

Embolie pulmonaire sans signe clinique de gravité: apport pronostique de l'angioscanner thoracique

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EMBOLIE PULMONAIRE SANS SIGNE CLINIQUE DE GRAVITE : APPORT PRONOSTIQUE DE L'ANGIOSCANNER THORACIQUE

THESE

PRESENTEE POUR L'OBTENTION DU DOCTORAT EN MEDECINE -DIPLÔME D'ETAT-

Par

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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effiqie d'HIPPO(RATE,

je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires. Admis dans l'intimité des maisons, mes yeux n'y verront pas ce oui s'y passe ; ma langue taira les secrets oui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.

A mon Président de thèse,

Monsieur le Professeur Gilbert FERRETI

A mon Directeur de thèse,

Monsieur le Professeur Jean-Luc BOSSON

A mes juges,

Madame le Professeur Françoise CARPENTIER

Monsieur le Professeur Gilles PERNOD

Merci d'avoir accepté de juger ce travail.

A Eloi,

A Noélie, notre fille,

A mes parents,

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LISTE DES ABREVIATIONS :

Pulmonary	Embolism.
	Pulmonary

- CT : Computed Tomography.
- RV : Right ventricule.
- LV : Left ventricule.
- RV/VD : Ratio between the diameters of right ventricule and left ventricule.
- PA : Pulmonary Artery.
- MDCT : Multi Detector Computed Tomography.
- DVT : Deep Venous Thrombosis.
- RVD : Right Ventricular Dysfunction.
- CTPA : Computed Tomography Pulmonary Angiography.
- ACP : Acute Cor Pulmonal.
- VSB : Ventricular Septal Bowing.

PREAMBULE

L'angioscanner thoracique est actuellement l'examen d'imagerie de première intention à réaliser devant toute suspicion d'embolie pulmonaire aiguë chez un patient hémodynamiquement stable. C'est un examen rapide, sensible, spécifique et facile d'accès. Il bénéficie également d'une forte valeur prédictive négative, surtout si la suspicion clinique est faible ou intermédiaire. Le scanner volumique permet le diagnostic positif de l'embolie pulmonaire aigue, l'évaluation de sa gravité, la caractérisation de la qualité du parenchyme pulmonaire sous jacent mais aussi la recherche de diagnostics différentiels.

Actuellement, comme pour la thrombose veineuse profonde (TVP), on voit émerger le concept d'embolie pulmonaire de très bon pronostic avec traitement ambulatoire possible. Les scores pronostics actuels combinent données cliniques et biologiques (taux de d-dimères, troponine....). Le scanner hélicoïdal étant devenu la référence pour le diagnostic de l'embolie pulmonaire, nous souhaitons évaluer son intérêt dans la construction d'un index pronostique à moyen terme en excluant de l'étude les patients avec instabilité hémodynamique synonyme d'embolie pulmonaire grave et donc, d'hospitalisation. Nous pensons que l'évaluation indirecte de la fonction cardiaque droite -rapport des diamètres des ventricules droit et gauche et position du septum inter ventriculaire- et la mesure de la charge embolique peuvent être des marqueurs de mauvais pronostic, évaluables sur les données classiques de l'angioscanner sans autre investigation.

Il existe à notre connaissance peu d'études testant les performances pronostiques à moyen terme de l'angioscanner thoracique dans l'embolie pulmonaire non grave. L'idée de ce travail est d'aider à définir une population à risque très faible, pouvant bénéficier d'une prise en charge ambulatoire -comme pour la TVP- et éviter ainsi des hospitalisations.

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Ce projet a obtenu le soutient de la Direction de Recherche Clinique (mai 2007). Il s'inscrit dans une stratégie continue de l'amélioration de la qualité des soins dans la gestion de l'embolie pulmonaire au CHU de Grenoble.

Pour que ce travail puisse servir à des fins utiles, il a été rédigé en anglais, afin d'être soumis pour publication.

ABSTRACT

Purpose : To retrospectively evaluate computed tomographic (CT) cardiovascular parameters and pulmonary artery (PA) clot load score as predictor of 3-month mortality in patients with clinically non-severe pulmonary embolism (PE).

Patients and Methods : 226 CT scans (4 and 16 MDCT) positive for PE in hemodynamically stable patients (112 women, 114 men ; mean age 67,1 years \pm 16,9) were included. CT were independently reviewed by two observers for clot burden and CT cardiovascular parameters. Patient deaths had been evaluated by an independent adjudication committee. Results were compared with risk of death within three months by using Cox regression.

