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Assessment of a Simplified Score of Reflux of Contrast into the Inferior Vena Cava in Acute Pulmonary Embolism CT Scan: Correlation with PE Biomarkers, Right Ventricular Dysfunction and in-Hospital Mortality

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Abstract

Purpose: A reflux of contrast into the inferior vena cava and hepatic veins (RC) can be seen on Computed Tomographic Pulmonary Angiography (CTPA) of PE. In PE patients, we aimed to assess RC with a simplify score and study its relationship with other well-known markers of PE severity and patients' outcomes.

Methods: 384 consecutive patients with PE confirmed by CTPA were included between March 2016 and December 2019. RC was graded by two independent observers then classified, in a goal of simplification, in two groups of severity: "no or trivial" *vs*. "major". The presence of RC was compared with other well-established prognosis parameters, in particular biomarkers and right ventricular dysfunction but also with early adverse outcomes defined as in-hospital clinical deterioration and mortality.

Results: In our population of 384 PE, using the new classification, no or trivial RC was frequent (83.8%) while major RC was uncommon (16.2%). An adverse outcome occurred in 5.2% of patients (n=20). On multivariate analysis, negative anterior T waves on ECG, high BNP level and Right Ventricular (RV) dysfunction on transthoracic echocardiography were strongly and independently associated with the extent of reflux. A major RC appears to be a powerful parameter to predict outcomes (p=0.001) with a strong correlation with biomarkers: right ventricular echocardiographic dysfunction, but also clinical outcomes including mortality at 30 days.

Conclusion: "Major" RC into the IVC and HV with a simplified classification is a radiologic sign to observe on CTPA of PE. It is strongly associated with PE severity in particular with biomarkers and right ventricular dysfunction and also short-term prognosis. It may help classify PE severity as soon as the diagnosis is done by CT scan.

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Abbreviations

BNP: Brain Natriuretic Peptide; CI: Confidence Interval; COPD: Chronic Obstructive Pulmonary Disease; CTPA: Computed Tomographic Pulmonary Angiography; DVT: Deep Vein Thrombosis; HR: Heart Rate; HV: Hepatic Veins; IVC: Inferior Vena Cava; OR: Odds Ratio; PASP: Pulmonary Artery Systolic Pressure; ROC: Receiver-Operating Characteristic; RVD: Right Ventricular Dysfunction; RV/LV diameter: Right Ventricular/Left Ventricular diameter; SBP: Systolic Blood Pressure; TAPSE: Tricuspid Annular Plane Systolic Excursion; TTE: Trans Thoracic Echocardiography; VTE: Venous Thromboembolism

Introduction

Risk stratification is an important step in Pulmonary Embolism (PE) management [1]. Except when blood pressure is low, the prognosis parameters used to stratify the risk depends mainly on echocardiography or biology. RV function assessment by Trans-Thoracic Echocardiography (TTE) may be difficult to perform in an emergency ward while biomarkers results but also their precise correlation with PE severity can be delayed [2]. Computed Tomography Pulmonary Angiography (CTPA) is currently the first line-diagnosis modality for PE [3], beyond the visualization of clots it may give some other important information i.e.: pulmonary obstruction index, septal shape, main

pulmonary artery diameter, Right Ventricular to Left Ventricular (RV/LV) diameter ratio, three-dimensional right ventricular volume.

The presence of RC is a radiological sign that is easy to identify. In radiologic series it could have been correlated, although not consistently, with PE mortality but never with PE prognosis signs commonly advised in our guidelines [4-7]. Furthermore, the RC classification into 6 or even 3 categories deserves to be simplified for an easier clinical use.

The aim of our study was to seek for a simplified RC classification in acute PE patients CT scan and study its relationship with other well-known prognosis parameters and patients' outcomes.

Methods

We conducted a single center observational study. 384 consecutive adult patients admitted in our institution (Centre Hospitalier Universitaire de Nice, France) for acute PE diagnosed on CTPA, between March 2016 and December 2019, were included.

In order to avoid chronic RV dysfunction, which may lead to a RC, patients with history of pulmonary arterial hypertension, chronic thromboembolic disease, concomitant severe valvular disease or chronic atrial fibrillation were excluded. Patients whose assessment of RC was not possible on CTPA (mainly due to technical insufficiencies, poor enhancement of the right heart and pulmonary vessels) were also excluded.

