients who presented with more severe symptoms.

Although we observed that the majority of symptomatic patients correlated their exertional dyspnea to the acute PE, we could not establish pathophysiological grounds for this observation for two important reasons. First, single and multivariate analysis excluded predefined PE related characteristics as determinants for the presence of exertional dyspnea. Second, the included patients underwent extensive cardio- and pulmonary function tests. PE-related disease was indentified in only 4 patients and all remaining symptomatic patients were diagnosed with at least one non-PE related dyspnea explaining condition. We therefore hypothesized that the psychological impact of this serious cardiovascular event and the resulting deconditioning might very well contribute to subsequent increased perception of dyspnea. Hence, it would be interesting to study the effect of cardiopulmonary rehabilitation programs on long term dyspnea and physical fitness of patients with acute PE. Such programs have been shown very effective after other acute cardiovascular events.[24,25]

A different explanation for the reported temporal relation between PE and the occurrence or worsening of dyspnea was provided by a previous study, that reported either an abnormal right ventricular function on echocardiography or decreased exercise performance in 41% of previously healthy patients 6 months after acute PE was diagnosed.[6] Notably, 15% of the patients with normal baseline echocardiography had subsequently developed right ventricular dysfunction during the follow-up period. These findings suggest that a PE can cause persistent right ventricular injury or initiate a pathophysiological process damaging the right ventricle over time.[6] Since our study lacks baseline measurements of cardiac and pulmonary function, we were unable to support this interesting hypothesis. Although our results did not provide evidence for unexplained right ventricular dysfunction on large scale in our study population, this hypothesis requires further study.

Our results are in accordance with previous reports on exertional dyspnea in other patient cohorts: the independent determinants of dyspnea and the specific diagnoses established in our study are well comparable to those described in the literature.[1-4] Furthermore, our observation that patients with objectively confirmed dyspnea-related disease as asthma or COPD did not report any symptoms at all, is a well known phenomenon.[1-4] Nonetheless, some aspects of this study require comment. First, a considerable number of eligible patients declined visiting our hospital, reducing the external validity of our results. Second, we could not put our results in perspective due to the lack of a control population without PE. Third, the risk of CTEPH after PE reported in this study is lower than previously reported.[7,8] This might be explained by different selection and diagnostic criteria applied in those studies, or by underdiagnosis of CTEPH in our cohort. Indeed, due to our study design, objective testing to rule out CTEPH could not be performed in all study patients. Since the diagnostic management of CTEPH is complex and involves right heart catheterization, there is great need for future studies to focus on the utilization of simple and noninvasive diagnostic tests for ruling out this very serious condition.

In summary, exertional dyspnea is a frequent symptom in the long term clinical course of acute PE. Increased sensation of dyspnea is accompanied by higher burden of cardiopulmonary comorbidity and decreased exercise capacity. This dyspnea could not be related to PE in the majority of patients. The clinical consequence of our study is that exertional dyspnea in the clinical course of acute PE is mainly caused by pre-existing comorbid conditions and alarming direct complications of PE such as CTEPH are rare. Nonetheless, physicians should remain alert on this serious but potentially treatable disease.

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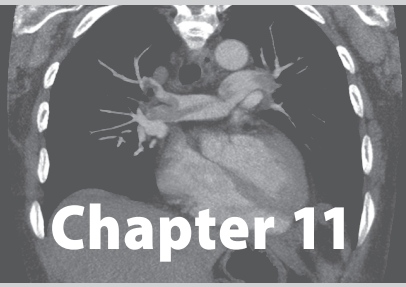

Chapter 11

Risk of arterial cardiovascular events in patients after pulmonary embolism

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ABSTRACT

Introduction

Studies have reported inconsistent evidence for an association between venous thromboembolism (VTE) and arterial cardiovascular events. We further studied the association between both diseases by comparing the occurrence of cardiovascular events in patients diagnosed with acute pulmonary embolism (PE) contrasted to patients in whom PE was clinically suspected but ruled out.

Methods

Patients with a first provoked or unprovoked PE and patients in whom a first PE was clinically suspected but ruled out were followed for the occurrence of arterial cardiovascular events. Patients diagnosed with PE were treated with vitamin K antagonists (VKA) for six months. All patients with an additional indication for VKA other than PE were excluded.

Results

259 patients with provoked PE, 95 patients with unprovoked PE and 334 control patients without PE were included. Median follow-up was 4.2 years. Sixty-three arterial cardiovascular events were registered (incidence 5.1/100 py). Adjusted hazard ratio (HR) was not different between patients with all cause PE and control patients (1.39, 95% CI 0.83-2.3), but increased for patients with unprovoked PE versus both patients with provoked PE and control patients without PE (HR 2.18; 95% CI 1.1-4.5 and 2.62; 95% CI 1.4-4.9 respectively). This effect was confirmed after redefining the study start date to the moment the VKA were discontinued.

Conclusion

Our study underlines the association between unprovoked VTE and arterial cardiovascular events. However, risk differences between patients with provoked PE and patients in whom PE was clinically suspected but ruled out could not be demonstrated.

INTRODUCTION

Recent epidemiological studies have shown an association between venous thromboembolism (VTE), that is deep venous thrombosis (DVT) as well as pulmonary embolism (PE), and arterial cardiovascular events.[1,2] This association can at least in part be explained by the presence of common risk factors for venous and arterial disease, such as obesity and the metabolic syndrome.[3-5] It was previously shown that, compared to population controls, the risk of arterial cardiovascular events after a first DVT or a first acute PE was increased in the first year after the VTE as well as in 20 years of follow-up.[6] Furthermore, patients with VTE of unknown origin (unprovoked VTE) are at higher risk of developing arterial cardiovascular events than patients with provoked VTE.[7-9] However, evidence of the relation between VTE and arterial cardiovascular events is inconsistent. Two observational studies could not identify increased risk of overall or unprovoked VTE in patients with non-invasively measured subclinical atherosclerosis.[10,11] In addition, there are no reports in which the risk for arterial cardiovascular events in patients with VTE has been compared with this risk in controls without VTE, but with similar baseline risk characteristics. This is important since population controls in general have a lower a-priori risk for arterial disease than patients with established VTE.[6]

We intended to further study the association between VTE and arterial cardiovascular events by defining a control population with a more comparable baseline risk characteristics for cardiovascular disease than population controls. We hypothesized that patients in whom PE was clinically suspected but ruled out would provide such a control group. Accordingly, we assessed the incidence of arterial cardiovascular events in patients diagnosed with a first all cause PE as well as with provoked PE and unprovoked PE separately, and contrasted them with patients in whom a first suspected PE was ruled out.

METHODS

Study design

A cohort study was performed to evaluate the risk of arterial cardiovascular events and the event-free survival in patients with a confirmed first PE compared to a population in which a clinically suspected first PE was ruled out. Study endpoints were arterial cardiovascular events defined as otherwise unexplained death, clinically adjudicated acute myocardial infarction, stroke or transient ischemic attack, claudication, unstable angina, carotid endarterectomy, coronary artery bypass graft, peripheral arterial bypass or angioplasty.[11] Both patients with and without PE were followed from the start dates to 1-1-2008 or the occurrence of one of the endpoints, whichever came first. After the study period, we searched the medical charts of the study patients for the occurrence of study endpoints and we contacted them by mail or phone to complete our data with the latest information on their medical history and clinical

condition. If patients could not be reached, we used the last medical report of their treating physician or general practitioner. When a patient with or without PE had died, the pathology report was scrutinized to establish the cause of death. In case autopsy was not performed, the likely cause of death was verified with the treating physician or general practitioner. Otherwise unexplained death was classified as caused by an arterial cardiovascular event. All endpoints were adjudicated by an independent committee. In addition to information on the endpoints, we also collected information on sex, age at inclusion, risk factors for PE, recurrent VTE during the study period and medical history of cardiovascular events in both patients with and without PE. This study was approved by the Institutional Review Board of the Leiden University Medical Center and all participants provided informed consent.

Patients with acute PE

All patients with proven PE in our hospital are registered in the hospital administration database. Consecutive adult patients with no medical history of VTE and who were diagnosed with a first PE between January 2001 and July 2004 were included in this study. The diagnosis of PE was based on either a positive CT angiogram or a ventilation perfusion scintigraphy indicating a high probability for PE. Data on risk factors for PE were derived from the discharge status of the patients. Unprovoked PE was defined as PE occurring in the absence of risk factors, i.e. active malignancy, immobility more than 3 days or recent long flight, recent surgery or fracture of extremity, pregnancy or peri-partum period, hormone replacement therapy and use of oral contraception. Patients were treated according to hospital policy, initially with therapeutic doses of unfractionated heparin or low molecular weight heparin followed by vitamin K antagonists (VKA). Since VKA therapy has been shown to reduce the risk for myocardial infarction[12], patients with an additional indication for VKA therapy, in whom these anticoagulants could not be withdrawn after a six months treatment period, were excluded from this analysis.

Patients in whom acute PE was suspected but ruled out

The control cohort consisted of patients in whom PE was clinically suspected but ruled out by either an unlikely probability (Wells rule ≤4 points[13]) in combination with a normal D-dimer test or a CT scan without signs of PE, followed by a three months follow-up period without the occurrence of subsequent symptomatic VTE. Consecutive patients without PE were recruited between November 2002 and September 2004 and included in a diagnostic management study.[14] Only patients that had presented to our hospital and without a medical history of VTE or indication for VKA therapy were included in the present analysis.

Statistical analysis

We assessed the incidence of subsequent arterial cardiovascular events in patients with provoked and unprovoked PE in comparison to patients in whom PE was ruled out. Because we intended to study the role of PE as risk factor for arterial cardiovascular events by defining

patient groups with similar baseline risk characteristics, we performed the same analysis after exclusion of patients who had experienced prior arterial cardiovascular events. In addition, to rule out the initial effect of oral anticoagulation therapy, a third analysis was performed in which the start date was set at the time the oral anticoagulant therapy was discontinued, i.e. the treatment duration was six months, and no recurrent VTE had occurred in the patients with PE, and six months after PE was excluded in the control patients. The Kaplan-Meier life table method was used to estimate the cumulative event rate. Patients with recurrent VTE during follow-up or death not associated with any cardiovascular event were censored. A Cox proportional hazard model was used to calculate hazard ratios (HR). After multivariate analysis, these were adjusted for potentially important confounders including sex, age, malignancy, smoking status, blood pressure or lipid lowering medication, anti-platelet therapy, hormonal contraception, diabetes and history of cardiovascular events. SPSS version 14.02 (SPSS Inc, Chicago, IL) was used for all analysis.

RESULTS

Patients

In the study period, 379 patients were diagnosed with a first PE of whom 356 patients had no additional indication for VKA therapy. In addition, 364 controls were registered.[12] We were not able to collect full study information in 30 patients without PE and 2 patients with PE because they refused cooperation (n=2), lived abroad (n=7), were not registered with a general practitioner (n=12) or we did not succeed in retrieving up-to-date contact specifications (n=11). The final diagnosis in the 334 patients in whom acute PE was suspected but ruled out was musculoskeletal disease in 37 patients (11%), non infectious or malignancy associated pulmonary disease in 43 (13%), gastrointestinal disease in 17 (5.1%), infectious disease in 84 (25%), malignancy related in 47 (14%), cardiovascular disease in 33 (9.9%) and other/unknown in 73 patients (22%). Of the 33 patients with cardiovascular disease, 13 had no prior history of cardiovascular events and were discharged with newly prescribed secondary preventive medication, e.g. statins, anti-platelet or blood pressure lowering medication. The remaining 20 patients were already treated with these medications.

General characteristics of the total study population (n=688) are depicted in Table 1. There was a difference in the male to female ratio, age and prevalence of active malignancy between the study groups. The fraction of active smokers, the prevalence of diabetes and the use of blood pressure lowering, anti-platelet and lipid-lowering medication was not different between the three study groups. The median follow-up period of the patient cohort was 1451 days (interquartile range 337-1867) and of the control population 1558 days (interquartile range 1320-1789). The total number of patient years was 1284 for the controls, 817 for the patients with provoked PE and 349 for the patients with unprovoked PE.

Table 1. General characteristics of the study population.

	Control patients (n=334)	Patients with provoked PE (n=259)	Patients with unprovoked PE (n=95)
Sex (Female, %)*	211 (63)	137 (53)	49 (55)
Age (mean ±SD)*†	48 ±17	52 ±18	55 ±17
History of arterial cardiovascular events (n, %)†	40 (12)	38 (15)	17 (18)
Active malignancy (n, %)*†	46 (14)	103 (40)	-
Diabetes (n, %)†	17 (5.1)	12 (4.6)	6 (6.3)
Active smoker (n, %)†	110 (33)	78 (30)	30 (32)
Use of blood pressure lowering medication (n, %)‡	107 (32)	91 (35)	34 (36)
Use of anti platelet therapy (n, %)‡	50 (15)	37 (14)	17 (18)
Use of lipid lowering medication (n, %)‡	57 (17)	42 (16)	18 (19)
Number of patient years in follow-up	1284	817	349

‡After hospital discharge; †at time of presentation with clinically suspected acute PE; *significantly different. PE=pulmonary embolism, SD=standard deviation.

Venous events

Thirty-seven patients experienced symptomatic recurrent VTE during follow-up. Recurrent VTE occurred in 12 patients with unprovoked PE with a total of 55.2 patient years (py; incidence 16/100 py), in 17 patients with provoked PE with a total of 68.4 py (8.4/100 py) and in 8 patients without PE with a total of 22.7 py (1.8/100 py; Table 2). The risk for recurrent VTE was increased in patients with unprovoked PE compared to patients with provoked PE and patients without PE (relative risk 1.92, 95% confidence interval [CI] 0.96-3.9 and 5.27, 95% CI 2.2-13, respectively), and in patients with provoked PE compared to patients without PE (2.74, 95% CI 1.2-6.3).

Table 2. Distribution of arterial cardiovascular events and (recurrent) venous thromboembolic events during the follow-up period.

