Pulmonary embolism : diagnostic management and prognosis

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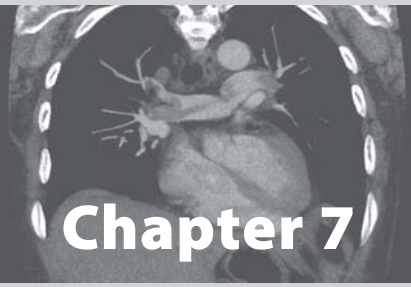

Chapter 7

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.

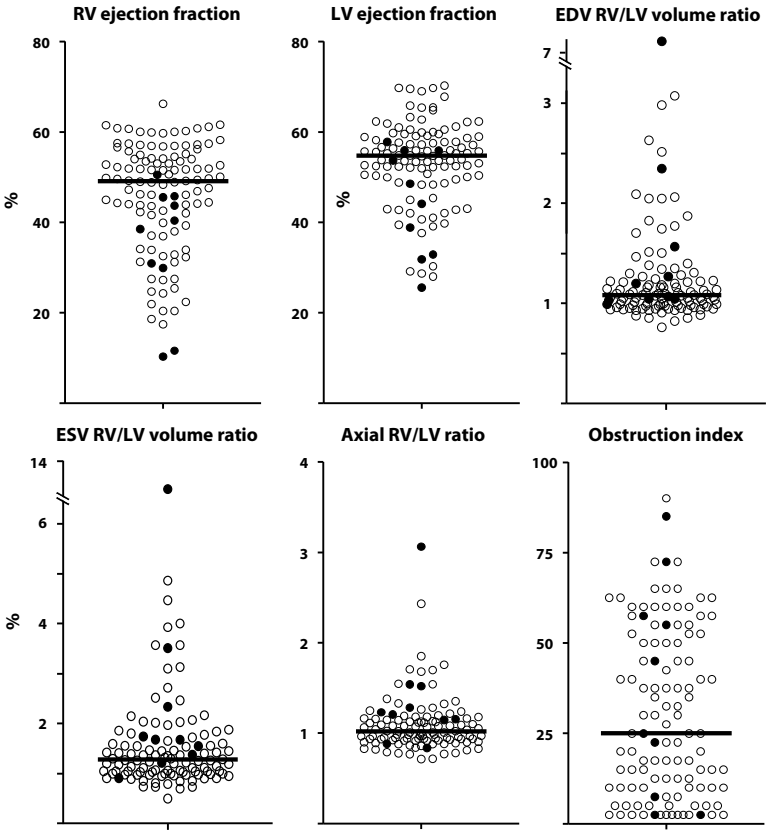

Figure 1. Distribution of the left and right ventricular (LV and RV) ejection fractions, ventricular ratios and obstruction index in the patients with acute pulmonary embolism. Horizontal bars represent medians, black circles represent patients with adverse clinical outcome. ESV=end-systolic volume,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