All CTPA were obtained by using a 64-slice multi-detector row scanner, non-ECG-gated, acquired in a caudo-cranial direction at end of inspiration during a single breath-hold. A uniform injection protocol was used with 60 ml of contrast Omnipaque© injected by antecubital intravenous injection (3 ml/sec). CT scans DICOM data were stored on the workstation PACS (Picture Archiving and Communication System). Two experienced operators, blinded to each other and to clinical data, carried out off-line analysis of reflux of contrast into the IVC and HV. In order to simplify the assessment of the severity of RC, initially classified into 6 grades (10) (Figure 1): 1= no reflux into the IVC; 2= trace of reflux into the IVC; 3= reflux into IVC but not in hepatic veins; 4= reflux into IVC and opacification of proximal hepatic veins; 5= reflux into the IVC and opacification of mid-part of hepatic veins; 6= reflux into IVC and opacification of distal hepatic veins, we divided the intensity of RC in two groups: "no or trivial" RC group (from 1 to 3) *vs.* "major" RC group (from 4 to 6).

Demographic information and medical history were noticed on the basis of patients' medical records.

Standard 12-lead ECG was realized on admission, then every day. A particular attention was paid to collect ECG signs of severity [8]. For laboratory parameters, Troponin I and BNP were measured at baseline (on admission) respectively with the Siemens Centaur® and the Alere Triage Beckman Coulter®. The positivity threshold was >200 ng/l for Troponin I and >100 pg/ml for BNP.

TTE was performed within the first 12 h of diagnosis with a particular interest in RV function assessment which was performed according to the ASE guidelines [9].

RV dysfunction was diagnosed when one of the following items was present:

- RV dilatation determined by a ratio of end diastolic right ventricular diameter to end diastolic left ventricular diameter equal or greater to 0.9 in apical 4-chamber view.
- RV hypokinesis defined by Tricuspid Annular Plane Systolic Excursion (TAPSE) <16 mm and/or by tricuspid annular systolic velocity (S') <10 cm/sec.
- Pulmonary hypertension which was considered when Pulmonary Artery Systolic Pressure (PASP) was greater than 35 mmHg. The measure was determined from peak tricuspid regurgitation jet velocity using the simplified Bernoulli equation and combining this value with the right atrial pressure estimated from IVC diameter and respiratory change.

Management

All patients received unfractionated heparin or low-molecular-weight heparin (Enoxaparin). Then, oral anticoagulation therapy (vitamin K antagonist but mainly non-vitamin K antagonist oral anticoagulant) was initiated. The decision to use thrombolytic therapy was considered according to the hemodynamic status of the patient: i.e. persistent hypotension or presence of cardiogenic shock and the presence of right heart clots.

All clinical outcomes were notified: including in-hospital clinical deterioration i.e.: Cardiogenic shock, need for catecholamine infusion, thrombolysis, emergency embolectomy or cardiopulmonary resuscitation. All patients were followed at 1 month.

Statistical analysis

Data are presented as mean ± standard deviation for continuous variables and number of individuals (percentage) for categorical variables. Chi-square test was used to compare categorical variables. Student's t test was used to compare normally distributed variables; those not normally distributed were tested by Mann & Whitney's U test. Variables associated with the extent of reflux of contrast into the IVC and/or HV were determined using linear regression analysis. Logistic regression tests were used to identify predictors of adverse outcomes. Inter-observer variability was assessed using Cohen's kappa statistic. For all analyses, statistical significance was defined as $p<0.05$. Statistical analyses were performed using SPSS version 22.0 (Armonk, NY: IBM Corp).

Results

Study population

A total of 384 patients with acute PE were included. Baseline characteristics of the study population are presented in Table 1. The average age was 63.8 ± 18.1 years. A Deep Vein Thrombosis (DVT) was present in 182 (47.4%) patients. Acute PE was provoked in 202 (52.6%) patients. A raise in troponin level was present in 78 (20.5%) patients while BNP was increased in 142 (37.6%) patients. RV dysfunction on TTE was present in 82 (21.4%) patients. Follow-up was completed in all patients. A clinical deterioration occurred in 20 patients (5.2%).

- Thrombolysis therapy was administered in 10 patients: 8 because of a cardiogenic shock (after inotrope and pressor amines therapy); 2 because of a hemodynamic instability associated with a mobile RV clot and a severe RV dysfunction. None of these patients treated with thrombolytics died.
- Two other patients with cardiogenic shock received catecholamine infusion with a good recovery.
- Eight patients (2.1%) died, all of them during the initial phase of hospitalization.
- None underwent emergency embolectomy.

- In all, at day 30, 18 patients (4.6%) presented an event. Three patients died after initial hospitalization: Two from advanced cancer and one from sudden death.

Reflux of Contrast into the IVC and/or HV and simplified classification.