	Total population	Control population	Patients with provoked PE	Patients with unprovoked PE	RR patients vs. controls		RR unprovoked PE vs. controls		RR provoked PE vs. controls		RR unprovoked vs. provoked PE	
	n, % patient year	n, % patient year	n, % patient year	n, % patient year	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
CVE	63 (5.1)	26 (4.1)	17 (3.4)	20 (13)	1.34	0.83-2.2	2.70	1.6-4.6	0.84	0.47-1.5	3.21	1.8-5.8
MI	14 (0.89)	4 (0.31)	4 (0.40)	6 (4.2)	2.35	0.93-6.0	5.27	1.9-14	1.29	0.42-4.0	4.09	1.5-11
ST	21 (1.3)	6 (0.87)	6 (0.92)	9 (3.7)	2.35	0.93-6.0	5.27	1.9-14	1.29	0.42-4.0	4.09	1.5-11
OT	28 (2.9)	16 (2.9)	7 (2.1)	5 (5.0)	0.71	0.34-1.5	1.10	0.41-2.9	0.56	0.24-1.4	1.95	0.63-6.0
VTE	37 (6.0)	8 (1.8)	17 (8.4)	12 (16)	3.42	1.6-7.4	5.27	2.2-13	2.74	1.2-6.3	1.92	0.96-3.9

CVE=any cardiovascular event, MI=myocardial infarction, ST=stroke, OT=other, VTE=(recurrent) venous thromoembolism, RR=relative risk, PE=pulmonary embolism, CI=confidence interval.

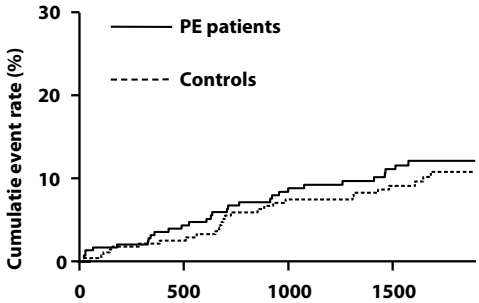
Deaths

A total of 176 deaths were recorded during the study period. The most frequent cause of death was malignancy (93 cases, 53% of all deaths). Five patients died as a result of myocardial infarction and five as result of severe stroke.

Arterial cardiovascular events

In total, 63 arterial cardiovascular events occurred with a total of 125 py (incidence 5.1/100 py; Table 2). Patients with unprovoked PE had a higher incidence of arterial cardiovascular events (20 events in 44.7 py; 13/100 py) than the patients with provoked PE (17 arterial cardiovascular events in 28.1 py; 3.4/100 py) and control patients without PE (26 events in 52.6 py; 4.1/100 py). In addition, risks for the occurrence of any arterial cardiovascular event as well as for myocardial infarction and for stroke were increased in the patients with unprovoked PE compared to the patients with provoked PE and patients without PE (Table 2). Only slight, non significant differences in the incidence of arterial cardiovascular events were found between overall PE patients and controls.

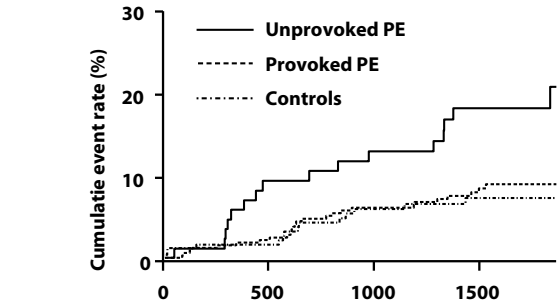
Kaplan Meier analysis showed no differences between the event free survival of all PE patients compared to control patients without PE (Figure 1). Corrected for prior arterial events, sex, age, active malignancy and use of oral anticonceptive medication, HR of all patients with PE was only marginally increased compared to the control patients without PE (1.39, 95% CI 0.83-2.3).



At risk:				
Controls	334	291	268	189
Patients	287	247	218	135

Figure 1. Cumulative arterial cardiovascular event rate in PE patients and control patients without pulmonary embolism (PE).

When PE patients were categorized in provoked and unprovoked PE, clear differences emerged in the arterial cardiovascular event free survival between patients with unprovoked PE and both the patients with provoked PE and without PE (Figure 2). The event free survival was not



At risk:				
Controls	334	291	268	189
Provoked	259	182	156	121
Unprovoked	95	75	71	51

Figure 2. Cumulative arterial cardiovascular event rate in patients with unprovoked pulmonary embolism (PE), with provoked PE and in control patients without PE.

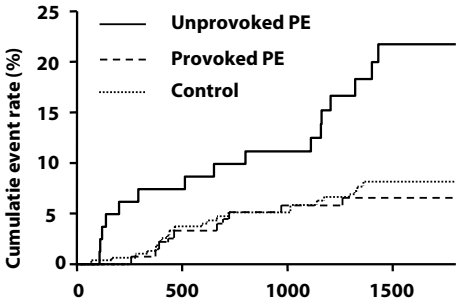
much different between patients with provoked PE and control patients without PE. Adjusted HR of patients with unprovoked PE was increased compared to patients with provoked PE (2.18; 95% CI 1.1-4.5) and control patients without PE (2.62; 95% CI 1.4-4.9).

Prior arterial cardiovascular events were found to be an important predictor for the reoccurrence of arterial cardiovascular events in the follow-up period (OR 3.10; 95% CI 1.8-5.3). When all study patients with and without PE with a history of arterial cardiovascular events (n=95) were excluded from the analysis, adjusted hazards of patients with unprovoked PE was increased versus both patients with provoked PE (2.73; 95% CI 1.1-7.0) and control patients without PE (3.72; 95% CI 1.6-8.4). No differences were detected between the patients with provoked PE and the control patients without PE.

The corrected HR of the third analysis six months after initial presentation and after discontinuation of anticoagulant therapy was not different between all patients with PE and the control patients without PE (1.31; 95% CI 0.74-2.3). In contrast, the cumulative arterial cardiovascular event rate in patients with unprovoked PE was higher than this cumulative event rate in patients with provoked PE (HR 3.24; 95% CI 1.4-7.7) and control patients without PE (HR 2.85; 95% CI 1.4-5.6, Figure 3).

DISCUSSION

Our data demonstrate that the incidence of arterial cardiovascular events for all patients with PE was not increased compared to the control patients without PE. However, patients diagnosed with a first unprovoked PE were at higher risk of developing subsequent arterial cardiovascular



At risk:				
Controls	312	279	261	125
Provoked	206	171	146	93
Unprovoked	81	74	69	36

Figure 3. Cumulative arterial cardiovascular event rate in patients with unprovoked pulmonary embolism (PE), with provoked PE and in control patients without PE starting after a six months treatment period for acute PE or six months after the exclusion of acute PE.

vascular events than patients with a first provoked PE and our control population without PE. In addition, this event free survival disadvantage was still demonstrated after exclusion of all PE and control patients with prior arterial cardiovascular events and after redefining the study start date to the moment the VKA treatment was discontinued in the patients initially diagnosed with acute PE.

Our study design was different from previous reports on selection of control patients, start date and definition of end-points. Since our study was designed to compare the incidence of arterial cardiovascular events in PE patients and control patients without PE but with comparable risk characteristics, the results firmly establish the earlier described increased occurrence of arterial cardiovascular events after unprovoked VTE.[7-9] In addition, we performed an additional analysis to rule out the possible confounding effect of VKA and censored all patients that developed VTE during the study period. Our finding that control patients without PE and patients with provoked PE have the same arterial cardiovascular event-free survival supports the hypothesis that a shared but yet unidentified mechanism causes events in both venous and arterial systems. Suggested attributive factors are shared risk factors or etiological pathways as thrombogenesis, endothelial damage or inflammation.[2] Unfortunately, our dataset does not allow us to determine whether unprovoked PE and (early) arterial cardiovascular events are each caused separately by a shared pathway or the occurrence of (early) arterial cardiovascular events after venous thromboembolism is related more causally. Future studies should further investigate the pathogenesis behind the observed associations.

Strengths of our study include the long term follow-up of a large and unselected, consecutive patient cohort. Second, we have used a very comparable control population of patients with

clinically suspected but ruled out PE.[12] Third, we used clear definitions for our inclusion criteria and endpoints. The latter are serious medical events that are likely to be recorded accurately.

Limitations of this study comprise the lost to follow-up rate of 4.4% and the relatively limited number of patients in the unprovoked PE cohort. Also, although we aimed at including a control group for patients with acute PE with similar baseline risk characteristics for cardiovascular disease, several relevant demographics as age, sex, medical history and use of medication were different between the patients with and the patients without PE. Nonetheless, HRs proved to be significantly elevated for patients with unprovoked PE after adjusting for these factors. Furthermore, since contrast echocardiography was not routinely assessed after the diagnosis of PE, we could not evaluate the possibility of paradoxical embolism as the cause of subsequent arterial events in some patients. Finally, although a predefined diagnostic algorithm for patients with suspected acute PE has been used in all patients, we could not fully correct for possible differences in sensitivity of the diagnostic tests or changes in diagnostic algorithms for our endpoints over time.

In summary, this study demonstrates that patients with a first unprovoked PE are at higher risk of developing arterial cardiovascular events than patients with a first provoked PE and specific control patients in whom PE was clinically suspected but ruled out. These results justify large studies to study the underlying pathophysiological mechanisms that cause the increased risk of arterial cardiovascular events after PE and to identify specific patients at very high risk. These latter patients might benefit from modified treatment regimens to prevent the occurrence of arterial cardiovascular disease, including preventive use of antiplatelet and cholesterol synthesis inhibiting treatment.

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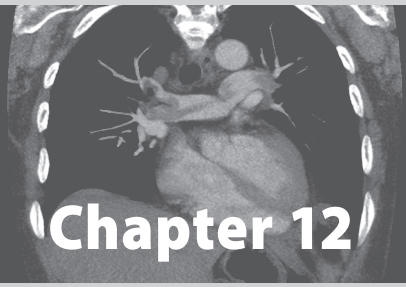

Chapter 12

Patient outcomes after acute pulmonary embolism: a pooled survival analysis of different adverse events

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ABSTRACT

Aim

To assess the long term risk for adverse events after acute pulmonary embolism (PE).

Methods

Consecutive patients diagnosed with PE between January 2001 and July 2007, and patients in whom PE was ruled out from a previous study were followed until July 2008 for the occurrence of adverse clinical events: mortality, symptomatic recurrent venous thromboembolism (VTE), cancer, arterial cardiovascular events and chronic thromboembolic pulmonary hypertension (CTEPH). Hazard ratios (HR) for all endpoints and a combined endpoint were calculated and adjusted for potential confounders.

Results

308 patients with unprovoked, 558 with provoked and 334 without PE were studied with a median follow-up period of 3.3 years. Patients with unprovoked PE had lower overall risk for mortality than patients with provoked PE (HR 0.59, 95% CI 0.43-0.82), but higher risk for non-malignancy related mortality (HR 1.8, 95% CI 1.3-2.5), recurrent VTE (HR 2.1, 95% CI 1.3-3.1), cancer (HR 4.4, 95% CI 2.0-10), cardiovascular events (HR 2.6, 1.5-3.8) and CTEPH (1.5% vs 0%). The risk for the combined endpoint did not differ between both groups (HR 0.98, 95% CI 0.82-1.1). Patients without PE had similar risks for malignancy and cardiovascular events than patients with provoked PE, but lower risks for the remaining outcomes. The fraction of both patients with provoked and unprovoked PE without events after 1 year was only 70%, and decreased to fewer than 60% after 2 years and fewer than 50% after 4 years, whereas this latter was 84% for the control patients.

Conclusion

The clinical course of acute PE is complicated by high rates of serious adverse events, which occur in half of the patients within 4 years.

INTRODUCTION

Acute pulmonary embolism (PE) is a common and potentially serious medical condition.[1] The interaction of an extensive pulmonary artery obstruction rate and presence of cardiopulmonary comorbidity may lead to right ventricular dysfunction, which is associated with hemodynamic instability and, in severe cases, with death.[2] This PE attributable mortality occurs in approximately 2-6% of patients with hemodynamically stable PE and in 30% or more of patients with PE presenting with hemodynamic instability or in shock.[2-4] Of note, 25% of the patients do not survive the first year after diagnosis, although the majority of deaths during this time are related to underlying conditions, such as cancer or chronic heart disease, rather than to PE itself.[3,4] Even after surviving the acute episode, the clinical course of acute PE can be complicated by several thrombotic and non-thrombotic adverse events. Bleeding complications and recurrent episodes of venous thromboembolism (VTE) are common and chronic obstruction of the pulmonary vessels with organized blood clots may lead to chronic thromboembolic pulmonary hypertension (CTEPH).[4-8] This latter disease is further characterized by pulmonary arteriopathy and progressive right heart failure.[8] Furthermore, it has been well established that patients with acute PE are at higher risk of being subsequently diagnosed with cancer as well as with arterial cardiovascular events than population controls.[9,10] The prognosis of patients diagnosed with unprovoked PE, i.e. PE occurring in the absence of established risk factors or predisposing illnesses, might be less favorable than that of patients suffering from provoked PE. Several studies have shown that patients with unprovoked PE are at particular risk for recurrent PE, CTEPH, arterial cardiovascular events and the detection of cancer.[10-15]

Although all individual complications of PE have been studied extensively, the combined risk for all adverse clinical events has not been reported yet. Knowledge of this short and long term prognosis after acute PE is of great importance since this should guide clinical decision making regarding treatment regimes, specific preventive screening programs and follow-up duration. Accordingly, we have performed a prospective cohort study evaluating the overall occurrence of complications in the clinical follow-up of patients diagnosed with acute PE. We contrasted the studied complication rate in patients with unprovoked PE to patients with provoked PE and to a control group of patients in whom PE was suspected but ruled out.