Results : 24 (10.6%) patients died, of whom 9 were probably related to PE. Interobserver variability was only fair for the shape of interventricular septum (κ =0.41), and for the ratio between the diameters of right and left ventricule (RV/LV) (r=0.76). Observers found no association between interventricular septum and death. RV/LV diameter ratio>1, was predictive of death (OR, 3,83 ; p<0,01), only when we took care into account the value of embolic burden (<40%). In multivariate model, CT cardiovascular parameters were not associated with death, with the exception of main pulmonary artery (PA) diameter (OR, 1.1 ; p=0.05). Concomitant lower limb DVT and comorbid conditions were important predictors of death.

Conclusion : In clinically non severe PE, VD/VG diameter ratio>1 is predictive of death when embolic burden is low (<40%), but with high degree of interobserver variability. Main PA diameter, is an independent CT prognostic finding. Neither the shape of interventricular septum nor embolic burden are predictive of death.

INTRODUCTION

Pulmonary embolism (PE) is a common cardiovascular disorder, with an incidence of around 1.5 per 1000 person-years in the U.S. (1). The prognosis of acute PE is variable and still poorly understood. One reason to risk-stratify patients with PE, is to identify those with acute massive PE, who may benefit from fibrinolytic therapy (2). Conversely, those with non-life-threatening PE can be treated with low-molecular-weight heparin, as outpatients with deep venous thrombosis (DVT), improving the quality of life and reducing the health care costs (3, 4). In recent years, many attemps have been made to stratify patients according to their risk of death due to PE. Clinical presentation is still considered the most powerful predictor of mortality (5, 6). Results of previous studies have shown that echocardiography may be a useful method to predict right ventricular dysfunction (RVD) and clinical outcome in patient with acute PE (7, 8). Nevertheless, echocardiography is not routinely available in most centers.

As computed tomographic pulmonary angiography (CTPA) is now the first-line technique to diagnose PE (9-11), many attemps have been made to further risk-stratify patients with imaging, in the early management of PE. Recent studies have evaluated the accuracy of cardiovascular CT measurements in the severity assessment of acute PE (12-16). Some have investigated their relation with patient outcome, but with discrepancies (17-23). Studies to date have had limited multivariate analysis. Only one study evaluated patients with clinically non severe PE, but, without control for clinical presentation variables (18).

Thus, the purpose of the present study was to define independent morphologic cardiovascular CT parameters which may predict 3-month mortality, in hemodynamically stable patients. An objective and simple CT prognostic model could be helpful in guiding initial treatment and management for patients with clinically non severe PE.

SUBJECTS AND METHODS

Patients.

The institutional review board of the University Hospital of Grenoble approved this study (Direction de Recherche Clinique – Grenoble - May 2007) with waiver of informed consent. For the purpose of this retrospective study, we identified patients with CT scans coded positive for PE from January 1, 2005, to December 31, 2006. For patients with more than one scan, only their first CT scan was included, so that a patient could not be included more than once. Exclusion criteria were hemodynamic instability, initiation of a thrombolytic therapy, admission to the intensive care unit, use of inferior vena cava filter, history of lobectomy or pneumonectomy, patients with known of chronic PE or with CT signs of chronic PE. A total of 246 patients were thus identified. Of the 246 CT pulmonary angiograms, twenty were not available for review (Flow chart). Therefore, our final study group included 226 patients. All patients were treated by means of anticoagulant therapy.

Flow chart :



CT acquisition.

All patients had CTPA. 90 CT examinations were performed on a 4-detector row CT scanner : HiSpeed Advantage CT unit (Siemens Volume Zoom, Erlangen, Germany.) and 136 CT examinations were performed using a 16-detector row CT scanner (Siemens Sensation 16; Siemens AG, Medical solutions, Erlangen, Germany). Patients were scanned at 120 kVp, 150-250 mA according to subject body weight, with 1-mm thick sections. Images were reconstructed at 1-mm reconstruction interval with a standard reconstruction algorithm. In all cases, images were acquired in a caudocranial direction, started at the level of the lower hemidiaphragm and ending at the top of the aortic arch enabling visualization of the heart and pulmonary arteries up to the subsegmental branching order. Acquisitions were performed during a single breath hold when possible or during quiet breathing periods when patients were short of breath. Patients received intravenous injection of 120 ml of 30% iodinated contrast medium (Xenetix[®], Guerbet, Aulnay-sous-Bois, France). The injection rate was 3cc/sec. Scanning delay was determined by automatic bolus detection or fixed 15- to 20-s delay was applied.

CT interpretation.