According to CTPA, RC initially graded from 1 to 6, was observed respectively in 148 (38.5%), 108 (28.1%), 66 (17.2%), 24 (6.3%), 20 (5.2%) and 18 (4.7%) patients. For an easier clinical use, the classification has been simplified: Grade 1 to 3 were gathered into a "No or trivial RC" classification and grade 4 to 6 constituted the "Major RC group". Considering this new classification, no or trivial RC was found to be frequent: n=322; 83.8%, while major RC was less common: n=62; 16.2% (Figure 2).

Inter-observer variability for grading RC into "trivial" or "major" was excellent with a Cohen's kappa statistic of 0.925 (p<0.001). This result suggests that little inter-individual difference exists in the reproducibility of CT sign of RC.

Table 1: Baseline characteristics of patients.

Clinical variables on admission:	n=384
Age (years ±)	63.5 ± 19.1
Female n (%)	186 (48.4%)
Smoking n (%)	68 (17.7%)
Hypertension n (%)	134 (34.9%)
Diabetes mellitus n (%)	40 (10.4%)
Hypercholesterolemia n (%)	64 (16.7%)
Obesity n (%)	46 (12%)
COPD n (%)	20 (5.2%)
Previous VTE n (%)	86 (22.4%)
Active cancer n (%)	50 (13%)
DVT n (%)	182 (47.4%)
Clinical findings on admission:	
Chest pain n (%)	124 (32.3%)
Syncope/Lipothymia n (%)	46 (12%)
Dyspnea n (%)	242 (63%)
SBP (mm Hg)	133.5 ± 20.8
HR (bpm)	87.6 ± 20.5
Electrocardiographic findings on admission:	
Atrial fibrillation n (%)	24 (6.3%)
Negative anterior T waves n (%)	64 (16.7%)
Diffuse negative T waves n (%)	20 (5.2%)
Cardiac biomarkers on admission:	
Troponin I >200 ng/l n (%)	78 (20.5%)
BNP > 100 pg/ml n (%)	142 (37.6%)
Echocardiographic findings on admission:	
Right heart systolic dysfunction n (%)	82 (21.4%)
Outcomes:	
Inotrope or vasopressive therapy n (%)	10 (2.6%)
Thrombolysis therapy n (%)	10 (2.6%)
Cardiogenic Shock n (%)	10 (2.6%)
In hospital Death n (%)	8 (2.1%)
Composite endpoint at day 30 n (%)	18 (4.6%)

BNP: Brain Natriuretic Peptide; COPD: Chronic Obstructive Pulmonary Disease; DVT: Deep Vein Thrombosis; PE: Pulmonary Embolism; VTE: Venous Thromboembolism; HR: Heart Rate; SBP: Systolic Blood Pressure

Factors correlated with the extent of RC are reported in Table 2. On multivariate analysis, variables associated with the extent of reflux into the IVC and HV were negative T waves in anterior leads on ECG (p=0.046), troponin peak level (p=0.04), BNP peak level (p<0.001) and presence of a RV dysfunction on TTE (p<0.001).

When comparing major versus no or trivial RC groups as listed in Table 3, Mean age was higher in major RC group (0.005). Negatives anterior T waves on ECG (48.4 *vs.* 10.6% (p<0.001)), troponin on admission and peak troponin value (54.9 *vs.* 13.8% (p<0.001) and 816 ± 1079 *vs.* 102 ± 93 (p=0.006)); BNP on admission and BNP peak value 83.9 *vs.* 28.5% (p<0.001) and 567 ± 234 *vs.* 58 ± 25 (p<0.001) and RV dysfunction assessed on baseline TTE (58.0 *vs.* 14.3% (p<0.001)) were much more frequent or high in the major RC group:

Prognostic value of RC into the IVC and HV in PE patients

A bad in hospital outcome occurred in 14 patients of major reflux group (14/62; 22.5%) but in 6 patients of nor or trivial reflux group (6/322; 1.9%); p<0.001. On univariate analysis, major RC was a predictor of adverse outcomes with an odds ratio (OR) of 15.36 (95% CI 3.72-63.49), while, elevated BNP or troponin levels at baseline and RV dysfunction on TTE were also predictors of outcomes with an OR of 2.1 (95% CI 1.7-3.3); 4.2 (95% CI 1.4-16.4) and 10.2 (95% CI 2.5-41.3) respectively. Finally, in-hospital mortality was higher in the major RC group (p<0.001).

Table 2: Predictors of the extent of contrast reflux into the IVC and/or HV on linear regression.