METHODS

Patients

The original admission charts of all consecutive in- and outpatients diagnosed with acute PE between January 1st 2001 and July 1st 2007 in an academic (Leiden University Medical Center, Leiden, the Netherlands) and affiliated teaching hospital (Medical Center Haaglanden, The Hague, the Netherlands) were systematically reviewed using predefined criteria for the diagnosis of

acute PE, i.e. intraluminal filling defects on pulmonary angiography or computed tomography pulmonary angiography (CTPA), high probability ventilation perfusion scintigraphy (VQ-scan) or intermediate probability VQ-scan in combination with objectively diagnosed deep vein thrombosis (DVT).[15,16] All patients fulfilling these criteria were included in this analysis. Patients were initially treated with at least 5 days of either unfractioned heparin or weight based therapeutic doses of low molecular weight heparin, followed by vitamin K antagonists for a period of at least 6 months with a target international normalized ratio (INR) of 2.0 to 3.0.[17] In patients with severe acute PE presenting with hemodynamic instability, anticoagulant treatment was preceded by administration of thrombolytic drugs, thrombosuction or surgical embolectomy according to the judgment of the attending clinician. The control cohort consisted of patients in whom PE was clinically suspected but ruled out by either an unlikely probability (Wells rule ≤4 points) in combination with a normal high sensitive D-dimer test or a CT scan without signs of PE. These patients were recruited for participation in a previous outcome study between November 2002 and September 2004.[18]

Procedures

Detailed information regarding diagnostic management, cause, treatment and documented clinical course of the index PE were extracted from the medical charts of the included patients with and without PE. When a patient had died, the pathology report was scrutinized to establish the cause of death. In case autopsy was not performed, the likely cause of death was verified with the treating physician or general practitioner. All surviving patients were contacted by mail or phone and were asked to complete our data with the latest information regarding their medical history and clinical condition. Patients living abroad or for whom up-to-date contact specifications were not available were excluded. This study was approved by the Institutional Review Board of both participating hospitals and all patients provided informed consent.

Outcome

Unprovoked PE was defined as PE occurring in the absence of the following risk factors: active malignancy, immobility more than 3 days or recent long flight, recent surgery or fracture of extremity, pregnancy or peri-partum period and use of oral contraception or hormone replacement therapy.[1] All cause mortality, symptomatic recurrent VTE, i.e. acute PE as well as deep vein thrombosis, CTEPH, arterial cardiovascular events or detection of a previously unknown malignancy were considered to be adverse events in the clinical course of acute PE. Only information on anticoagulant related fatal bleeding was available. Recurrent PE was defined as 1) a new filling defect revealed by pulmonary angiography or spiral CTPA or 2) a new high probability perfusion defect revealed by VQ-scan or 3) any new defects after earlier normalizing of the scan.[6,7] Criteria for the diagnosis of CTEPH were mean pulmonary artery pressures assessed by right heart catheterization exceeding 25 mmHg respectively and normal pulmonary capillary wedge pressure in combination with an abnormal perfusion scintigram and signs for CTEPH on

pulmonary angiography.[8] Arterial cardiovascular events were defined as clinically adjudicated acute myocardial infarction, stroke or transient ischemic attack, claudication, unstable angina, carotid endarterectomy, coronary artery bypass graft, peripheral arterial bypass or angioplasty.[13,19] Apart from standard clinical work-up for expected acute PE, the included patients were not systematically screened for occult cancer in neither of the 2 participating hospitals. Thus, the patients in whom cancer was detected had developed symptomatic malignant disease or the cancer was an accidental finding during regular clinical care.

Statistical analysis

All patients were followed from the index event to the date of death or July 1st 2008, whichever came first. The Kaplan-Meier life table method was used to estimate the event free survival for all individual study endpoints and for the combined endpoint of adverse outcome in patients with unprovoked, provoked and without PE. For this latter analysis, the adverse event that occurred first was accounted for. The Log-Rank test was used for comparing the 3 study groups for statistical differences. A Cox proportional hazard model was used to calculate hazard ratios (HR) for adverse clinical events. HRs were adjusted for age, sex and in addition all further relevant patient demographics; recurrent VTE and CTEPH for initial treatment; malignancy for active smoking; cardiovascular events for active smoking, diabetes and use of anti-platelet/lipid-lowering/blood pressure-lowering medication; mortality for left sided heart failure, COPD and active malignancy; and overall adverse events for all above mentioned potential confounders. SPSS version 14.02 (SPSS Inc, Chicago, IL) was used for all analysis.

RESULTS

Patients

The diagnosis of acute PE had been established in 877 patients between January 1st 2001 and July 1st 2007 in the 2 participating hospitals. Eleven patients were excluded because of geographical inaccessibility (1.3%), leaving 866 patients for analysis. In addition, 334 patients without PE were included. The final diagnosis in the 334 patients in whom acute PE was suspected but ruled out was infectious disease in 84 (25%), non infectious or malignancy associated pulmonary disease in 43 (13%), complications of an active malignancy in 47 (14%), musculoskeletal disease in 37 patients (11%), cardiovascular disease in 33 (9.9%), gastrointestinal disease in 17 (5.1%) and other/unknown in 73 patients (22%). General characteristics of the study patients are presented in Table 1: the patients without PE were significantly younger than the patients with provoked and unprovoked PE (48 ±17 vs. 55 ±18 and 59 ±17 years respectively). In addition, the fraction of male patients was lowest in the patients without PE (37% vs. 47% and 48% respectively). Further, the presence of comorbidity and cardiovascular risk factors was similar between the three study groups, except for active malignancy, which

Table 1. Patient demographics.

	Unprovoked PE (n=308)	Provoked PE (n=558)	No PE (n=334)
Age at index event (years ±SD)	59 ±17*¶	55 ±18¶	48 ±17
Male sex (n, %)	149 (48)¶	261 (47)¶	123 (37)
Initial treatment†			
Low molecular/unfractioned heparin (n, %)	285 (93)	523 (94)	NA
Thrombolysis (n, %)	14 (4.5)	24 (4.3)	NA
Surgery, VCF or both (n, %)	9 (2.9)	11 (2.0)	NA
COPD† (n, %)	26 (8.4)	57 (10)	33 (9.9)
Left sided heart failure† (n, %)	16 (5.2)	26 (4.7)	11 (3.3)
Active malignancy† (n, %)	0 (0)*¶	201 (36)¶	46 (14)
Diabetes† (n, %)	18 (5.8)	27 (4.8)	17 (5.1)
Active smoking† (n, %)	102 (33)	172 (31)	110 (33)
Anti-platelet/lipid-lowering/blood pressure-lowering medication‡ (n, %)	151 (49)	240 (43)	147 (44)

†At index event; ‡at hospital discharge after index event; *p<0.05 vs. provoked PE; ¶p<0.05 vs. No PE. Continuous parameters were compared using ANOVA with Bonferroni post-hoc testing; bivariate variables were compared by the Chi-Square test. PE=pulmonary embolism, SD=standard deviation, n=number, VCF=vena cava filter, COPD=chronic obstructive pulmonary disease, NA=not applicable.

was most frequently present in patients with provoked PE. Lastly, the patients with unprovoked and provoked PE received comparable anticoagulant treatment. The median follow-up period for the complete study population was 3.3 years.

Risk for recurrent VTE and CTEPH

Symptomatic recurrent VTE was diagnosed in 64 (21%) patients with unprovoked PE and in 54 (9.7%) patients with provoked PE (Table 2, Figure 1) during follow-up. The adjusted HR for recurrent VTE was increased for patients with unprovoked versus provoked PE (2.1, 95% CI 1.3-3.1) and versus patients without PE (10, 95% CI 4.9-28). Patients with provoked PE had higher risk on recurrences than the control patients as well (adjusted HR 6.0, 95% CI 2.8-13). Recurrent PE was fatal in 22 of the 118 patients initially diagnosed with PE (19%, 95% CI 12-27%), and in 1 of the 4 (25%, 95% CI 0.06-81%) VTE diagnoses in the control patients. Recurrences within the first 3 weeks after the index diagnosis were associated with significantly higher mortality (Odds Ratio 7.9, 95% CI 1.2-51). CTEPH was only diagnosed in 4 patients after unprovoked acute PE (cumulative incidence 1.5%), and not in the patients with provoked PE or without PE (Table 2). The 4 patients diagnosed with CTEPH were all in stable clinical condition at the end of the follow-up period.

Risk for malignancy and arterial cardiovascular events

The risk for cancer was higher for the patients after unprovoked PE than for the patients with provoked (adjusted HR 4.4, 95% CI 2.0-10) and without PE (adjusted HR 2.5, 95% CI 1.1-2.7;

Table 2. Event free survival and hazard ratios for patients with provoked and unprovoked acute PE.

Adverse event	Unprovoked PE		Provoked PE		No PE		HR† (95% CI) unprovoked vs. provoked PE	HR† (95% CI) unprovoked vs. no PE	HR† (95% CI) provoked vs. no PE
	N	Event free survival§ (±SE)	N	Event free survival§ (±SE)	N	Event free survival§ (±SE)			
Recurrent VTE	64	0.75 ±0.029	54	0.84 ±0.024	8	0.96 ±0.015	2.1 (1.3-3.1)	10 (4.9-28)	6.0 (2.8-13)
CTEPH	4	0.99 ±0.007	0	*	0	*	*	*	*
Malignancy	23	0.91 ±0.017	8	0.98 ±0.007	8	0.97 ±0.010	4.4 (2.0-10)	2.5 (1.1-2.7)	0.78 (0.26-1.4)
Cardiovascular event	41	0.82 ±0.029	30	0.90 ±0.024	26	0.91 ±0.018	2.6 (1.5-3.8)	2.4 (1.2-3.7)	1.1 (0.72-1.5)
Mortality	67	0.72 ±0.038	193	0.60 ±0.026	29	0.87 ±0.037	0.59 (0.43-0.82)	1.4 (1.1-1.8)	3.0 (2.0-4.5)
Adverse outcome‡	155	0.42 ±0.038	252	0.47 ±0.028	58	0.76 ±0.041	0.98 (0.82-1.1)	2.6 (1.9-3.6)	2.9 (2.1-3.8)

§Estimated by Kaplan-Meier life table method after 2500 days; †hazard ratio's were adjusted for age, sex and in addition all further relevant patient demographics; recurrent VTE and CTEPH for initial treatment, malignancy for active smoking, cardiovascular events for active smoking, diabetes and use of anti-platelet/lipid-lowering/blood pressure-lowering medication, mortality for left sided heart failure, COPD and active malignancy, and overall adverse events for all above mentioned; ‡combined endpoint; *could not be calculated due to 0-value. PE=pulmonary embolism, VTE=venous thromboembolism, CTEPH=chronic thromboembolic pulmonary hypertension, SE=standard error, n=number, CI=confidence interval.

Table 2, Figure 1). There was no difference in the rate of newly diagnosed malignancies between patients with provoked and without PE (adjusted HR 0.78, 95% CI 0.26-1.4). In 27 of the 31 patients with PE (87%, 95% CI 70-96%) who were diagnosed with cancer, this malignancy was detected within the first year after the index PE. Patients with unprovoked PE suffered severe cardiovascular disease 2 to 3 times more often than the patients from the other two study cohorts (adjusted HR 2.6, 95% CI 1.5-3.8 and 2.4, 1.2-3.7 respectively; Table 2, Figure 1). Patients with PE, who suffered arterial cardiovascular events or were diagnosed with cancer had case fatality rates of 14% (95% CI 7.0-24) and 19% (95% CI 7.5-37) respectively.

Risk for mortality

In total, 259 (30%) patients with PE died, mainly as a result of a malignancy (110 patients, 13%). Furthermore, 67 (7.7%) patients died of (recurrent) PE, 6 (0.69%) because of severe bleeding from anticoagulant therapy, 30 (3.5%) of cardiovascular disease, 11 (1.3%) of non-malignant pulmonary disease and 35 (4.2%) of other causes. Twenty-nine patients without PE died during the study period (8.7%): 1 of acute PE (0.30%), 1 of myocardial infarction (0.30%), 4 of non-ischemic heart diseases (1.2%), 3 of non-malignant pulmonary disease (1.2%), 12 of malignancies (3.6%) and 8 by other causes (2.4%). Risk for overall mortality in patients after unprovoked PE was lower than in patients after provoked PE (adjusted HR 0.59, 95% CI 0.43-0.82; Table 2, Figure 1). Intriguingly, the patients with unprovoked PE who by definition did not suffer from

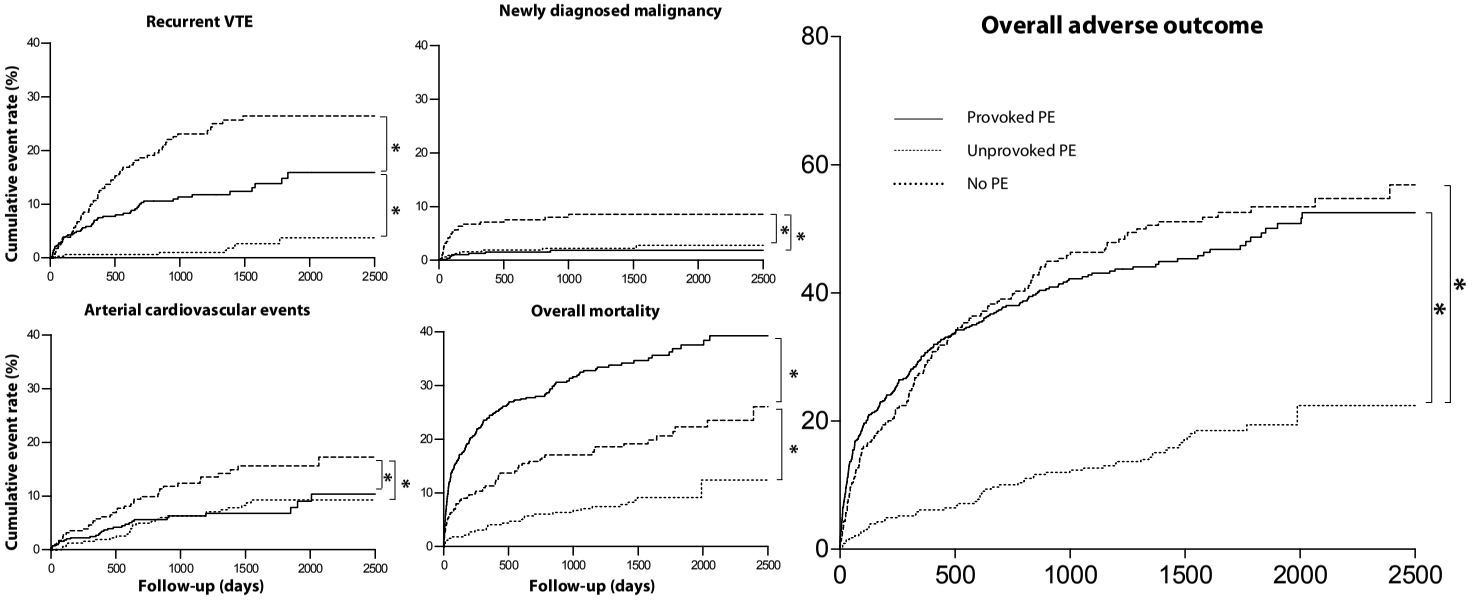

Figure 1. Cumulative adverse event rates by Kaplan-Meier life table method for recurrent venous thromboembolism (VTE), newly diagnosed malignancy, arterial cardiovascular events, mortality and the occurrence of the combined endpoint of adverse outcome in patients with provoked, unprovoked and no pulmonary embolism (PE); *p<0.05 by Log-Rank test.

active malignancies at time of the index event, were at higher risk for dying than the non-cancer patients with provoked PE (adjusted HR 1.8, 95% CI 1.3-2.5). Patients with unprovoked as well as with provoked PE had higher risks for death than the control patients (adjusted HR 1.4, 95% CI 1.1-1.8 and 2.9, 95% CI 2.1-3.8 respectively).