The remaining CT scans were reviewed retrospectively and independently in random order by two radiologists using cine mode at a PACS workstation (AGFA, Impax V.5, Mortsel, Belgium). Images were viewed at standard lung (window width, 1600 UH, window level, - 400 UH) and mediastinal settings (window width, 350 UH, window level, 50 UH). Observer 1 was a chest radiologist with 5 years of experience in reading thoracic CT scans. Observer 2 was a general radiologist in training (fourth-year resident). The readers were blinded to clinical data, but they knew that patients had CTPA positive for PE. The presence of

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endoluminal clots on CT scans were considered diagnostic of embolism. Both observers reviewed the scans for signs of chronic PE, as defined by Han et al. (24).

CT predictor variable.

Each radiologist scored the embolic burden, evaluated the shape of interventricular septum, measured the RV/LV diameter ratio, the main PA and the superior vena cava diameters, the presence or absence of pulmonary infarct.

Embolic burden.— Qanadli et al. (13) evaluated a specific index for quantifying arterial obstruction with helical CT in acute PE and showed that their proposed score was reproducible and correlated highly to the pulmonary angiography index. In this study, we used the same scoring system based on the site of obstruction and the degree of occlusion of the pulmonary arteries. Detail on Qanadli's scoring system is presented in the Appendix.

CT signs of acute cor pulmonale (ACP).— The CT scans for all patients were assessed using parameters derived on the axial plane. We evaluated the shape of the interventricular septum on a 3-point scale : 0 = normal position (convex toward RV) ; 1 = rectilinear ; and 2 =convex toward LV (25). Cardiac measurements were obtained by measuring the minor axes of the right and left ventricles of the heart in the transverse plane at their widest points between the inner surface of the free wall and the surface of the interventricular septum. These maximum dimensions may be found at different levels. The RV/LV ratio was then calculated. CT scans were considered to show no right ventricular dysfunction (RVD) if the ratio was 1,0 or less, and to show RVD if the ratio was greater than 1,0, as recommended in the literature (14, 25, 26).We measured the transversal diameter of the main PA (on the CT image passing through the pulmonary trunk just before its branching off into left and right pulmonary

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arteries), and the transversal diameter of the superior vena cava at the level of the azygos vein (Figure 1).

Pulmonary findings.- Concomitant pulmonary infarct were also recorded.

Chart review.

To assess the outcome of the patients with PE, medical data concerning each patients were retrospectively collected from medical records.

Patients comorbidities.— In addition to sex and age, charts were reviewed for 7 comorbidities : congestive heart failure, chronic obstructive or restrictive lung disease, malignancy, pneumonia, surgery preceding PE, occurrence and level of lower limb DVT diagnosed on the basis of doppler ultrasound.

Three-month follow up and outcome.— Patient outcome during hospital stay was retrospectively analyzed on the bases of medical charts by a radiologist. In instances in which informations could not be available, the patient's general practitioner was contacted, by telephone, to establish whether the patients were alive or had died during the follow-up period. The outcome was evaluated in terms of mortality within 3 months after the initial diagnosis of PE. All patients death during the follow-up period had been retrospectively evaluated by an independent adjudication committee that had full access to all available clinical and diagnostic patient data. The adjudication committee determined and recorded whether a patient death should definitely or most probably be attributed to PE or whether it should be attributed to a cause unrelated to PE. Furthermore, the adjudication committee determined if malignancy was associated with a good or a poor prognosis according to the organ involved and to the cancer staging.

Statistical analysis.

Statistical analysis were performed using Stata Software (version 10,0 ; Stata Corp, College Station, Texas). The end point for the analysis was death within 3 months. Interobserver variations were evaluated by means of the Pearson correlation coefficient for continuous variables and by using Cohen Kappa statistics for qualitative variables. CT findings, comorbid conditions and lower limb DVT were compared with death by using univariate Cox regression. Lower limb DVT were compared with embolic burden by using Student's test. Multivariate Cox regression was used to determine the incremental prognostic value of CT findings over clinical information. P values less than 0,05 were considered to indicate a significant difference.

Figure 1A-B : Measurements of the main PA diameter and of the RV/LV diameter ratio on axial CT pulmonary angiograms in 73-year-old woman with proved PE.

A- The transversal diameter of the main pulmonary artery was 35 mm. Axial transverse CT scan shows multiple bilateral large emboli. The obstruction index was scored as 50%



B- (a) The short axis of the RV is measured at the level of the tricuspid valve from inner wall to inner wall, at the widest point, which is typically in the basal third of the ventricle. (b) The short axis of the LV is measured at the level of the mitral valve from inner wall to inner wall, at the widest point, which also is typically in the basal third of the ventricle. Note the leftward bowing of the ventricular septum. RV/LV diameter ratio was 1,9.



RESULTS

Patients demographics and deaths.

Our final study group included 226 patients of which 112 (49,6%) were women and 114 (50,4%) were men. History of malignancy and recent surgery were the most comorbid condition (Table 1). Hospital stay ranged from 1 to 120 days (mean, 14 days \pm 15).