Variables	p value
Age	0.315
Negative T waves on ECG	0.046
Troponin I	0.408
BNP	<0.001
Right ventricular dysfunction	<0.001

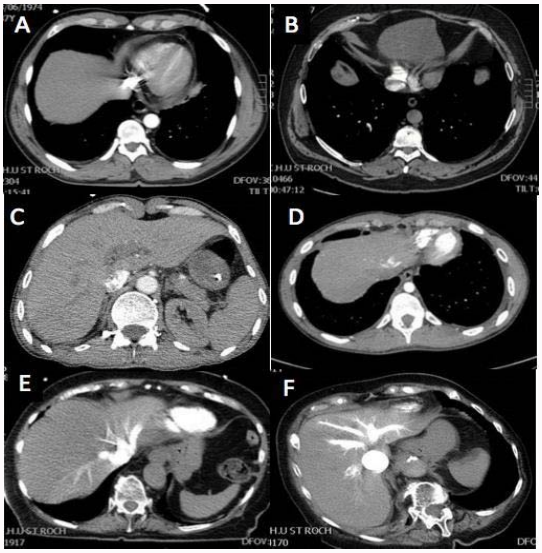

Figure 1: Axial CT pulmonary angiography sections through the liver showing varying degrees of intravenous contrast reflux into Inferior Vena Cava (IVC) and hepatic veins (HV). A.B.C: No or trivial RC. D.E.F: Major RC.

Table 3: Baseline characteristics of patients with « no or trivial » *vs.* « major » contrast reflux.

Characteristics	Trivial Reflux (1-3) (n=322)	Major Reflux (4-6) (n=62)	p value
Clinical data:			
Age (years)	61.8 +/- 18.5	72.3 +/- 20.2	0.005
SBP (mmHg)	133.7 ± 21.1	132.2 ± 19.3	0.756
Obesity (%)	11.20%	16.10%	0.437
COPD (%)	5.00%	6.90%	0.734
Current provoked PE (%)	52.20%	54.80%	0.786
Cancer (%)	13%	12.90%	0.983
HR (bpm)	86.5 ± 19.6	93.2 ± 24.5	0.126
ECG data:			
Negative anterior T waves (%)	10.60%	48.40%	<0.001
Cardiac biomarkers:			
Troponin I >200 ng/l (%)	13.80%	54.90%	<0.001
Peak Troponin I (ng/l)	102 ± 93	816 ± 1079	0.006
BNP >100 pg/ml (%)	28.50%	83.90%	<0.001
BNP (pg/ml)	58 ± 25	567 ± 234	<0.001
Echocardiography :			
Right ventricular dysfunction (%)	14.30%	58%	<0.001
Outcomes :			
Composite endpoint at 30-day n (%)	6 (1.9%)	14 (22.6%)	<0.001
In-hospital death n (%)	2 (0.6%)	6 (9.7%)	0.001
Cardiogenic shock n (%)	2 (0.6%)	8 (12.9%)	<0.001
Use of thrombolytic therapy n (%)	2 (0.6%)	6 (9.7%)	0.007
Use of inotropes or vasopressors n (%)	2 (0.6%)	8 (12.9%)	<0.001

BNP: Brain Natriuretic Peptide; COPD: Chronic Obstructive Pulmonary Disease; DVT: Deep Vein Thrombosis; PE: Pulmonary Embolism; VTE: Venous Thromboembolism; HR: Heart Rate; SBP: Systolic Blood Pressure

Based on ROC curve analysis, a major RC had a high prognosis value to determine adverse outcomes (Area under Curve (AUC) 0.891, CI 0.800-0.983, p<0.01; with a sensitivity and specificity of 70% and 86% respectively.

Discussion

The great challenge immediately after the diagnostic of acute PE is to identify patients for whom prompt treatment and intensive surveillance are needed, especially in intermediate-risk patients without hemodynamic instability [1].

A high performance TTE is not always easily and rapidly available in all centers and biological results and interpretation may need some delay [2]. In this context, an easy radiologic sign available as soon as the diagnosis is certified on the initial CTPA may help stratify the risk.

In this observational study, we reported several findings: Using a simplified classification, a major RC in acute PE is seen in 1 patient out of 6 (16.2%). A major RC is independently associated with high BNP/troponin levels and the presence of RV dysfunction on TTE. Finally, a major RC is a strong predictor of adverse outcomes including mortality.