Risk for overall adverse outcome

The prognostic differences between patients with unprovoked and provoked PE disappeared after combining all adverse events to one pooled endpoint of adverse outcome (adjusted HR 0.98, 95% CI 0.82-1.1; Table 2, Figure 1). Nonetheless, both groups had significantly worse prognosis than the control patients without PE (adjusted HR 2.6, 95% CI 1.9-3.6 and 2.9, 2.1-3.8 respectively). Importantly, the fraction of PE patients without any event after 1 year was only 69% and decreased to 60% after 2 years and 50% after 4 years (Table 3, Figure 1). These numbers were applicable to both patients with unprovoked as well as with provoked PE. The patients without PE had significant higher event free survival with 84% of the patients surviving without any of the adverse events after a follow-up period of 4 years.

Table 3. Yearly overall event free survival for patients with unprovoked, provoked and without acute PE.

Follow-up period	Unprovoked PE (n=308)		Provoked PE (n=558)		Overall PE (n=866)	No PE (n=334)	
	NLFA	Event free survival[§] (±SE)	NLFA	Event free survival[§] (±SE)	Event free survival[§] (±SE)	NLFA	Event free survival[§] (±SE)
1 year	212	0.70 ±0.026	379	0.68 ±0.020	0.69 ±0.016	298	0.94 ±0.014
2 years	151	0.59 ±0.028	280	0.61 ±0.021	0.60 ±0.017	275	0.90 ±0.017
3 years	108	0.52 ±0.030	195	0.56 ±0.022	0.54 ±0.018	265	0.87 ±0.019
4 years	78	0.48 ±0.031	122	0.54 ±0.023	0.51 ±0.018	203	0.84 ±0.021
5 years	52	0.45 ±0.032	76	0.50 ±0.025	0.48 ±0.019	78	0.80 ±0.024
6 years	31	0.44 ±0.034	37	0.48 ±0.027	0.46 ±0.021	26	0.77 ±0.038
7 years	14	0.42 ±0.038	16	0.47 ±0.028	0.45 ±0.024	9	0.76 ±0.041

[§]Estimated by Kaplan-Meier life table method. PE=pulmonary embolism, SE=standard error, n=number, NLFA=number left for analysis.

DISCUSSION

We aimed to evaluate the long term overall prognosis of patients after acute PE. Two important conclusions can be drawn from this analysis. First, we have demonstrated that after 1 year of follow-up, only 70% of the patients are free of adverse outcome and notably, after a period of 4 years, half of the patients developed one or more serious clinical complications. A control cohort consisting of patients in whom PE was suspected but ruled out had significantly higher event free survival. Second, although risks for the occurrence of specific adverse events differed significantly between patients with unprovoked and provoked PE, the risk of the combined

endpoint of adverse outcome was similar between the two patient groups, both higher than for the control patients without PE.

The importance of our findings is underlined by the complication specific prognosis, which is poor for all adverse events studied in this analysis. First, the index PE itself had a mortality rate of 5.2%, which compares well to the existing literature.[1-4] Second, recurrent VTE was diagnosed in 118 patients. Previous studies have shown that thrombotic recurrences are associated with increased mortality.[6,7] The case fatality rate in our study was 19% in the complete study period and even 60% within the first 3 weeks after the index diagnosis. This 3 weeks mortality rate is comparable to the range of 51-79% that was reported in earlier studies.[6,7,20] In addition, according to the latest ACCP guidelines, recurrent VTE should be treated with long term anticoagulant therapy (Grade 1A), which is associated with an increased risk of often severe bleeding complications.[17] Third, cancer diagnosed at the same time as or shortly after the diagnosis of VTE is a bad prognostic sign, as this is associated with more advanced stages of cancer and a poor prognosis.[21] Sørensen et al have shown that patients in whom cancer was diagnosed within one year after the diagnosis of VTE had an increased risk of distant metastasis at the time of diagnosis and a relatively low rate of survival compared to patients with cancer without a history of VTE.[21] In our population, cancer diagnosed after the index PE proved to be fatal in 19% of the cases within the follow-up period. The association between unprovoked PE and the subsequent development of clinically overt cancer is most likely explained by the fact that these cancers are already present at the time of, and may even be causally related to the PE, although not yet detected.[11] Fourth, although the exact mechanism underlying the association between arterial cardiovascular events and VTE is unknown, evidence exists that both diseases are closely linked.[9,13] The observation that control patients without PE and patients with provoked PE have the same risk for arterial cardiovascular events, which is significantly lower than for patients after unprovoked PE, supports the hypothesis that a shared but yet unidentified mechanism causes events in both the venous and the arterial system.[13] Arterial events such as myocardial infarction or stroke have great implications for the patients' health and lead to high morbidity and mortality rates and decreased quality of life.[22] Lastly, four patients were diagnosed with CTEPH (cumulative incidence in patients with unprovoked PE 1.5%). This percentage is relatively low compared to some recent studies reporting incidences of 3.8 and even 8.8% in patients after PE.[14,23] This discrepancy might very well be explained by different selection criteria than in previous studies, or by underdiagnosis of CTEPH in our cohort, although the included patients with PE were systematically screened for the presence of pulmonary hypertension.[15] Even though none of our four patients with CTEPH died during the study period, it has previously been shown in larger cohorts that the prognosis of patients with CTEPH is rather poor, unless a successful pulmonary endarterectomy is achievable.[8]

Thus, we have combined 4 very serious complications of PE as well as all cause mortality in this analysis. The pooled endpoint of adverse outcome was reached by 50% or more of the patients with PE after 4 years of follow-up, which is significantly more than for the control

patients. Remarkably, this overall prognosis is comparable for patients with unprovoked and patients with provoked PE. This latter observation was mainly driven by the malignancy related high mortality rates in the patients with provoked PE. Further analysis showed that patients with unprovoked PE have in fact the highest risk on non-malignancy related mortality and all the other included endpoints. These findings emphasize that acute PE is an important clinical problem with poor prognosis for short and long term survival and the occurrence of serious thrombotic or non-thrombotic adverse events.

Many risk stratification and screening strategies including intensified or prolonged anti-thrombotic therapy regimes to identify and treat patients with high risk for PE-related mortality, recurrent VTE or detection of cancer have been proposed, but all remain insufficient or controversial.[17,24-27] An earlier study concluded that treatment of heparin and anticoagulants is not enough for all PE patients.[28] Our results, although almost 30 years later, confirm this conclusion and once more emphasize the poor overall prognosis of patients with acute PE. In current clinical practice and despite the increased risk for serious clinical complications, patients with a first episode of acute PE stop their anticoagulant therapy usually after three to six months.[17] From then on, they are usually no longer subject to clinical supervision by a medical specialist. Importantly, by lack of scientific based evidence and proven cost-efficacy, standard screening for classic cardiovascular risk factors, hidden cancer or CTEPH is at this moment not part of routine clinical work-up of patients with PE. Our results underline the importance of close clinical surveillance in the first months after PE, especially in those patients with unprovoked PE, to evaluate the basic risks for future adverse events and in addition, treat patients accordingly. Therefore, future outcome studies should focus on 1) better individual assessment of the risk for recurrent venous thromboembolism and CTEPH to enable the physician to identify those patients who could benefit from prolonged anticoagulant therapy or specific screening for pulmonary hypertension; 2) effectiveness of cardiovascular risk factor evaluation and proper treatment measures to prevent arterial cardiovascular events; and 3) effect of specific screening programs for underlying malignancies, to achieve very early identification of hidden malignancies thereby potentially improving the patients' prognosis.

Our study has strengths and limitations. Our findings are likely to be generalizable to most patients with PE since we have included all consecutive patients diagnosed with this disease in an academic and non-academic teaching hospital independently of their clinical condition or comorbidity. Even though our study endpoints are severe clinical events that are likely to be recorded in detail, we have additionally verified the accuracy and completeness of the data from the medical charts with the surviving patients. Only 11 patients with PE (1.3%) who could not be reached due to geographical inaccessibility, were excluded. Furthermore, our findings are in accordance with the extensive literature on this subject, although we are the first to combine all adverse events into 1 pooled endpoint. We acknowledge that we were not able to report on all bleeding events, which are important complications in the clinical course of acute PE. Nonetheless, the adverse effect of bleeding is often transient and the period at risk is limited

to the first six months after diagnosis in the majority of patients. Moreover, the most severe bleedings that resulted in mortality could in fact be accounted for.

We conclude that acute PE remains a very serious clinical condition with high mortality and high risk on PE associated severe complications. Remarkably, there was no difference in the pooled risk for adverse outcome of patients with unprovoked and provoked PE, although the risk on all separate endpoints except for overall mortality was markedly higher for the patients with unprovoked PE. Physicians should be well aware of the fact that in four years time, half of the patients diagnosed with acute PE has died or is diagnosed with cancer, recurrent VTE, CTEPH or arterial cardiovascular disease. The challenge of future trials remains to enable the treating physician to use accurate prediction tools for adjusting treatment regimes and clinical surveillance to the personalized prognosis of the individual patient.

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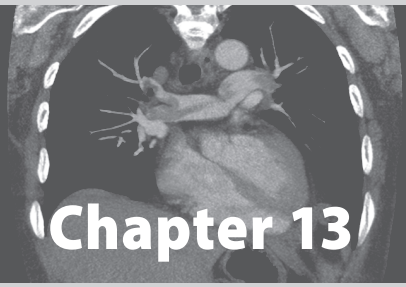

Chapter 13

Quality of life after pulmonary embolism: validation of the PEmb-QoL questionnaire

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ABSTRACT

Background

Even though quality of life (QoL) has become a key component of medical care, there is no instrument available that specifically measures QoL after pulmonary embolism (PE). Recently, the Pulmonary Embolism Quality of Life (PEmb-QoL) questionnaire has been developed to address this gap. We have evaluated the validity of this questionnaire.

Methods

The PEmb-QoL questionnaire and the Short Form-36 (SF-36) questionnaire were distributed twice among consecutive subjects with a history of objectively confirmed acute PE. Internal consistency reliability, test-retest reliability, convergent and criterion validity, and correlations between the PEmb-QoL and clinical patient characteristics were assessed using standard-scale construction techniques.

Results

90 participants completed the questionnaires twice. Internal consistency was adequate (Cronbach's α 0.62-0.94), as well as test-retest reliability (intra-class correlation coefficients 0.78-0.94). Furthermore, correlation between the PEmb-QoL questionnaire and the SF-36 questionnaire supported the convergent and criterion validity of the PEmb-QoL. Age, obesity, cardiopulmonary comorbidity, centrally located PE and a family history of venous thromboembolism were shown to be independent determinants of disease-specific QoL.

Conclusion

The PEmb-QoL questionnaire is a reliable instrument to specifically assess QoL following PE, which is helpful in the identification of patients with decreased QoL following acute PE.

INTRODUCTION

Pulmonary embolism (PE) is a common disorder characterized by the obstruction of the pulmonary arterial tree by floating thrombi predominantly originating from the leg or pelvic veins.[1] Although PE has traditionally been considered to be an acute disease, the long term natural course in patients surviving the acute thromboembolic event can be complicated by recurrent episodes of PE or deep vein thrombosis, bleeding complications caused by anticoagulant treatment, arterial cardiovascular events and in rare cases by chronic thromboembolic pulmonary hypertension (CTEPH).[1-4] CTEPH may present as fatigue, limited exercise tolerance or shortness of breath and might even affect 3.8% of PE patients within 2 years following the initial event.[3] In addition, patients often have residual dyspnea complaints years after the acute thromboembolic event.[5]

Quality of life (QoL) has become an important outcome aspect of medical care. QoL can be assessed by generic or disease-specific questionnaires. The latter are more sensitive than generic questionnaires to detect and quantify small changes that are relevant to patients. Several disease-specific QoL instruments have been developed for deep venous thrombosis (DVT), a condition closely related to PE and considered a manifestation of the same disease entity.[6-10] Furthermore, there are several specific questionnaires for symptoms of the respiratory tract, such as the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR)[11] or the Chronic Respiratory Disease Questionnaire (CRQ).[12] However, since respiratory or other symptoms that affect QoL after PE have never been purposely studied, we have developed a new measure -the Pulmonary Embolism Quality of Life (PEmb-QoL) questionnaire-, based on symptoms as reported by 10 interviewed participants with severe complaints following PE. Details on the development of the PEmb-QoL questionnaire have been described previously.[13]

The PEmb-QoL was modelled on the quality of life after DVT (VEINES-QOL/Sym) questionnaire.[6,7,9] Both questionnaires assess the frequency of symptoms, the time of day at which the complaints are at their worst and activities of daily living (ADL) as well as work related problems. However, the PEmb-QoL questionnaire is distinct from the VEINES-QOL/Sym in the inclusion of pulmonary specific symptoms, adding questions on limitations in daily physical activities, and extending the number of questions on emotional functioning. Moreover, in order not to lose valuable information, we decided to assess the different areas of limitations as separate dimensions, instead of combining items into two subscales (symptoms and QoL), as is the case in the VEINES-QOL questionnaire. In the present paper, we report results from the validation study that was performed to assess the psychometric and clinical characteristics of the questionnaire.