No. of patients (%)	All patients, n=226
Mean age (y) ± SD.	67,1 ± 16,9
Female.	112 (49,6%)
Male.	114 (50,4%)
Inpatient.	113 (50%)
-medicine.	87
-surgery.	26
Outpatient.	113 (50%)
Malignancy.	51 (22,6%)
Congestive heart failure.	31 (13,71%)
Ischemic heart disease.	15 (6,63%)
Pulmonary chronic disease.	15 (6,63%)
Pneumonia	18 (7,96%)
Recent surgery (< 1 month).	53 (23,4%)
Post partum.	2 (0,88%)
Current thromboembolic disease.	128 (56,64%)
Death	24 (10,6%)

Table 1 : Patient demographics, comorbid conditions and deep venous thrombosis.

Note : unless otherwise indicated, data are the number of patients. SD = standard deviation.

Twenty four (10,6 %) patients died during the 3-month follow up period. According to the independent adjudication committee, death was probably related to PE in 9 cases (Table 2). Average time of death was 36 days after CT pulmonary angiography (minimum, 3 days ; maximum, 90 days ; median, 22 days).

Patient No	Cause of death	Time (days)	Patient No	Cause of death	Time (days)
1	Malignancy	9	13	Malignancy	64
2	Malignancy	24	14	Septicemy	82
3	Malignancy	75	15	Malignancy	20
4	PE	3	16	PE	12
5	Malignancy	86	17	PE	7
6	Malignancy	73	18	PE	4
7	Malignancy	26	19	Respiratory failure	32
8	PE	3	20	PE	15
9	PE	3	21	PE	11
10	PE	90	22	Malignancy	57
11	Multi-organ failure	64	23	Malignancy	17
12	Heart failure	56	24	Indeterminate	19

Table 2 : Cause and time of death in patients who died during 3-month follow-up.

PE = pulmonary embolism

Univariate analysis : comorbid conditions, deep venous thrombosis.

Comorbid conditions.

Because of the low number of cardiac and pulmonary comorbid conditions, they were combined into one event to allow univariate analysis (table 3). Two of seven comorbid conditions were significantly associated with death. Of these, malignancy (with poor prognosis) was associated with the highest risk of death (odds ratio, 13,95; p<0,01).

57 % of patients with PE had a concomitant DVT. Patients with DVT had a PE clot load significantly higher than those without DVT (p<0,01). Proximal DVT were associated with higher embolic burden than in distal DVT (p=0,02). Current DVT was not associated with death (p=0,14).

Variable	Survivor (n=202)	Death (n=24)	pValue	Odds Ratio	Lower 95% Confidence Limit	Upper 95% Confidence Limit
Male sex.	98/202	16/24	0,10	2,01	0,86	4,7
Age > 70y.*	107/202	18/24	0,05	2,50	0,99	6,3
Malignancy. -good prognosis. -poor prognosis. *	14/202 20/202	1/24 16/24	0,62 <0,01	1,69 13,95	0,2 5,73	13,72 33,98
Cardio-pulmonary disease.	45/202	7/24	0,48	1,37	0,57	3,31
Pneumonia	14/202	4/24	0,08	2,56	0,88	7,50
Recent surgery (< 1 month).	46/202	7/24	0,50	1,35	0,56	3,26
Deep venous thrombosis.	111/202	17/24	0,14	1,94	0,80	4,67

Table 3 : Univariate Cox analysis : Comorbid condition, deep venous thrombosis.

*These variables are significantly associated with death.

Univariate analysis : patient outcome and CT findings :

Embolic burden.

The mean CT pulmonary angiographic clot burden score percentage was 25,4% (SD, 18,9%;

range, 2,5-78,8%). Excellent intraclass correlation of 0,98 (p<0,01) was found between the

two radiologist's evaluations of clot burden scores percentages. Statistical analysis were performed with the mean clot burden scores of each observers. The mean clot burden score percentage for patients who were alive was 25,9% (SD, 19%; range 2,5-77,5%) and for those who had died at the 3-month follow up, was 21,4% (SD, 18,1; range 2,5-75%). Unexpectedly, a higher embolic burden (>40%) was associated with a non significant decreased risk of death (OR, 0,46; p=0,16) (Figure 1, Table 4).

Figure 1 : Kaplan Meier's curve of survival between patients with high (>40%) and low (<40%) embolic burden.



CT signs of acute cor pulmonale (ACP).

Because of the discrepant results between readers 1 and 2 for the shape of the interventricular septum and for RV/LV diameter ratio, the cases for which these readers disagreed were selected. Final interpretation was reached by consensus. The univariate and multivariate

analyses of these two parameters were performed, by using the results of readers 1 and 2, in those cases when these readers agreed, and by using the final interpretation reached by consensus, when readers disagreed. Results of CT findings for both observers are presented in the Appendix.

