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Benefit of combining quantitative cardiac CT parameters with troponin I for predicting right ventricular dysfunction and adverse clinical events in patients with acute pulmonary embolism

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ABSTRACT

Objective: To prospectively evaluate the diagnostic accuracy of quantitative cardiac CT parameters alone and in combination with troponin I for the assessment of right ventricular dysfunction (RVD) and adverse clinical events in patients with acute pulmonary embolism (PE).
Materials and results: This prospective study had institutional review board approval and was HIPAA compliant. In total 83 patients with confirmed PE underwent echocardiography and troponin I serum level measurements within 24 h. Three established cardiac CT measurements for the assessment of RVD were obtained (RV/LV_{axial}, $RV/LV_{4\text{-}CH}$, and RV/LV_{volume}). CT measurements and troponin I serum levels were correlated with RVD found on echocardiography and adverse clinical events according to Management Strategies and Prognosis in Pulmonary Embolism Trial-3 (MAPPET-3 criteria. 31 of 83 patients with PE had RVD on echocardiography and 39 of 83 patients had adverse clinical events. A RV/LV_{volume} ratio > 1.43 showed the highest area under the curve (AUC) (0.65) for the prediction of adverse clinical events when compared to RV/LV_{axial}, RV/LV_{4Ch} and troponin I. The AUC for the detection of RVD of RV/LV_{axial}, RV/LV_{4Ch}, RV/LV_{volume}, and troponin I were 0.86, 0.86, 0.92, and 0.69, respectively. Combination of RV/LV_{axial}, RV/LV_{4Ch}, RV/LV_{volume} with troponin I increased the AUC to 0.87, 0.87 and 0.93, respectively.
Conclusion: A combination of cardiac CT parameters and troponin I measurements improves the diagnostic accuracy for detecting RVD and predicting adverse clinical events if compared to either test alone.

1. Introduction

Acute pulmonary embolism (PE) is a common disease with a variable prognosis which ranges from incidental clinical unimportant small embolism to massive embolism with sudden death. Thus, risk stratification relies on early detection of right ventricular dysfunction (RVD) in order to identify normotensive high-risk patients who might benefit from more aggressive therapies, such as thrombolysis or embolectomy [1]. For this purpose echocardiography is considered to be the clinical reference standard. However, recently a multitude of recent studies have evaluated promising morphometric parameters from pulmonary CT angiography (CTPA) for predicting adverse outcomes or early death in patients with acute PE [2–6].

Beyond imaging signs, troponin I has been proposed as a predictor of clinical outcome in patients with acute PE [7]. Several meta-analyses have demonstrated an association between elevated serum levels of troponin and RVD or adverse clinical events in patients with acute PE (specificity 77–90% and sensitivity 23–100%) [8,9]. Given the wide range in specificity it has been suggested that a combination of troponin with right ventricular (RV) function or size measurements may have an advantage for identifying normotensive, high-risk PE patients when compared to a single test alone [10,11].

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Therefore, the objective of this study was, to prospectively evaluate the accuracy of quantitative cardiac CT parameters and troponin I serum levels, alone and in combination, for predicting RVD and adverse clinical events in patients with acute PE.

2. Materials and methods

2.1. Study population

This study was part of a larger investigation evaluating the accuracy of quantitative CTPA parameters and cardiac biomarkers for predicting RVD in patients treated for PE at the University medical center Mannheim. Initial results of this investigation have been previously published by Henzler et al. [10]. However, the publication by Henzler et al. only looked at presents of RVD as a potential outcome parameter. More importantly from a clinical prospective, is patient outcome in terms of clinical course in patients with acute PE. Therefore this study differs from the previously mentioned study by further investigating clinical outcome in a larger study population. Our local ethics committees approved this prospective study, and all patients gave written informed consent. In total 83 consecutive patients with confirmed PE underwent echocardiography and troponin I serum level measurements within 24 h. These included 45 men (mean age 61 ± 13) and 38 women (mean age 64 ± 18). Patient medical records were reviewed for co-morbidities.

2.2. Echocardiographic assessment of RVD

In the present study echocardiography served as the gold standard for the assessment of RVD in this study. Transthoracic echocardiography was performed in a standardized fashion on Vivid 7 and Vivid 1 (GE Healthcare, Chalfont St Giles, UK) ultrasound scanners. For study purposes echocardiograms were obtained within 24 h after onset of symptoms by two experienced investigators with 15 and 7 years of experience, respectively, and who were blinded from the results of troponin I serum levels and CT measurements. Data were analyzed as previously reported [10] resulting in three different classifications of PE patients: no RVD, moderate RVD or severe RVD.