METHODS

Participants

The PEmb-QoL in Dutch was distributed among consecutive participants of a large follow-up study of patients with a history of acute PE referred to the Leiden University Medical Center. Inclusion criteria were objectively confirmed PE diagnosed between January 1st 2001 and July 1st 2007. All surviving patients were invited for a control visit in our outpatient clinic. We asked a random, consecutive subsample of 93 participants to complete the PEmb-QoL and Short-Form 36 (SF-36) questionnaires shortly before this visit. After first review, incomplete questionnaires were completed at the study visit. For assessment of test-retest reliability, participants were instructed to complete both questionnaires for a second time (within a two week period) at home shortly after the visit and return these by mail. Incomplete returned questionnaires were completed by the patients following contact by telephone. We excluded participants with language barriers who could not complete the questionnaires in Dutch. The study protocol was approved by the Institutional Review Board of the Leiden University Medical Center and all patients provided written informed consent.

PEmb-QoL questionnaire

We applied the disease specific PEmb-QoL questionnaire which we developed to assess QoL in patients with PE.[13] The PEmb-QoL questionnaire contains 6 dimensions: frequency of complaints, ADL limitations, work related problems, social limitations, intensity of complaints and emotional complaints. Higher scores indicate worse outcome.

SF-36 questionnaire

The SF-36 is a generic QoL measure containing 8 scales (physical functioning, social functioning, physical role functioning, emotional role functioning, mental health, vitality, bodily pain, and general health), scoring 0 to 100, with higher values indicating better health.[14] Two summary scores are created by combining scales into a physical health summary score and mental health summary score.

Outcome measures

We expected that the PEmb-QoL dimensions frequency of complaints, ADL limitations, work related problems, social limitations and intensity of complaints would have higher correlations with the physical health summary score of the SF-36, whereas emotional complaints would have a higher correlation with the mental health summary score. Furthermore, we did not expect that patient characteristics at time of the acute PE would be important determinants of the results of the PEmb-Qol, given the results of a previous study.[15] This study showed that QoL after deep vein thrombosis as assessed by the VEINES-QOL and SF-36 was mostly determined by the presence of the postthrombotic syndrome and less by severity of the acute clinical event,

comorbid conditions, sex or age. To test this hypothesis, we assessed the following patient characteristics and correlated those to the results from the PEmb-QoL: age, sex, obesity (body mass index>30kg/m^2), active malignancy (cancer with ongoing treatment, treatment within the previous 6 months or in the palliative stages), cardiopulmonary comorbidity (clinically relevant obstructive or restrictive pulmonary function impairment, or systolic or diastolic ventricular dysfunction), centrally located PE according to the original radiological reports, family history of venous thromboembolism and the duration of follow-up from the index thromboembolic event to study inclusion.

The outcome measures of this analysis were internal consistency reliability (which assesses whether several items that propose to measure the same general construct produce similar scores), test-retest reliability, convergent validity, criterion validity (as assessed by comparing the PEmb-QoL dimensions with the dimensions of the SF-36 disease generic questionnaire) and the association of patient demographics, comorbid conditions and PE characteristics with higher or lower QoL in our patient population.

Statistical Analyses

Means and standard deviations were calculated for normally distributed variables. Skewed distributed variables were expressed in medians with ranges. We performed a factor analysis on the items of the PEmb-QoL with varimax rotation to examine the underlying constructs. Internal consistency reliability was calculated with Cronbach's α.[16] Following the recommendations of DeVellis, internal consistency reliability was considered adequate if Cronbach's α was higher than 0.7.[17] Test-retest reliability was expressed as intra-class correlation coefficients. We calculated inter-dimension correlations and criterion validity with bivariate Spearman correlation coefficients. For the assessment of significant predictors of QoL in our patient cohort, backward conditional linear regression analyses with direct entry were performed to identify independent determinants of QoL. A p-value <0.05 was considered statistically significant.

RESULTS

Patients

The questionnaires were distributed amongst 93 participants, of whom 90 completed the questionnaire after a median period of 38 months (range 10–91 months) following PE. Three participants (3.2%) were excluded due to inability to complete this questionnaire in Dutch because of language barriers. The number of missing items was very low; however the exact number could not be calculated as all missing items were completed by the respondents following contact by phone with the researchers. The included participants were 56 ±14 years old, 44 (47%) were males, 19 (20%) had cardiopulmonary comorbidity, 12 (13%) had active malignancy, 36 (39%) were obese, 31 (33%) were diagnosed with centrally located PE,

Table 1. Demographics of included patients.

	Study patients (n=90)
Male sex (n, %)	43 (48)
Age (years ±SD)	56 ±14
Cardiopulmonary comorbidity (n, %)	18 (20)
Active malignancy (n, %)	12 (13)
Obesity* (n, %)	35 (39)
Centrally located PE (n, %)	31 (34)
Invasive treatment for PE† (n, %)	6 (6.7)
Recurrent PE (n, %)	18 (20)
Time to registration event‡ (range)	3 years and 2 months (10 months – 7 years and 7 months)

*Body mass index >30kg/m^2; †thrombolysis, Surgery or VCF for first acute PE; ‡time span between registration acute PE and study inclusion. PE=pulmonary embolism, n=number.

6 (6.5%) received invasive treatment for PE and 19 (20%) suffered from recurrent episodes of PE (Table 1).

Scores of the 6 dimensions of the PEmb-QoL were 1.5 (interquartile range 1.1-2.4; max 5 points) for frequency of complaints, 1.2 (1.0-1.8; max 3 points) for limitations in activities of daily living (ADL), 1.0 (1.0-1.5; max 2 points) for work related problems, 1.0 (1.0-1.2; max 5 points) for social limitations, 2.0 (1.0-3.0; max 6 points) for intensity of complaints and 1.6 (1.1-2.4; max 6 points; Figure 1). For all dimensions, a score of 1 point designates no complaints.

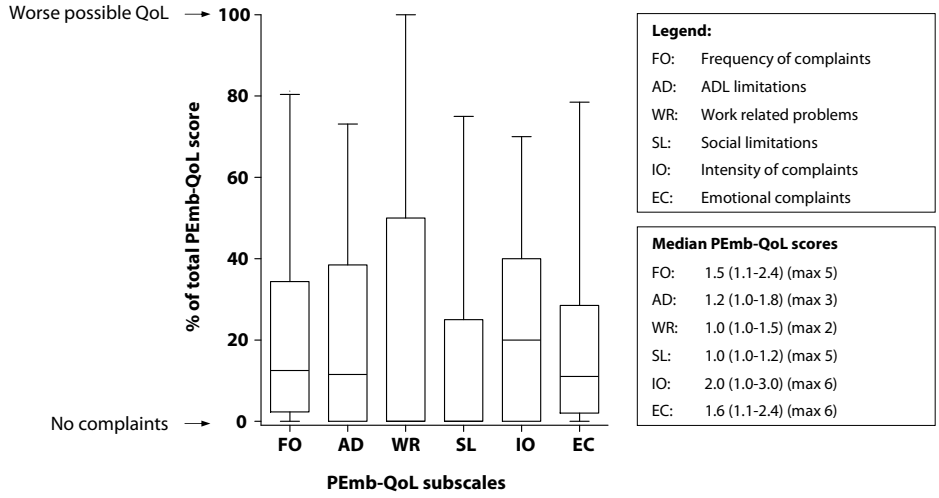

Figure 1. Results of the PEmb-QoL scores of patients with a history of acute pulmonary embolism. Scores are presented as median with interquartile range. Minimum score for all 6 subscales was 1, maximum scores are presented between brackets. Higher PEmb-QoL scores are associated with decreased quality of life. ADL=activities of daily living, Qol=quality of life.

Psychometric characteristics of the PEmb-QoL questionnaire

Factor analysis (with varimax rotation) supported the underlying dimensions producing 6 factors which accounted for 72% of the total variance. Table 2 lists the internal reliabilities of the dimensions, as expressed by Cronbach's α, as well as test-retest reliability and inter-dimension correlations between the PEmb-QoL dimensions. Internal reliability was high (α≥0.87) for the dimensions frequency of complaints, ADL limitations, work related problems, and emotional complaints but lower for the dimension intensity of complaints (α=0.62). We assessed whether deletion of any of the items in the various dimensions could increase the internal reliability of any of the dimensions and hence, whether the PEmb-QoL questionnaire could be abridged. However, deletion of any of the items from the various dimensions did not lead to substantial improvements of the dimensions' internal consistency reliability.

Table 2. Internal consistency reliability, test-retest reliability and correlations between PEmb-QoL dimensions.

PEmb-QoL dimensions	**PEmb-QoL questions**	**Number of items**	**Cronbach's α**	**Intra-class correlation coefficient**	Frequency of complaints	ADL limitations	Work related problems	Social limitations	Intensity of complaints
Frequency of complaints	Question 1*	8	0.90	0.94***		-	-	-	-
ADL limitations	Question 4*	13	0.94	0.87***	0.67**		-	-	-
Work related problems	Question 5*	4	0.87	0.78***	0.49**	0.66**		-	-
Social limitations	Question 6	1	NA	0.83***	0.62**	0.69**	0.64**		-
Intensity of complaints	Questions 7/8	2	0.62	0.85***	0.82**	0.73**	0.60***	0.66**	
Emotional complaints	Question 9*	10	0.91	0.81***	0.60**	0.60**	0.56**	0.63**	0.71***

*Items reversely scored (higher scores indicate more complaints); **p<0.01; ***p<0.001. ADL=activities of daily living, NA=not applicable.

Intra-class correlation coefficients for test-retest analysis varied between 0.78 for work related problems and 0.94 for frequency of complaints, indicating adequate test-retest validity. The highest correlations between dimensions were found between intensity of complaints and all other dimensions (0.60≤ r ≤0.82). Except for work related problems and frequency of complaints (r=0.49), all dimensions were moderately correlated (0.56≤ r ≤0.82).

The results of the criterion validity are reported in Table 3. As expected, the PEmb-QoL dimensions frequency of complaints, ADL limitations, work related problems, social limitations and intensity of complaints had higher associations with the physical health summary score of the SF-36 questionnaire, whereas emotional complaints were most strongly associated with the

Table 3. Correlations between PEmb-QoL dimensions and SF-36 subscales.

	SF-36									
PEmb-QoL	Physical functioning	Social functioning	Physical role functioning	Emotional role functioning	Mental health	Vitality	Bodily pain	General health	Physical health summary	Mental health summary
Frequency of complaints	-0.46**	-0.55**	-0.33**	-0.28**	-0.45**	-0.56**	-0.42**	-0.55**	-0.44**	-0.42**
ADL limitations	-0.78**	-0.61**	-0.53**	-0.39**	-0.45**	-0.66**	-0.49**	-0.63**	-0.66**	-0.39**
Work related problems	-0.53**	-0.50**	-0.58**	-0.43**	-0.40**	-0.54**	-0.29**	-0.53**	-0.51**	-0.39**
Social limitations	-0.54**	-0.55**	-0.45**	-0.31**	-0.38**	-0.53**	-0.35**	-0.51**	-0.50**	-0.35**
Intensity of complaints	-0.62**	-0.66**	-0.44**	-0.32**	-0.55**	-0.67**	-0.49**	-0.60**	-0.55**	-0.48**
Emotional complaints	-0.45**	-0.60**	-0.38**	-0.43**	-0.57**	-0.69**	-0.41**	-0.59**	-0.40**	-0.57**

**p<0.01.

mental health summary score. Frequency of complaints was most strongly correlated with vitality (r=-0.56), social functioning (r=-0.55) and physical functioning (r=-0.46). The strongest correlations for ADL limitations were physical functioning (r=-0.78), social functioning (r=-0.61) and vitality (r=-0.66). Work-related problems most strongly correlated with physical role functioning (r=-0.58) and physical functioning (r=-0.53). The dimension social limitations was correlated with several SF-36 dimensions. We observed strong correlations with physical functioning (r=-0.54), social functioning (r=-0.55) and vitality (r=-0.53). Intensity of complaints was strongly correlated with the same SF-36 dimensions as frequency of complaints, but with higher correlation coefficients. The strongest correlations for emotional complaints were mental health (r=-0.57), vitality (r=-0.69) and social functioning (r=-0.60).

Associations between clinical characteristics and the PEmb-QoL

After multivariate analysis including all patient demographics, comorbid conditions and PE-characteristics, younger age, obesity, cardiopulmonary comorbidity and centrally located PE were shown to be independent predictors for decreased disease-specific QoL (Table 4). Inversely, a family history of venous thromboembolism independently predicted lower intensity of complaints and emotional complaints and also was a predictor of better social function. Markedly, the multivariate models including these independent determinants of QoL predicted the measured QoL in the individual dimensions of the PEmb-QoL only for 5.7% to 16% (linear regressions' coefficient of determination).

Table 4. Multivariate linear regression of PEmb-QoL dimensions and SF-36 subscales.

	Frequency of complaints	ADL limitations	Work related problems	Social limitations	Intensity of complaints	Emotional complaints
Gender‡						
Age (per year)	-0.15*					
Obesity∂†		0.26**	0.18*	0.36*	0.49*	
Cardiopulmonary comorbidity†		0.26*			0.21*	
Active malignancy†						
Centrally located PE†	0.45*	0.23*				
Follow-up period (per day)‡						
Family history of VTE†				-0.40*	-0.50*	-0.55*

Unstandardized regression (beta) coefficients with p-values only of independently significant determinants of quality of life are displayed. Higher PEmb-QoL scores are associated with decreased quality of life. †0=not present, 1=present; ‡1=male, 2=female; ∂body mass index >30kg/m^2; †0=not present, 1=present; ‡time span between registration acute pulmonary embolism and study inclusion in days; *p<0.05, **p<0.01. ADL=activities of daily living.