Displacement of the interventricular septum

Displacement of the interventricular septum was noted in 82 (36,3 %) of 226 patients, as follow : flattening septum in 56 (24,8 %) patients and inversion convex toward left ventricle in 26 (11,5 %) patients. Displacement of the interventricular septum was not associated with death in univariate model (Table 4).

RV/LV diameter ratio.

The mean RV/LV diameter ratio was $0,97 \pm 0,23$ (range 0,58-1,89) in patients who survived and $1,08 \pm 0,35$ (range 0,77 to 2,38) in patients who died. Right ventricular dysfunction (RVD) defined by RV/LV diameter ratio >1 (14, 25, 26), was present in 33,7% of survivor and in 45,8% of patients who died. The mortality rate through three months was not statistically higher in patients with, than without RVD (p=0,24) (Table 4).

Main PA and superior vena cava diameters.

Interobserver variability for main PA and superior vena cava diameters was very good (intraclass correlation coefficient were respectively 0,89 and 0,91). Statistical analysis were performed with the mean values of each observers. The mean value of main PA diameter was 27,18 \pm 4,32 cm ; main PA diameter was found to be a significant risk factor for mortality (OR, 1,08 ; p=0,05). No cutoff value could be determinated. The mean value of superior vena cava diameter was 15,9 \pm 3,86 cm. We didn't find any significant relationship between superior vena cava and mortality (p=0,23) (Table 4).

Pulmonary infarct.

Pulmonary infarct was present in 35,5% of patients who survived and in 21,7% of patients

who died (p=0,18).

Table 4 : Univariate Cox analysis of CT findings for predicting death in patients with PE (consensus analysis).

CT Predictor and Observer No	Survivor (n=202)	Death (n=24)	pValue	Odds Ratio	Lower 95% Confiden ce Limit	Upper 95% Confiden ce Limit
Embolic burden : ≥40%	62/202	4/24	0,16	0.46	0.16	1.36
RV/LV diameter ratio : >1	68/202	11/24	0,24	1.61	0.72	3.60
Ventricular septum : Rectilign Bowing	51/202 22/202	5/24 5/24	0,84 0,19	0.90 1,99	0,32 0,72	2.50 5,53
Pulmonary artery diameter* :	27±4,3	28,8±4,4	0,05	1,08	1,00	1,18
Superior vena cava diameter :	15,8+/- 3,8	16,8+/- 4,2	0,23	1,06	0,96	1,18
Pulmonary infarct	71/202	5/24	0,17	0,50	0,19	1,34

*These variable are significantly associated with death.

Correlation between PA clot load scores and cardiovascular CT measurements.

When the recommended cutoff value of 40% for the pulmonary vascular obstruction index was used (13), among patient with clot load score lower than 40%, patients with RV/LV diameter ratio >1, had a statistically higher risk to die, than patients without RVD (OR, 4,4; p<0,01) (Table 5). RVD within patients with higher embolic burden (\geq 40%) had no influence on mortality (p=0,18). RV/LV diameter ratio >1 was predictive of death only when we took care into account the value of embolic burden.

 Table 5 : Univariate Cox analysis of VD/VG diameter ratio>1 by embolic burden.

Embolic burden	All patients (n=226)	pValue	Odds Ratio	Lower 95% Confidence Limit	Upper 95% Confidence Limit
<40%	160	p<0,01	3,83	1,59	9,21
>40%	66	p=0,12	0,17	0,02	1,60

Multivariate modeling.

In multivariate analysis of CT data, the hazard ratio of RV/LV diameter ratio > 1 for predicting 3-months death was 2,49 (95% CI, 0,99-6,28 ; p=0,05). Unexpectedly, patients with an index of 40% or greater were associated with a decreased risk of dying (OR, 0,3 ; 95% CI, 0,09-0,99 ; p=0,05). However, after adjusting for comorbid conditions, DVT and pulmonary infarct, RV/LV diameter ratio and embolic burden were no more statistically associated with mortality. Nevertheless, main PA diameter was still associated with short term death (OR, 1,1 ; p=0,05). Presence of DVT and comorbidities as, in particular, age upper 70 years, malignancy, and pneumonia were significant predictors of death in patients with non severe PE (Table 6).