The earliest description of retrograde contrast opacification of the hepatic veins was reported by Omell et al. in patients without

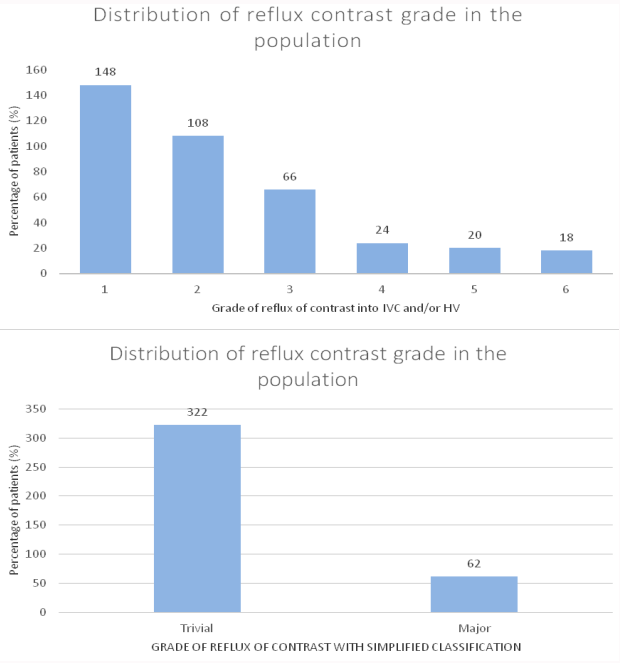

Figure 2: Distribution of patients hospitalized for acute pulmonary embolism with respect to the grades of contrast reflux into the inferior vena cava and hepatic veins (initial and simplified classification).

PE [10]. Groves et al. [11] described 6 varying degrees of RC with 90% sensitivity and 100% specificity in the assessment of tricuspid regurgitation. In these non-selected populations, a correlation was found between RC and, in particular, heart disease, pulmonary hypertension, tricuspid regurgitation, high injection rate (>4 ml/mn) and female sex.

Collomb et al. [4] were the first in an 81-patient cohort of PE to assess whether RC indicates the clinical severity of PE. They found no relationship between the presence of RC and the severity of PE while Ghaye et al. [5] in 82 patients with acute PE did found that RC is a predictor of mortality. The mortality rate in this last study was 15%. Aviram et al. [7] using a 6 scales classification of RC also suggested, in a sub group of 145 patients with acute PE, that a major RC is a predictor of early mortality. Very unusual 30-day mortality 34.5% in the more severe group, of which the specific causes were unknown, was reported in this paper.

This interesting somewhat discordant data deserves to be confirmed. In particular most of these studies focused on radiological aspects with a 6 to 3 grades classification which may be more difficult to use by non-radiologists' practitioners. In all these studies, no data was reported on management of PE. The information about the causes of mortality are lacking. The PE mortality rates are not the one observed nowadays in departments that are experienced in the management of PE. Finally, the presence of RC has not been adequately linked with well-established prognosis parameters used in clinical practice i.e.: Biomarkers and echocardiographic RV dysfunction.

The physiopathology of major RC in PE may be explained by the acute increase in RV volume and/or pressure overload and concomitant massive tricuspid regurgitation [12,13]. In acute PE, It may suggest that the cardiac capacities to contain the overwork of the right ventricle, of which we know the bad prognosis, are exceeded.

In our study in which clinical deterioration occurred in 3.1% of

patients (n=12) and mortality in only 2.1% (n=8), we demonstrate that a major RC is strongly correlated to well-known markers of severity but is also a reliable clue to predict clinical outcomes (AUC=0.891, sensitivity 70%, specificity 86%, p<0.01). Furthermore, finding a link between RC and biomarkers and RV dysfunction, both well correlated with mortality of PE, is somewhat reassuring and strengthens the possible link between RC and PE prognosis.

This means that among patients with a severe PE but no hemodynamic instability, the presence of a major RC on CTPA, which can be easily seen by any practitioner, should be regarded as a severity sign and encourage us to discuss the proper orientation of patients in specialized environment.

Conclusion

In hemodynamically stable acute PE, using a simplified classification, the degree of RC seen on CTPA is independently and strongly associated with biomarkers, RV dysfunction and early adverse outcomes. This simple, radiologic sign could be used for early-risk stratification in patients with acute PE.

Acknowledgment

Author contributions: P.B., FS and E.F. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. FS, PB, DB, BS, ML, PM. and E.F contributed to the study conception. FS, PB, DB, BS, ML, PM and E.F contributed to the data acquisition, analysis and interpretation BP and CR analyzed CT scan. FS, PB, ML, PM. and E.F contributed to drafting the manuscript and FS, PB, DB, BS, ML, PM and E.F contributed to revising the manuscript for important intellectual content and approving the final copy.

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