DISCUSSION

The results from this validation study indicate that this newly developed disease-specific health-related QoL instrument PEmb-QoL is a valid and reliable instrument to assess QoL following PE. Internal reliability for all dimensions (except intensity of complaints) was adequate and comparable to the reliability of the VEINES-QOL/Sym scales.[6] Test-retest reliability was also adequate. The inter-correlations between the PEmb-QoL dimensions demonstrated logical relationships. Intensity of complaints correlated with a worse outcome in all other dimensions. This was expected as this dimension might actually affect a person's well-being in general. Also, its association with frequency of complaints is high, suggesting these dimensions could be taken together to form one summary score for symptom severity, comparable to the VEINES-QoL/Sym summary score.

We observed a tendency towards small floor and ceiling effects in some of the PEmb-QoL dimensions. This was assumed to be attributable to the time between the events and completion of the questionnaires. Therefore, we expect that other patient samples including those with a more recent event will show less floor or ceiling effects. Furthermore, we observed that work related problems most strongly correlated with physical role functioning and physical functioning. We hypothesized that this observation is explained by the fact that both dimensions focus on the extent of limitations performing work or physical exercise. Emotional complaints were more strongly associated with mental health and vitality than to emotional role functioning. This is also conceivable, as the wording of the items of this PEmb-QoL dimension closely match the items of the SF-36 dimensions mental health and vitality. Also, the correlation between social limitations and social functioning was (almost) as high as the correlation with physical

functioning and vitality. This is a plausible observation as well, since social activities are also influenced by the capability to perform exercises such as climbing stairs or walking a certain distance.

After multivariate analysis, several demographic and symptom factors associated with better or worse health related QoL were identified. Higher age, obesity and comorbid conditions predicted decreased QoL in our study population. This is to be expected, as these factors have previously been shown to be important determinants of health status in healthy persons and patients suffering from various diseases.[15,18,19] Notably, the presence of family members who have a history of the same condition was associated with improved social status, decreased intensity of complaints and a smaller amount of emotional complaints. We hypothesized that this phenomenon might be attributed to enhanced social support which is an important aspect of QoL.[20,21] Although we were able to identify several significant determinants of QoL in our patient population, combining these in multivariate prediction models did not result in precise prediction of the QoL for individual patients since our models predicted only 5.7% to 16% of the variance in PEmb-QoL scores. This observation is in accordance with the result of a previous study, which indicated limited effects of patient demographics and comorbid conditions on the QoL of patients with DVT.[15]

Limitations of our study comprise the exclusion of 3 participants due to language barriers and the lack of detailed comparison to healthy subjects. This comparison is difficult since the PEmb-QoL was designed for patients with acute PE and is by definition not applicable to subjects without this disease. Finally, we were unable to assess responsiveness in this cohort.

This disease specific questionnaire was developed to assist physicians in monitoring treatment interventions after acute PE. The advantage of disease specific questionnaires over generic instruments of QoL is that these can be considered to have higher sensitivity for detecting subtle but clinically relevant alterations in QoL caused by the studied condition or treatment.[22] Although we were able to show correlations between the outcome of the PEmb-QoL and the condition of patients with a history of acute PE, our study design did not allow assessing whether this QoL instrument could be used in treatment decisions. Hence, further studies are needed.

In summary, the PEmb-QoL is a valuable instrument for determining the disease-specific QoL in patients with previous acute PE. This questionnaire is a valid and reliable instrument of QoL following acute PE and discriminates patients with impaired health perception. The clinical applicability of the PEmb-QoL and its potential role in the management of patients with acute PE remains to be studied in clinical outcome studies.

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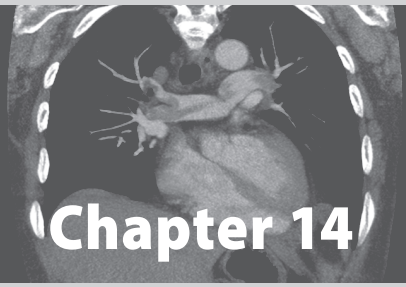


Chapter 14

General discussion and summary

The main objectives of this thesis are to validate and simplify current diagnostic strategies for clinically suspected acute pulmonary embolism (PE) and to predict the short and long term prognosis of patients diagnosed with and treated for acute PE. Therefore, several studies were performed focusing on the safety of different diagnostic algorithms and several aspects of the patients' prognosis. **Chapter 1** provides a general introduction to the pathophysiology of acute PE and its associated clinical course. Furthermore, it evaluates current clinical insights regarding diagnostic and treatment strategies and addresses scientific gaps yet to be bridged.

PART I: DIAGNOSTIC MANAGAMENT OF ACUTE PE

Many clinical decision rules to estimate the pretest probability of the individual patient for having PE have been proposed. The most widely used one, the Wells rule, includes the subjective judgment of the clinician and as a result, this rule has average reproducibility. **Chapter 2** describes a study on the clinical validity and performance of the recently developed and more objective revised Geneva score in a patient cohort in whom the Wells rule was initially utilized for clinical practice. In 300 consecutive patients with suspected PE, the predictive accuracy of both scores was compared by the area under the receiver operating characteristic curves (AUC of ROC). These AUCs were not different for both rules: 0.72 (95% confidence interval [CI] 0.65–0.80) and 0.67 (95% CI 0.59–0.76) respectively. Furthermore, after three months of follow-up, no patient classified into the low or intermediate clinical probability category by the revised Geneva score and a normal D-dimer result was subsequently diagnosed with acute venous thromboembolism (VTE). In **chapter 3**, we simplified the revised Geneva score by attributing 1 point to each item of the original clinical decision rule, as an alternative for the original different weights of the individual items. These different weights might be more difficult to remember and could lead to miscalculations in an acute setting. This simplification of the revised Geneva rule did not result in decreased AUC of the ROC analyses in 1049 patients with suspected PE: 0.75 (95% CI 0.71-0.78) for the original and 0.74 (95% CI 0.70-0.77) for the simplified rule. Further analysis indicated that during a three months follow-up period, no patient with a combination of either a low or intermediate clinical probability, or a "PE unlikely" assessment with the simplified score and a normal D-dimer test result was diagnosed with symptomatic VTE. These study results suggest that the performances of the simplified and original revised Geneva score are equivalent to that of the Wells rule. Furthermore, it was safe to rule out acute PE by a combination of a "low", "intermediate" or "unlikely" probability assessment by the simplified or original revised Geneva score, in combination with a normal highly sensitive D-dimer test result.

A negative computed tomography pulmonary angiography (CTPA) result alone is considered to be a controversial criterion for the safe exclusion of PE in a high risk population, since the negative predictive value (NPV) of this imaging modality might be reduced in case of high pretest

probability for having PE. **Chapter 4** is a meta-analysis to determine the safety of ruling out PE by a normal CTPA in a specific group of patients with a strict indication for CTPA, i.e. likely or high clinical probability for PE, an elevated D-dimer concentration, or both. The pooled NPV after three months was 98.8% (95% CI 98.2-99.2) based on a normal CTPA as a sole test and 98.9% (95% CI 98.0-99.4) based on normal CTPA followed by negative compression ultrasonography of the legs. In addition, risk of fatal PE did not differ between both diagnostic strategies (0.6% vs. 0.5%). Since these test characteristics compare favorably with those of normal conventional pulmonary angiography, we conclude that a normal CTPA alone can safely exclude PE in all patients in whom CTPA is required to rule out this disease.

PART II: SHORT TERM CLINICAL OUTCOME AFTER PE

The ability of accurately predicting adverse clinical outcome in hemodynamic stable patients with acute PE is of great importance for the therapeutic management of these patients. In **chapter 5**, the potential role of brain-type natriuretic peptides (BNP) in the differentiation of patients suffering from acute PE at risk for adverse clinical outcome is evaluated. A meta-analysis of all previous studies on this subject revealed that patients with elevated levels of BNP or NT-pro-BNP were at higher risk of complicated in-hospital course (odds ratio [OR] 6.8, 95% CI 4.4-10) and 30-day mortality (OR 7.6, 95% CI 3.4-17).

In a prospective study, the clinical utility of NT-pro-BNP for predicting adverse outcome after PE was further studied by comparing that to the utility of other biomarkers and right ventricular enlargement assessed on static CTPA images (**chapter 6**). We included 113 consecutive normotensive patients with CT pulmonary angiography (CTPA) proven PE. All predictors under study were associated with adverse outcome in patients with PE, with ORs of 3.7 (95% CI 0.74-19) for right/left ventricular ratio >1 on axial CTPA view, 9.0 (95% CI 1.1-79) for right/left ventricular ratio >1 on 4-chamber CTPA view, 3.5 (95% CI 0.86-15) for D-dimer >3000 pg/mL FEU, 6.3 (95% CI 1.3-31) for Troponin-T >0.09 ng/mL and 31 (95% CI 3.6-257) for NT-pro-BNP >600 pg/mL. The NPV of NT-pro-BNP was highest (99%). Importantly, 72% of patients had a NT-pro-BNP ≤600 pg/mL; 4-chamber RV/LV-ratio <1 had equally excellent NPV (98%), but less patients were categorized as having low risk for complications (43%). We concluded that NT-pro-BNP had the highest discriminative power and clinical utility as predictor of adverse events after PE in our study population. This conclusion could point towards using NT-pro-BNP as stratification tool for identifying patients for outpatient treatment.

The positive predictive value (PPV) of NT-pro-BNP or the other predictors was not sufficient to justify more invasive treatment measures in normotensive patients with PE. We hypothesized that CT-measured right ventricular ejection fraction would be a more specific predictor for adverse outcome, and therefore involve a higher PPV. In the identical patients who are described in chapter 6, the right ventricular ejection fraction was assessed by electrocardiography

(ECG)-synchronized multi-detector row CTPA (**chapter 7**). RV dysfunction was defined as RV ejection fraction below 47%, which was present in 45% of the patients. In addition, the AUC of its ROC analysis proved to be higher than simple, right/left ventricular ratio assessment. RV dysfunction was identified in 90% of the patients with adverse events (OR 36, 95% CI 2.2-590). In spite of this OR and high NPV (98%), this technique was not able to identify patients with such high risk for adverse events, that patients with RV ejection fraction below 47% are likely to benefit from more invasive treatment measures (positive predictive value 18%). Furthermore, the NPV of the ECG-synchronized ventricular measurements was comparable to those of the simple CTPA measurements. Importantly, ECG-synchronized cardiac CT involves increased radiation and contrast dose which should be considered before this technique is considered for integration in routine clinical care.

PART III: LONG TERM CLINICAL COURSE AFTER PE

In **chapter 8**, we discuss the results of a cohort screening study for chronic thromboembolic pulmonary hypertension (CTEPH) in an unselected series of 866 consecutive patients diagnosed with acute PE. All patients who were not previously diagnosed with pulmonary hypertension (PH) and had survived until study inclusion, were invited for transthoracic echocardiography. Patients with echocardiographic suspicion of PH underwent complete work-up for CTEPH, including ventilation-perfusion lung scan and right heart catheterization. For the patients who had died, the cause of death was extracted from autopsy reports or verified with the general practitioner. The presence of CTEPH in patients who were unable to visit our hospital for echocardiography was assumed not present in case of absence of unexplained clinical symptoms of this disease. After an average follow-up of 34 months, PH was diagnosed in 19 patients by routine clinical care and in 10 by our screening program; 4 patients had CTEPH, who were all diagnosed by routine clinical care. The cumulative incidence of CTEPH after all cause acute PE was 0.57% (95% CI 0.02-1.2%) and after unprovoked PE 1.5% (95% CI 0.08-3.1%). Because of this low incidence and the very low yield of the echocardiography based screening program, wide scale implementation of prolonged follow-up including echocardiography of all patients with PE to detect CTEPH seems not warranted.

Dyspnea is one of the key clinical symptoms of CTEPH. Although we found CTEPH to be a rare complication after acute PE, persistent dyspnea is reported by one third of patients at 3.6 ±1.7 years after the PE. This subjectively reported dyspnea is significantly correlated to decreased exercise performance. Therefore, the possibility of CTEPH is frequently considered. In **chapter 9**, we study several non-invasive clinical tests for ruling out CTEPH in symptomatic patients with a history of PE. ECG criteria of right ventricular overload were more frequent in patients with CTEPH (77%) than in symptomatic patients without pulmonary hypertension (11%; $p<0.01$).

Also, clotting factor FVIII activity and levels of NT-pro-BNP, growth differentiation factor-15, C-reactive protein and urate were higher in the patients with CTEPH, in contrast to D-dimer levels. A diagnostic model including ECG criteria and NT-pro-BNP levels had a sensitivity of 94% (95% CI 86-98), a specificity of 65% (95% CI 56-72) and an AUC of the ROC analysis of 0.80 (0.74-0.85) for the presence of CTEPH in dyspnoeic patients. Adding other or additional biomarkers to ECG and NT-pro-BNP assessment resulted in a decrease of predictive value of the model. Even with unrealistically high disease prevalences up to 10%, the negative predictive value of our final model proved very high (>99%). We concluded that additional diagnostic tests to rule out CTEPH in dyspnoeic patients after acute PE are not necessary in absence of ECG criteria of right ventricular overload and a normal NT-pro-BNP level.

Chapter 10 extends the findings presented in chapters 8 and 9 by evaluating determinants and alternative causes of chronic dyspnea after acute PE. After multivariate analysis, cardio-pulmonary comorbidity (OR 12; 95% CI 6.5-20), advanced age (OR 1.02 per year; 95% CI 1.01-1.03), higher BMI (OR 1.06 per kg/m^2; 95% CI 1.01-1.1) and a smoking history (OR 1.6; 95% CI 1.02-2.6) were identified as independent predictors of chronic dyspnea after PE. An alternative diagnosis reasonably explaining the dyspnea could be established in all patients. The clinical consequence of our study is that chronic dyspnea in the clinical course of acute PE is mainly caused by pre-existing comorbid conditions and alarming direct complications of PE such as CTEPH are very rare.