Parameters	Odds Ratio	Lower 95% Confidence Limit	Upper 95% Confidence Limit	pValue
Male sexe	1,95	0,76	5,02	0,17
Age > 70 years*	3,21	1,18	8,76	0,02
Bad prognosis cancer*	16,12	6,44	40,31	<0,001
Deep venous thrombosis*	2,81	1,07	7,39	0,04
Pneumonia*	4,75	1,45	15,64	0,01
Pulmonary infarct	0,61	0,21	1,75	0,36
Embolic burden >40%	0,53	0,16	1,72	0,29
Pulmonary artery diameter*	1,1	1	1,19	0,05

Table 6 : Multivariate Cox regression analysis of CT and Clinical data.

*These variable are significantly associated with death.

DISCUSSION

Our results show that, in patients admitted for clinically non severe PE, VD/VG diameter ratio>1 is predictive of death when embolic burden is low (<40%) but, with a high degree of interobserver variability. Main PA diameter, is associated with an increased risk of death. Neither the shape of interventricular septum nor embolic burden are predictive of death. Few discrepant previous studies, have tried to assess PE prognosis on CTPA , by measuring signs indicating ACP and by assessing the obstruction burden of the pulmonary artery (17-23). The goal of our study was to assess the potential role of cardiovascular CT parameters, to estimate the prognosis of patients with clinically non severe PE. Such evaluation may help to select patients that are suitable for an outpatient management, in order to improve the quality of life and reducing the health care costs (3, 4).

Embolic burden :

Our study showed no statistically significant correlation between the embolic burden and the 3-month mortality rate. Unexpectedly, in univariate analysis, a higher embolic burden (>40%) was associated with a non significant decreased risk of death (OR, 0,45 ; p=0,15). Aaroz et al. reported the same findings (21). In our study, this is likely due to a survival bias. Indeed, it has long been recognized that two thirds of patients with clinically severe PE, will die within 1 hour after the onset of symptoms (27, 28). Patients with a large clot burden may have died before CTPA was performed. Then, patients with a large clot burden, who survive long enough to undergo CT, have a certainly better hemodynamic tolerance than average patients. PA clot load score indicates the extent of the clot but can not be used as a predictor of RV failure and death in hemodynamically stable patients. According to Wood et al. (28), hemodynamic instability secondary to right ventricular failure as a function of embolism size and underlying cardiopulmonary status is thought to be a more accurate indicator of the

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magnitude of PE than the degree of PA obstruction. In our study, we did not take care into account the patient's history of associated cardiopulmonary disease.

Our findings that embolic burden is not associated with an increased risk of death is consistent with the bulk of the literature (20-22, 29, 30).

CT signs of acute cor pulmonale (ACP) :

Inter-ventricular septum.— In our study, the shape of interventricular septum was not predictive of death. This is consistent with previous studies (18, 20, 29) for which this sign does not seem to be an indicator of outcome. According to Aaroz et al. (21), ventricular septal bowing was predictive of death due to PE but with low sensivity and high interobserver variability.

RV/LV diameter ratio.— In our serie, Cox analysis of CT data, showed that RV/LV diameter ratio > 1, which is a CT sign of RVD, was associated with a statistically higher risk of death, only in patients with low embolic burden (<40%). RV/VD diameter ratio in these patients may reflect an underlying hemodynamic derangement that places patients at increased risk of death. In contrast, RV/LV diameter ratio had no prognostic relevance in patients with higher embolic burden (>40%). It joins the idea that, in non severe PE, patients with higher embolic burden (>40%) have a better hemodynamic tolerance than the other. It means that we need to pay attention to patients hemodynamically stable, with small pulmonary emboli and CT signs of RVD, who are risky to die than patients with larger pulmonary emboli.

In multivariate analysis, we found no association between the RV/LV diameter ratio and death. These results do not confirm those of three previous studies (16, 18, 20). Schoepf et al. (16) retrospectively studied 431 patients, and reconstructed all the images into a four-chamber view, which is more suited to the measurement of RV/LV diameter ratio than the transverse images used in our study. In the prospective series of Van der Meer et al. (18), RV/LV

diameter ratio was found to be predictive of death due to PE in univariate analysis, but did not attempt multivariate analysis. Ghaye et al. (20) showed that, RV/LV diameter ratio was predictor of mortality in patients with clinically severe PE. On the other hand, Aaroz et al. (21, 29) in two previous studies, found no association between RV/LV diameter ratio and death. The main limitation in their study was an important interobserver variability, like in our series, but without consensus measurement of the RV/LV diameter ratio.

Nevertheless, given our findings that RV/LV diameter ratio is predictive of death in patients with low embolic burden, and the results of previous studies (16, 18, 20), it seems possible that the CT-defined RV/LV ratio may be a predictor of death due to PE, even thought it was not found to be so in our study. Results of studies have shown that echocardiography might be a useful method to predict RVD and clinical outcome (7, 8, 31). As CT images obtained in the axial plane are not four-chamber view, relative measurements may be different from those of echocardiography. However, in our study and in Aaroz et al. one, RV/LV diameter ratio measurements are not very reproducible and can not be use in daily radiological practice (21). Further studies should take care to account for the variability in the measurement of the RV/LV diameter ratio. The advent of CTPA performed with electrocardiographic gating may permit new advances in the assessment of RVD such as measurement of the RV ejection fraction.