2.3. CT protocol

All patients underwent non-ECG-gated standard pulmonary CTA examinations on multi detector-row CT (MDCT) systems. 42 patients were examined on a 16-slice MDCT system (SOMATOM Emotion, Siemens Healthcare Sector, Forchheim, Germany). The remaining 41 patients were examined using 64-slice dual-source CT (DSCT) system (SOMATOM Definition, Siemens Healthcare Sector, Forchheim, Germany). Scan parameters used for the 16-slice scanner were 130 kV, 70 ref mAs using automated tube current modulation (CARE Dose 4D, Siemens Healthcare Sector, Forchheim, Germany), collimation of 0.6 mm, pitch of 0.8, rotation time of 0.6 s, and a reconstructed slice thickness of 2 mm. Scan parameters used for the DSCT were 120 kV tube voltage, 125 ref mAs using automated tube current modulation (CARE Dose 4D, Siemens Healthcare Sector, Forchheim, Germany), detector collimation of 0.6 mm, pitch of 1.4, tube rotation time of 0.5 s, and a reconstructed section thickness of 2 mm. Contrast enhancement was achieved by injecting 100 ml of iodinated contrast material (Imeron 400, Bracco Imaging S.p.A., Milan, Italy) through an antecubital vein at a flow rate of 4 ml/s followed by a saline flush of 20 ml at the same flow rate. For all contrast injections a double-barrel power injector (Stellant D, Medrad, Warrendale, USA) was used. Bolus tracking was used with a region of interest placed within the pulmonary trunk using a threshold of 100 HU for initiating data acquisition [12].

2.4. CT analysis

All CT studies were analyzed on a multi-modality 3D-enabled workstation (Syngo VE36A, Siemens). CT studies were evaluated in consensus by two radiologists with 11 and 4 years experience in thoracic radiology. The diagnosis of PE was confirmed by the presence of at least one filling defect within the pulmonary artery tree. As previously described the RV/LV axial view ratio [13] and the RV/LV 4-Ch view ratio [5] was measured in each patient. Additionally the RV/LV_{volume} ratio was calculated for each patient, too. 3D volumetric analysis of both ventricles was performed offline on a workstation using a volume analysis software (Volume Analysis [Version: VE31A], Syngo VA36A, Siemens Healthcare Sector, Forchheim, Germany). From the valvular plane to the inferior aspect of both ventricles endocardial contours were semi-automatically segmented. On the transverse sections which contained minimal and maximal expanse of the ventricle endocardial contours were manually outlined. To facilitate the segmentation process, manually segmented contours were automatically propagated to the neighboring slices, which could then be manually corrected. RV/LV ratio was subsequently calculated. To improve the results of manual segmentation, pixels with a density in the range of myocardium were automatically excluded from the segmentation. For each patient, a circular region of interest (ROI) measuring attenuation of the septal myocardium, was generated and repeated three times. Pixels with density values within the 95% confidence interval of the mean density of the ROI were considered to be from myocardium. Volumetric analysis was only based on pixels within manual segmentation and with density values that were at least 30% greater than the density of myocardium [14].

2.5. Laboratory measurements

Troponin I serum levels were quantified from a venous blood sample, which was drawn within 24 h after the diagnosis of PE using a conventional Troponin I two-site immunoenzymatic immunoassay (Access AccuTnI, Beckmann Coulter, GmbH – Diagnostic, Krefeld, Germany). The assay's threshold level for the upper limit of normal was 0.06 μg/L (coefficient of variation < 10%).

2.6. Clinical outcome

Fatal clinical outcome was defined as death within 2 months after the diagnosis of PE. Non-fatal adverse clinical outcomes were defined as escalation of therapy, according to the Management Strategies and Prognosis in Pulmonary Embolism Trial-3 (MAPPET-3) criteria, including cardiopulmonary resuscitation, required ventilator support, vasopressor therapy, rescue thrombolysis, and surgical or catheter embolectomy [15].

2.7. Statistical analysis

Statistical analysis was performed using JMP 9.0 (SAS Institute, Cary, North Carolina, USA). Continuous variables are expressed as mean ± SD. The Shapiro–Wilk test was applied to determine probability distribution; a two-tailed Student's *t*-test was subsequently used to compare groups with normal distribution, while the Mann–Whitney *U*-test was used if the data were not normally distributed. The chi-square test was applied for dichotomous variables. To determine the diagnostic accuracy of troponin I and CT parameters for RVD, receiver operating characteristic (ROC) plots were analyzed and areas under the curve (AUCs) were calculated. An additional measure was composed to assess RVD, moderate RVD, severe RVD and adverse clinical events incorporating information from RV/LV ratios and troponin I cut-off values. This ordinal measure ranged from 1 to 6 where a score of 1 denotes RV/LV