In **chapter 11**, the association between venous thromboembolism and arterial cardiovascular disease is assessed by comparing the cumulative incidence of serious cardiovascular events (defined as clinically adjudicated acute myocardial infarction, stroke or transient ischemic attack, claudication, unstable angina, carotid endarterectomy, coronary artery bypass graft, peripheral arterial bypass or angioplasty) in patients with unprovoked PE to that of patients with provoked PE and a control population of patients in whom PE was suspected but ruled out. After a median follow-up period of 4.2 years, the adjusted hazard ratio (HR) for arterial cardiovascular events was not different between patients with all cause PE and control patients (1.4, 95% CI 0.83-2.3), but increased for patients with unprovoked PE versus patients with provoked PE as well as control patients without PE (HR 2.2; 95% CI 1.1-4.5 and 2.6; 95% CI 1.4-4.9 respectively). This observation underlines the hypothesis of a shared but yet unidentified mechanism causing events in both venous and arterial systems.

In addition to arterial cardiovascular events and CTEPH, further adverse clinical events which are associated with acute PE and have a major impact on the long term prognosis of patients with PE include mortality, newly diagnosed malignancies and recurrent VTE. In **chapter 12**, we explore the risk of suffering from any of these conditions in the first years after the diagnosis of PE. Patients with unprovoked PE had lower overall risks for mortality than patients with provoked PE (adjusted HR 0.59, 95% CI 0.43-0.82), but higher risk for non-malignancy related

mortality (adjusted HR 1.8, 95% CI 1.3-2.5), recurrent VTE (adjusted HR 2.1, 95% CI 1.3-3.1), cancer (adjusted HR 4.4, 95% CI 2.0-10), cardiovascular events (adjusted HR 2.6, 95% CI 1.5-3.8) and CTEPH (cumulative incidence 1.5% vs 0%). The risk for the combined endpoint did not differ between both groups (adjusted HR 0.98, 95% CI 0.82-1.1). A control cohort consisting of patients without PE had similar risks for malignancy and cardiovascular events compared to patients with provoked PE, but significantly lower risks for the remaining outcomes and the combined outcome in patients with provoked as well as with unprovoked PE. Importantly, the fraction of both patients with provoked as well as with unprovoked PE without events after 1 year was only 70%, and decreased to fewer than 60% after 2 years and fewer than 50% after 4 years, whereas this latter was 84% for the control patients without PE.

In **chapter 13**, we validate a disease specific quality of life instrument for patients after acute PE. The recently developed Pulmonary Embolism Quality of Life (PEmb-QoL) questionnaire and the Short-Form 36 were distributed twice among 90 PE survivors, with a mean period of 38 months after diagnosis. Internal consistency of the questionnaire was adequate with a Cronbach's α statistic ranging from 0.62 to 0.94. The test-retest reliability was good as well (intra-class correlation coefficients 0.78-0.94). Furthermore, good correlations between the PEmb-QoL questionnaire and the SF-36 questionnaire supported convergent validity between the 2 instruments. Multivariate analysis identified age, obesity, cardiopulmonary comorbidity, centrally located PE and a family history of venous thromboembolism to be independent determinants for disease-specific QoL. The PEmb-QoL questionnaire was shown to be a reliable instrument to specifically assess QoL following PE, which is helpful in the identification of patients with decreased QoL after surviving PE.

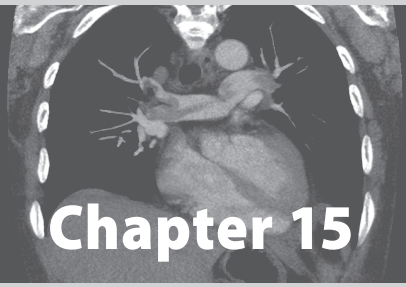
FUTURE PERSPECTIVES

Although the diagnostic management of suspected PE remains a challenge in clinical practice, physicians can fall back on a simple, non-invasive and well validated diagnostic algorithm consisting of a clinical decision rule, D-dimer tests and CTPA. This algorithm has been shown to be widely available and safe. Nonetheless, further studies are necessary to validate this -or an alternative- algorithm for recurrent PE, determine which of many clinical decision rules has the highest clinical efficacy and to address the increasing concern of radiation exposure by CTPA, especially in women of child bearing potential.

Risk stratification of normotensive patients with established PE can be based on high levels of biomarkers or measurements of right ventricular volume or function. Current evidence suggests that patients with a very low risk on adverse events can be treated on an outpatient basis, thereby saving costs and increasing patient satisfaction. However, the safety of home treatment, preferably based on a reproducible risk stratification scoring system, is yet to be

determined. On the other hand, with respect to identifying patients with very high risk who might benefit from thrombolytic therapy, evidence is scarce and inconsistent. Up till now, no stratification tool that can be easily integrated in routine clinical care and identifies a small patient group with particular high risk for complications, has been validated. Such a tool should be sought for in future trials.

Finally, although we have demonstrated that the risk of CTEPH after acute PE is very low, other very serious conditions occur frequent in the clinical course of acute PE. Especially those conditions that might be prevented, i.e. arterial cardiovascular events and recurrent PE, deserve a great deal of attention in the coming years. More accurate individualized assessment of the risk for recurrent PE followed by prolonged anticoagulant treatment for those patients with high recurrence risk, and individualized or population based proper preventive treatment measures to prevent arterial cardiovascular disease are likely to improve the patients' prognosis after acute PE. In addition, it would be very interesting to use the PEmb-QoL to measure the QoL in a larger cohort of patients and moreover, establish the effect of cardiopulmonary rehabilitation programs or other interventions on life style or coping mechanisms on QoL after PE.



Chapter 15

Nederlandse samenvatting

Dit proefschrift beschrijft studies naar het valideren en vereenvoudigen van de huidige diagnostische strategieën bij patiënten met een klinische verdenking op een acute longembolie, en naar methoden om de klinische prognose na een longembolie op korte en langere termijn beter te kunnen voorspellen. **Hoofdstuk 1** is een algemene inleiding in de pathofysiologie en klinische presentatie van acute longembolieën. Daarnaast worden de diagnostiek- en behandelingsstrategieën uit de dagelijkse praktijk en nog onopgeloste wetenschappelijk vragen hieromtrent besproken.

DEEL I: DIAGNOSTIEK NAAR ACUTE LONGEMBOLIEËN

In de literatuur zijn de afgelopen jaren verschillende klinische beslisregels gesuggereerd en gevalideerd. De best gevalideerde en daardoor meest gebruikte regel is de zogenaamde "Wells rule". Het gebruik van de Wells rule blijft echter ter discussie aangezien deze zwaar leunt op de subjectieve beoordeling van de arts over de waarschijnlijkheid van de diagnose longembolie vergeleken met de waarschijnlijkheid van een alternatieve diagnose. **Hoofdstuk 2** beschrijft een studie waarin de klinische validiteit en effectiviteit van de recent samengestelde en meer objectieve "revised Geneva score" wordt onderzocht in 300 patiënten die verdacht werden van het hebben van een longembolie. Hiertoe werd de voorspellende waarde van de revised Geneva score vergeleken met die van de Wells rule door middel van de oppervlakten onder de "receiver operating characteristic" (ROC) curves van beide regels. Deze bleken niet significant te verschillen: 0.72 (95% betrouwbaarheid interval [BI] 0.65–0.80) voor de Wells rule en 0.67 (95% BI 0.59–0.76) voor de revised Geneva score. Verder bleek dat bij geen van de patiënten die onbehandeld zouden blijven op basis van een lage of intermediaire revised Geneva score en een normale D-dimeer uitslag, in de eerste daarop volgende 3 maanden een veneuze tromboembolie (VTE) zou zijn gediagnosticeerd. In aansluiting hierop evalueren we in **hoofdstuk 3** de "vereenvoudigde revised Geneva score", waarbij we slechts 1 punt toekennen aan alle onderdelen van de score, in tegenstelling tot de uiteenlopende gewichten per item die voor de originele regel berekend waren. Deze vereenvoudigde regel is makkelijker te onthouden. Daarbovenop zou het verschillend aantal punten per onderdeel kunnen leiden tot verwarring bij het uitrekenen en interpreteren van de score in acute situaties. In 1049 patiënten met een verdenking op een longembolie bleek de oppervlakte onder ROC curve niet anders voor de vereenvoudigde dan voor de originele regel: 0.74 (95% BI 0.70-0.77) en 0.75 (95% BI 0.71-0.78). Ook in dit grote cohort bleek het veilig om antistollingsbehandeling te onthouden aan patiënten met een door middel van de vereenvoudigde revised Geneva rule berekende lage, intermediaire (3-delige indeling van de regel) of onwaarschijnlijke (2-delige indeling van de regel) voorafkans op een longembolie en een normale D-dimeer concentratie in het bloed. Deze resultaten suggereren dat de gesimplificeerde en originele revised Geneva scores, net als de Wells rule, veilig toepasbaar zijn in de klinische praktijk.

De meest gebruikte diagnostische test om longembolieën aan te tonen is de spiraal CT-scan. Verschillende deskundigen hebben gesuggereerd dat bij een patiënt met een hoge voorafkans op een longembolie, een negatieve uitslag van de spiraal CT-scan mogelijk niet afdoende is om een longembolie ook daadwerkelijk veilig uit te kunnen sluiten. Dit fenomeen wordt verklaard door de afhankelijkheid van de negatief voorspellende waarde (NVW) van een test voor de prevalentie van de betreffende ziekte in een zekere populatie. Deze NVW neemt namelijk af als de ziekte vaker voorkomt in de onderzochte patiënten groep. In **hoofdstuk 4** onderzoeken we de NVW van de spiraal CT-scan voor acute longembolieën door het uitvoeren van een meta-analyse van studies die op basis van een CT-scan uitslag de aanwezigheid van longembolieën uitsloten in alle patiënten bij wie volgens de huidige richtlijnen het maken van een CT-scan noodzakelijk is, namelijk bij patiënten met een hoge of waarschijnlijke voorafkans op een longembolie en/of een verhoogde D-dimeer plasma concentratie. De NVW van de CT-scan alleen was 98.8% (95% BI 98.2-99.2), en na een combinatie van de CT-scan gevolgd door compressie echografie van de benen om een diep veneuze trombose op te sporen 98.9% (95% BI 98.0-99.4). Het risico op een dodelijke longembolie 3 maanden na een negatieve CT-scan was erg laag (0.6%) en toevoegen van been echografie leverde geen significante additionele verlaging van dit risico op (0.5%). Omdat het risico op een al dat niet fatale longembolie na een negatieve CT-scan veilig laag bleek en goed overeenkwam met dat risico na een negatieve conventionele pulmonalis angiografie, welke nog steeds gezien wordt als gouden standaard voor de diagnose longembolie, concluderen wij dat een negatieve CT-scan uitslag afdoende is om een longembolie uit te sluiten in alle patiënten die hiervoor in aanmerking komen.

DEEL II: HET KORTE TERMIJN KLINISCH BELOOP VAN EEN LONGEMBOLIE

Het schatten van het risico op ernstige klinische complicaties door een longembolie bij patiënten die hemodynamisch stabiel zijn, is van het grootste belang voor het instellen van het juiste therapeutische beleid. **Hoofdstuk 5** betreft een meta-analyse naar de potentiële rol van brain-type natriuretic peptides (BNP) voor risicostratificatie van patiënten met een longembolie. Wij vonden een verhoogde Odds Ratio (OR) van verhoogde BNP of NT-pro-BNP bloedspiegels voor complicaties tijdens de ziekenhuisopname (6.8, 95% BI 4.4-10) en mortaliteit binnen 30 dagen na diagnose (7.6, 95% BI 3.4-17).

In **hoofdstuk 6** vergelijken wij de voorspellende waarde en potentiële klinische toepasbaarheid van NT-pro-BNP voor het stratificeren van hemodynamisch stabiele longembolie patiënten met andere biomarkers van hartfalen of embolus grootte, en de met een standaard CT-techniek gemeten rechter ventrikel omvang. Al deze voorspellers waren sterk geassocieerd met ons studie eindpunt, dat bestond uit overlijden binnen 6 weken, reanimatie na adem- of hartstilstand, noodzaak tot behandelen met trombolytica of inotropica, of opname op de intensive care afdeling voor mechanische beademing. De gecorrigeerde OR voor een hoge

NT-pro-BNP spiegel (>600 pg/mL) was 31 (95% BI 3.6-257), en deze was 3.7 (95% BI 0.74-19) voor een vergrote rechts/links ventriculaire omvang ratio op axiale CT coupes (> 1.0), 9.0 (95% BI 1.1-79) voor een vergrote rechts/links ventriculaire omvang ratio op geanguleerde 4-kamer CT coupes (>1.0), 3.5 (95% BI 0.86-15) voor een hoge D-dimeer concentratie (>3000 pg/mL FEU) en tenslotte 6.3 (95% BI 1.3-31) voor verhoogde Troponine-T spiegels (>0.09 ng/mL). De NVW van NT-pro-BNP was het hoogst van alle bestudeerde voorspellers (99%). Waarden onder dit afkappunt kwamen voor bij 72% van de patiënten. De NVW van de rechts/links ventriculaire omvang ratio op geanguleerde 4-kamer CT coupes was ook erg hoog (98%), maar een normale verhouding kon bij veel minder patiënten vastgesteld worden (43%). Hieruit concluderen wij dat NT-pro-BNP waarschijnlijk de nuttigste test is om hemodynamisch stabiele patiënten met een longembolie te categoriseren naar hun risicoprofiel.