Main PA and superior vena cava diameters.— Patients with severe PE, suffered from acute pulmonary hypertension, defined as an increase in mean pulmonary arterial pressure upper than 20 mm Hg (32). According to Kuriyama et al, a PA diameter greater than 30 mm indicates a PA pressure greater than 20 mm Hg (33). In our serie, mean diameters of main PA were significantly higher in nonsurvivors than in survivors (p=0,05). However, no cutoff value could be determinated. Correlation with PE pressure estimated at echocardiography was

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not available for comparison. Collomb et al (14) also found differences in the diameter of main PA between patients with severe PE and patients with non severe PE. In the study of Ghaye et al (20), main PA diameter was not an indicator of mortality in patients with clinically severe PE whereas azygos vein diameter was an accurate predictor of mortality in those patients.

Comorbidities and deep venous thrombosis :

In our study, comorbidities remain the most powerful predictors of death due to PE, as presented in previous large retrospective registries (5) and randomized trials of thrombolytics (34).

It is interesting to note that, in multivariate analysis, concomitant lower limb DVT, was associated with death in patient with clinically non severe PE. It means that when non severe PE is firstly diagnosed on the basis of CTPA, the presence of lower limb DVT must be investigated. Furthermore, radiologists must pay attention to venous system when they are looking for PE. Recently, Yamaki et al. investigayed the presence of lower limb DVT with compression ultrasound and created a prognostic score which identified patients at risk of an adverse outcome in patients with PE (35).

Limitations :

Some limitations of our study should be considered. First, it was a retrospective study, prevented us from comparing our findings with other diagnostics tests. Further prospective studies on the prognostic role of cardiovascular CT parameters for PE should also include echocardiography data and the determination of brain natriuretic peptide and troponin measurements, which are according to studies predictors of adverse outcome in patient with PE (36, 37). Second, our study group consisted of patients admitted for clinically non severe

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PE. In this population mortality is lower, consequently, the number of deaths was limited (9 deaths probably related to PE among 24 deaths at three months follow-up). Third, we could not classify patients into subgroups according to their history of associated cardiopulmonary disease, because of the low number of patients with history of cardiopulmonary disease.

CONCLUSION

In clinically non severe PE, our study shows that RV/LV diameter ratio >1 is predictive of RV failure and death when embolic burden is low (<40%). However, RV/LV diameter ratio should be evaluated with caution because of high interobserver variability. Main PA diameter is a reproducible and independent CT prognostic finding. Neither the shape of interventricular septum nor embolic burden are predictive of death. It is interesting to note that concomitant lower limb DVT is an indicator of mortality in patients with clinically non severe PE.

Thèse soutenue par : Anne-Line Moroni.

Titre : Embolie pulmonaire sans signe clinique de gravité : apport pronostique de l'angioscanner thoracique.

Conclusion :

L'embolie pulmonaire est une pathologie fréquente, dont le pronostic reste difficile à appréhender. Les scores actuels combinent données cliniques et biologiques, et sont complexes. L'angioscanner thoracique étant devenu l'examen diagnostique de référence de l'embolie pulmonaire, nous souhaitons évaluer son intérêt pronostique à moyen terme. Deux cent vingt six patients, présentant une embolie pulmonaire diagnostiquée à l'aide d'un angioscanner thoracique (quatre ou seize barrettes), et ne présentant pas de signes cliniques de gravité, ont été inclus dans l'étude de façon rétrospective. Deux radiologues ont revu indépendamment l'ensemble des scanners, et ont évalué pour chaque patient, la charge embolique selon le score de Qanadli, le rapport entre les plus grands diamètres du ventricule droit et du ventricule gauche (rapport VD/VG), la position du septum inter ventriculaire, les diamètres du tronc de l'artère pulmonaire et de la veine cave supérieure, la qualité du parenchyme pulmonaire (pneumopathie, infarctus). La présence de co-morbidités ainsi que l'existence d'une thrombose veineuse profonde associée, ont été recherchées pour chaque patient. Ces résultats ont ensuite été confrontés au risque de décès à trois mois, à l'aide d'analyses univariées et multivariées, par régressions logistiques. Un comité médical indépendant a déterminé la cause du décès des patients.