De positief voorspellende waarde (PVW) van NT-pro-BNP evenals van de andere bestudeerde voorspellers was niet toereikend voor het overwegen van meer invasieve behandeling van patiënten met een hoge test uitslag. Wij hypothetiseerden dat de CT gemeten rechter ventrikel ejectiefractie een veel specifiekere voorspeller zou kunnen zijn voor complicaties, gezien het feit dat dit een directe afspiegeling is van de systolische rechter ventrikel functie. In dezelfde patiënten groep die werd beschreven in hoofdstuk 6 werd door middel van ECG-gesynchroniseerde CT-scan opnamen de rechter ventrikel ejectiefractie gemeten (**hoofdstuk 7**). Wij definieerden een ejectiefractie lager dan 47% als passend bij rechterventrikel dysfunctie. Dit kwam voor bij 45% van alle patiënten en in 90% van de patiënten die één van onze klinische eindpunten bereikten. OR voor dit eindpunt was 36 (95% BI 2.2-590) en de NWV 98%. Desondanks was de PVW niet hoog genoeg (18%) om meer invasieve behandeling te rechtvaardigen. Verder bleek de NPV van de ECG-gesynchroniseerde opnamen van het hart gelijkwaardig aan die van de standaard opnamen. Een belangrijk bijkomend nadeel van de ECG-gesynchroniseerde techniek is de hogere dosering straling en contrast vloeistof waar de patiënten aan blootgesteld worden. Om deze redenen lijkt de ECG-gesynchroniseerde hart scan van patiënten verdacht van een longembolie weinig toegevoegde klinische waarde te hebben.

DEEL III: LANGE TERMIJN PROGNOSE NA EEN LONGEMBOLIE

In **hoofdstuk 8** worden de resultaten van een screening studie naar chronische trombo-embolische pulmonale hypertensie (CTEPH) besproken. Wij brachten 866 opeenvolgende patiënten met een acute longembolie nauwkeurig in kaart. Alle patiënten die nog in leven waren bij de start van ons onderzoek en die nog niet waren gediagnosticeerd met pulmonale hypertensie werden verzocht terug te komen naar het LUMC voor echocardiografie. Alle patiënten bij wie een echografische verdenking op een longembolie bestond ondergingen een gestandaardiseerd diagnostisch protocol bestaande uit in ieder geval een ventilatie-perfusie scan en

hartkatheterisatie. Van patiënten die overleden waren achterhaalden wij de doodsoorzaak. De kans op de aanwezigheid van CTEPH in de patiënten die niet naar ons ziekenhuis konden of wilden komen, werd geschat aan de hand van hun klachtenpatroon. Na een gemiddelde vervolg duur van 34 maanden na diagnose van de longembolie was pulmonale hypertensie vastgesteld in 19 patiënten door standaard klinische zorg voordat onze studie van start ging, en in 10 patiënten door ons screening programma. CTEPH was gediagnosticeerd in 4 van hen door standaard klinische zorg, maar in geen van de patiënten door ons screening programma. De cumulatieve incidentie van CTEPH was 0.57% (95% BI 0.02-1.2%) in de totale studie populatie en 1.5% (95% BI 0.08-3.1%) in de patiënten die een longembolie doormaakten zonder duidelijk aanwijsbare oorzaak, de zogenaamde idiopatische longembolie. Daar de incidentie van CTEPH relatief laag was en ons screening programma geen extra patiënten opleverde bovenop de standaard klinische zorg, achten wij het niet nuttig alle patiënten na het doormaken van een longembolie te screenen op CTEPH met behulp van echocardiografie.

Kortademigheid is het meest voorkomende klinische symptoom van CTEPH. Hoewel we in hoofdstuk 8 concludeerden dat CTEPH een zeldzame complicatie van longembolieën is, bleken klachten van kortademigheid wel frequent voor te komen (één derde van de patiënten, 3.6 jaar na diagnose). Deze subjectieve klachten zijn significant gecorreleerd aan objectief gemeten inspanningstolerantie. Bijgevolg hiervan wordt de diagnose CTEPH regelmatig overwogen, welke slechts bevestigd kan worden na hartkatheterisatie. In **hoofdstuk 9** wordt een studie naar de waarde van verschillende niet-invasieve testen voor het uitsluiten van CTEPH in symptomatische patiënten na een longembolie gepresenteerd. ECG afwijkingen passend bij rechter ventrikel overbelasting werden vaker aangetoond in patiënten met CTEPH dan in symptomatische patiënten die een longembolie hadden doorgemaakt, maar bij wie pulmonale hypertensie werd uitgesloten. Ook objectiveerden wij hogere stolling factor VIII activiteit en bloedspiegels van NT-pro-BNP, groei differentiatie factor-15, CRP en urinezuur in patiënten met CTEPH. D-dimeer bloedspiegels waren in tegenstelling hiermee vergelijkbaar tussen de twee groepen. Een diagnostisch model bestaande uit ECG beoordeling en NT-pro-BNP bepaling leverde een sensitiviteit voor CTEPH op van 94% (95% BI 86-98), een specificiteit van 65% (95% BI 56-72) en een oppervlakte onder de ROC curve van 0.80 (0.74-0.85). Het toevoegen van andere testen aan dit model leidde tot verslechtering van deze test karakteristieken. Zelfs als de incidentie van CTEPH in een willekeurig geteste populatie erg hoog zou zijn (tot 10%), bleef de NPV van ons uiteindelijke model zeer adequaat (>99%). Deze resultaten suggereren dat in het geval van klachten van kortademigheid in patiënten die een longembolie doorgemaakt hebben bij een normale ECG beoordeling en NT-pro-BNP spiegel, de kans op de diagnose CTEPH zeer gering is.

Hoofdstuk 10 vult de bevindingen van hoofdstuk 8 en 9 aan en beschrijft een evaluatie van de determinanten en alternatieve diagnoses van chronische kortademigheid na een longembolie. Na multivariate logistische regressie bleken cardiale en pulmonale comorbiditeit (OR 12, 95%

BI 6.5-20), hogere leeftijd (OR 1.02 per jaar, 95% BI 1.01-1.03), hogere BMI (OR 1.06 per kg/m^2, 95% BI 1.01-1.1) en roken (OR 1.6, 95% BI 1.02-2.6) onafhankelijke voorspellers van chronische kortademigheid na longembolieën te zijn. Verder werd bij alle patiënten met chronische kortademigheid een alternatieve diagnose gesteld die de kortademigheid kon verklaren. Het klinische belang van deze observatie is dat hoewel kortademigheid na een longembolie frequent voorkomt, deze voornamelijk kan worden verklaard door reeds aanwezige morbiditeit en dat ernstige complicaties als CTEPH hier slechts zeer incidenteel aan ten grondslag liggen.

In **hoofdstuk 11** wordt de associatie tussen veneuze trombose en arteriële cardiovasculaire ziekten besproken. Hiertoe werd het risico op arteriële cardiovasculaire ziekten voor patiënten met en zonder longembolie vergeleken. Na een mediane vervolgtijd van 4.2 jaar bleek de gecorrigeerde hazard ratio (HR) voor arteriële cardiovasculaire ziekten niet verhoogd te zijn voor patiënten met longembolie vergeleken met de controle patiënten zonder longembolie (1.4, 95% BI 0.83-2.3) maar wel voor patiënten met een idiopatische longembolie vergeleken met patiënten die een longembolie met duidelijke risicofactor hadden doorgemaakt (gecorrigeerde HR 2.2, 95% BI 1.1-4.5) evenals vergeleken met controle patiënten zonder longembolie (gecorrigeerde HR 2.6, 95% BI 1.4-4.9). Deze studie onderschrijft de associatie tussen arteriële cardiovasculaire aandoeningen en eerder doorgemaakte veneuze trombose, en ondersteunt de hypothese dat een nog onbekend mechanisme ten grondslag licht aan zowel veneuze trombose als arteriële cardiovasculaire aandoeningen.

Niet alleen CTEPH en arteriële cardiovasculaire aandoeningen, maar ook overlijden, nieuw gediagnosticeerde maligniteiten en recidief longembolieën komen relatief vaak voor na acute longembolieën en drukken hun stempel op de prognose van deze patiënten. **Hoofdstuk 12** behandelt het risico op het doormaken van één van deze 5 ernstige klinische complicaties in de eerste jaren nadat de diagnose longembolie gesteld was. Patiënten met een idiopatische longembolie bleken een lager risico te hebben op overlijden dan de patiënten die een duidelijke risicofactor voor hun longembolie hadden (gecorrigeerde HR 0.59, 95% BI 0.43-0.82). Aan de andere kant hadden deze eerste patiënten een hoger risico op niet-maligniteit gerelateerd overlijden (gecorrigeerde HR 1.8, 95% BI 1.3-2.5), recidief VTE (gecorrigeerde HR 2.1, 95% BI 1.3-3.1), nieuw gediagnosticeerde maligniteit (gecorrigeerde HR 4.4, 95% BI 2.0-10), arteriële cardiovasculaire aandoeningen (gecorrigeerde HR 2.6, 95% BI 1.5-3.8) en CTEPH (cumulatieve incidentie 1.5% versus 0%). Het risico op het gecombineerde eindpunt verschilde niet tussen de 2 groepen (gecorrigeerde HR 0.98, 95% BI 0.82-1.1). Een controle groep zonder longembolieën had een vergelijkbaar risico op een nieuw gediagnosticeerde maligniteit of een arteriële cardiovasculaire aandoening als patiënten na een longembolie met duidelijke risicofactor, maar een duidelijk lager risico op alle overige uitkomsten in patiënten met en zonder een duidelijke risicofactor voor hun longembolie. Uiteindelijk bleek de proportie van beide patiënten groepen met een longembolie die binnen het eerste jaar geen van de 5 complicaties ondervond slechts

70% te zijn. Deze proportie daalde naar 60% na 2 jaar en verder naar 50% na 4 jaar, terwijl dat laatste 84% was voor de controle patiënten.

In **hoofdstuk 13** wordt tenslotte de recent ontworpen ziekte-specifieke vragenlijst voor kwaliteit van leven na een longembolie, de PEmb-QoL, geëvalueerd. Een grote groep van 90 patiënten vulde gemiddeld 38 maanden nadat een longembolie aangetoond en behandeld was de Short-Form 36 en de PEmb-QoL in. De psychometrische kenmerken van de PEmb-QoL bleken van een hoog niveau te zijn, blijkens de goede interne consistentie, test-hertest betrouwbaarheid en logische correlaties met de uitkomsten van de Short-Form 36. Verder werd aangetoond dat leeftijd, overgewicht, cardiopulmonale comorbiditeit, centraal gelegen longembolieën en meerdere familieleden die trombose hebben doorgemaakt, significante en onafhankelijke voorspellers van kwaliteit van leven zijn. Wij concludeerden dat de PEmb-QoL een betrouwbare en klinisch toepasbare vragenlijst is om de ziekte-specifieke kwaliteit van leven na een longembolie te meten.

TOEKOMSTPERSPECTIEF

Hoewel diagnostiek naar longembolieën altijd een uitdaging zal blijven, kunnen artsen terug vallen op een simpel, niet-invasief en goed gevalideerd diagnostisch algoritme bestaande uit een klinische beslisregel, D-dimeer testen en spiraal CT-scans. Niettemin zijn verdere studies noodzakelijk om te evalueren welke van de vele bestaande klinische beslisregels de hoogste efficiëntie bewerkstelligt, hoe de diagnostiek naar recidief longembolieën zou moeten verlopen en hoe vooral voor vrouwen in de fertiele leeftijd het hoofd geboden kan worden aan de toenemende zorg voor stralingbelasting door CT-scans.

Wat betreft risicostratificatie van hemodynamisch stabiele patiënten met een longembolie is er thans genoeg bewijs dat deze gebaseerd kan worden op waarden van verschillende biomarkers en metingen aan het rechter ventrikel volume of zijn functie. Echter, er is nauwelijks tot geen bewijs dat alternatieve therapeutische interventies gebaseerd op deze voorspellers beter, veiliger of kosten effectiever zijn dan de huidige standaardbehandeling. Het lijkt zeker de moeite waard en veilig om patiënten met een laag risico thuis te behandelen, wat zou kunnen leiden tot lagere kosten en hogere patiënt tevredenheid. De waarde van het meer invasief behandelen van patiënten met een hoog risico staat minder vast, maar ook deze strategie heeft potentiële voordelen. Het is daarom van het grootste belang dat er op korte termijn studies worden uitgevoerd om beide alternatieve interventies ten opzichte van een standaard ziekenhuisopname te toetsen.

Tenslotte laten onze resultaten zien dat schrikbarend veel patiënten in de eerste jaren na een longembolie ernstige complicaties ondervinden. Een aantal van deze zou potentieel

voorkomen kunnen worden. Dit betreft voornamelijk recidief longembolieën en arteriële cardiovasculaire aandoeningen. Toekomstige studies zullen moeten aantonen of een meer accurate risico-inschatting voor, en daarmee samenhangende adequate behandeling van deze belangrijke complicaties kunnen leiden tot een verbetering van de prognose van patiënten met een longembolie. Evenzo is het effect van actieve revalidatie of andere interventies op leefstijl of ziektegedrag van longemboliepatiënten op de kwaliteit van leven een mogelijk onderwerp van toekomstig onderzoek.

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Nawoord

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Curriculum vitae

Frederikus Albertus Klok werd geboren op 8 mei 1982 te Delft. In juni 2000 haalde hij zijn gymnasium diploma aan het Reynaertcollege te Hulst. In dat zelfde jaar startte hij met de studie Geneeskunde aan de Universiteit Leiden. In 2004 behaalde hij zijn doctoraal examen na een afstudeerproject getiteld "Vascular risk reduction for obese women after weight loss" onder supervisie van prof. dr. A.E. Meinders en dr. A.J. Fogteloo. Verder verrichte hij in 2004 als student onderzoek op de afdeling Algemene Interne Geneeskunde naar het objectiveren van een klinische beslisregel in de diagnostiek van longembolieën bij dr. M.V. Huisman. In december 2004 startte hij zijn coschappen waarna hij in december 2006 zijn artsexamen behaalde. Aansluitend was hij tot december 2009 werkzaam als artsonderzoeker op de afdeling Algemene Interne Geneeskunde van het Leids Universitair Medisch Centrum onder begeleiding van dr. M.V. Huisman. De resultaten van deze werkzaamheden zijn beschreven in dit proefschrift. In januari 2010 is hij begonnen met de opleiding tot internist in het Bronovo Ziekenhuis te 's-Gravenhage (opleider dr. J.W. van't Wout).