Sur les vingt-quatre patients (10.6%) décédés à trois mois, l'embolie pulmonaire était probablement la cause du décès de neuf d'entre eux. Il existait une importante variabilité inter observateur pour l'évaluation de la position du septum inter ventriculaire (kappa=0,41) et pour

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l'analyse du rapport VD/VG (coefficient de corrélation=0,76). La position du septum n'était pas un facteur de mortalité à trois mois. Paradoxalement, en analyse univariée, une charge embolique élevée (>40%) était associée à une diminution du risque de décès (OR, 0,46 ; p=0,16). Un rapport VD/VG >1, était associé à une mortalité plus élevée, uniquement chez les patients dont la charge embolique était inférieure à 40% (OR, 3,83 ; p<0,01). L'analyse du rapport VD/VG, n'avait d'intérêt que lorsque l'on prenait en compte la valeur de la charge embolique. En analyses multivariées, il n'existait plus de lien statistique entre les paramètres scanographiques hémodynamiques et le devenir des patients, sauf pour le diamètre du tronc de l'artère pulmonaire (OR, 1,1 ; p=0,05). La présence d'une thrombose veineuse profonde (OR, 2,81; p=0,04) et les co-morbidités étaient également d'importants facteurs de mortalité. A l'issue de cette étude, il nous apparaît que, dans l'embolie pulmonaire non grave, le diamètre du tronc de l'artère pulmonaire et à un degré moindre, la mesure du rapport VD/VG sont associés à une mortalité précoce surtout quand la charge embolique est modeste. Néanmoins la non reproductibilité de la mesure du rapport VD/VG, rend inutile son évaluation en routine clinique, d'autant plus que les facteurs pronostiques majeurs, restent les facteurs cliniques.

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B. SELE

U.F.R DE DECINE

Le Président de la Thèse.

Professeur FERRETTI

APPENDIX

Pulmonary artery clot load scores

Qanadli Score :

The arterial tree of each lung is regarded as having 10 segmental arteries (three in the upper lobes, two in the middle lobe and the lingula, and five in the lower lobes). The presence of one embolus in a segmental artery is scored as one point, and embolus in a more proximal artery is scored according to the number of segmental arteries arising from this artery. To provide additional information about the residual perfusion distal to the embolus, a weighting factor is used for each value (0, no defect; 1, partial occlusion; and 2, complete occlusion). The maximum obstruction score is 40. Isolated subsegmental embolus is considered as a partially occluded segmental artery and assigned a value of 1. For further analyses, the clot load score in the pulmonary was expressed as a percentage. This was calculated by dividing the score obtained by the maximum possible score for the considered system and multiplied by 100.

CT Finding	Observer 1	Observer 2
Embolic burden† :	25,2±19*	25,7±19*
<40%	160	161
>40%	66	65
RV/LV diameter ratio†:	0.96±0,26*	1±0,27*
≤1	163	133
>1	63	93
Ventricular septum [†] :	155	117
-normal	52	64
-rectilingin	19	45
-bowing	18	45
Main PA diameter (mm) :	27,5±4,4*	26,9±4,4*
Superior veina cava diameter :	15,9±3,8*	15,9±4,1*

CT findings for both observers :

*Data are the mean \pm standard deviation. \dagger Data are the number of patients.

Univariate analysis of CT findings for both observers :

Interobserver variability for the shape of the inter ventricular septum was only fair (κappa = 0,41) as was interobserver variability for RV/LV diameter ratio (intraclass correlation coefficient = 0,76). Association of these CT findings with death was calculated independently for observers 1 and 2 (Table 1). Displacement of the interventricular septum, RV/LV diameter ratio, embolic burden and superior vena cava were not associated with death for both observers. Main PA diameter was statistically associated with death for observer 2.

Table 1 :

CT Predictor and Observer No	Odds Ratio	Lower 95% Confidence Limit	Upper 95% Confidence Limit	pValue
Embolic burden :		-		
-Observer 1 : ≥40%	0,46	0,16	1,36	p=0,16
-Observer 2 : ≥40%	0,47	0,16	1,39	p=0,17
RV/LV diameter ratio :				
-Observer $1 :> 1$	1,30	0,56	3,04	p=0,54
-Observer 2 : >1	1,73	0,77	3,85	p=0,18
Ventricular septum :				_
-Observer 1				
Rectilign	0,92	0,34	2,51	p=0,87
Bowing	1,62	0,47	5,57	p=0,44
-Observer 2				_
Rectilign	1,06	0,42	2,70	p=0,90
Bowing	1,09	0,38	3,10	p=0,87
PA diameter :				
-Observer 1	1,08	0,99	1,17	p=0,08
-Observer 2	1,08	1,00	1,17	p=0,05
Superior veina cava diameter :				
-Observer 1	1.05	0.95	1.17	p=0.31
-Observer 2	1,07	0,97	1,18	p=0,17

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