Accuracy of CT angiography in the detection of pulmonary embolism in patients with high body weight

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Purpose

Pulmonary embolism (PE) is the most serious manifestation of venous thromboembolism (VTE) and is the third most common cause of cardiovascular mortality in developed Western countries [1-4]. Several observational studies showed that obesity is an independent risk factor for VTE in both sexes [5-12]. As the prevalence of overweight and obesity in the population is increasing [13-15], the number of obese patients with PE is also expected to rise. The assessment of clinical probability of the disease in obese subjects can be challenging because they often present with dyspnea and tachycardia even without PE.

In the last decade, multidetector row CT pulmonary angiography (CTPA) became the primary imaging tool for excluding acute PE [1; 16-20]. The data in the literature on the diagnostic performance of CTPA are based on patient populations with mixed body habitus with various body weight (BW) and body mass index (BMI). We are not aware of any analysis of the accuracy of CTPA in obese patients or in those with high BW. However, such an analysis may be interesting because CT image quality is generally reduced in these patient groups as a result of the high absorption rate of x-rays by fat tissue, resulting in increased image noise. Decreased image quality might negatively affect the detection of emboli, especially smaller emboli. With the increasing proportion of overweight or obese patients with suspected PE, the problem is expected to be encountered during the clinical routine more frequently in the future.

The aim of the current retrospective analysis was to assess the diagnostic accuracy of CTPA in patients with high BW, defined as 100 kg (220 lbs).
Materials and Methods

Patient selection

Our database was retrospectively searched for patients weighing ≤100 kg who underwent CTPA to exclude PE on the emergency unit of a tertiary-care center (University Hospital Bern, Inselspital) between September 2007 and April 2011. There were no exclusion criteria. One hundred twenty-three consecutive patients were identified and entered into the analysis.

The control group consisted of 114 patients weighing 75 to 99 kg who underwent CTPA between September 2008 and April 2011. These subjects participated in the normal-dose arm of the Reduced Dose in Pulmonary Embolism Diagnosis (REDOPED) trial, which was a single-center, prospective randomized study conducted in the same hospital, comparing normal-dose and low-dose CTPA in patients weighing <100 kg [7]. These patients served as ideal control subjects because of their well-documented pretest probability for PE (Fig. 1).

All prospectively acquired patients in the <100 kg group gave written informed consent. In the ≥100 kg group, all patients who could be reached by phone during follow-up (see below) gave oral consent to the study. The IRB waived written informed consent in the ≥100 kg group and accepted the study protocol.

Clinical data and diagnostic tests

The simplified revised Geneva score was used to assess clinical probability of PE [8]. D-dimer tests were done at the discretion of the referring physician. Additional imaging modalities such as compression sonography with color Doppler of the lower limb veins and ventilation-perfusion (V/Q) scanning were performed only if indicated.

CTPA protocol

Patients were examined with the same 16-row CT scanner (Somatom Sensation 16, Siemens Medical, Forchheim, Germany) by using 16 x 0.75 mm collimation and 1.15 pitch. In all patients in the <100 kg group and in most patients in the ≥100 kg group, the tube voltage was set at 100 kVp and the quality reference tube current time product at 100 mAs. In 21 of 123 patients in the ≥100 kg group, tube energy of 120 kVp was used at the same tube current to keep image quality at a diagnostic level.

One hundred milliliters of standard contrast medium (CM) with 300 mg/mL iodine concentration was injected intravenously. Image acquisition was triggered by the CM bolus in the pulmonary trunk, the threshold to start scanning was 100 HU.
Analysis of CTPA

Three board-certified general radiologists with CT experience of 4 years, 9 years and 15 years, independently evaluated all CTPAs in randomized order on standard LCD monitors. Readers were asked to report the presence and location of PE down to the second subsegmental level. The diagnosis of PE was established in the case of a complete or partial filling defect in the pulmonary arteries on at least three contiguous transverse images of 1 mm thickness with no major movement artifacts. The readers were blinded to all clinical data.

Follow-up

Electronic patient records were searched for new admissions to our hospital in the 90 days after CTPA. Patients were interviewed by telephone 3 to 12 months after CTPA and asked for any admission to other medical institutions or primary-care doctors. They were also asked for any clinical signs and symptoms suggesting PE or deep venous thrombosis during the 90 days after initial CTPA: new or increasing dyspnea, chest pain, or swelling or pain in the lower extremities.

Reference standard

The radiological reference standard for CTPA was established by a chest radiologist with CT experience of 13 years, who did not act as a reader. He knew the original written reports and readers' data but not the results of additional imaging and follow-up. In a second step, a composite standard of reference was established in accordance with the guidelines of the European Society of Cardiology [1]. The final decision about whether PE was present or not was made from pretest probability (low, intermediate and high based on the simplified revised Geneva score), presence and localization (segmental or more central) of PE in the reference CTPA diagnosis, results on additional imaging and 90-day follow-up. Although missing data on follow-up did not necessarily lead to an indeterminate diagnosis, the reference standard diagnosis was equivocal for some special combinations of results (Table 1).

Statistical analysis

Readers' data on PE were compared with the composite reference standard. The 95% confidence interval (CI) was calculated for sensitivity, specificity, accuracy, and positive and negative predictive values. Differences in diagnostic accuracy between the study groups were assessed by calculating the odds ratio (OR) with 95% CI, and the P-value was computed by using Fisher's exact test. All comparisons were made not only between patients with a BW of <100 kg and a BW of #100 kg, but also between obese and non-obese (normal weight and overweight) patients, i.e., with a BMI of #30 and a BMI of <30.
kg/m\(^2\), respectively. Interobserver agreement was assessed by calculating the weighted kappa. Values of P < 0.05 were considered statistically significant.
Fig. 1: STARD flow chart depicting the patient collective and results of the reference CTPA compared with the composite reference standard diagnosis. REDOPED= Reduced Dose in Pulmonary Embolism Diagnosis; PE= pulmonary embolism

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Table 1: Composite reference standard diagnosis used in the trial. The reference standard diagnosis is based on the guidelines of the European Society of Cardiology and includes pretest probability, CTPA findings and additional imaging modalities accomplished with a 90-day follow-up. * The clinical probability was estimated using the simplified revised Geneva score. † When pretest probability is low, CTPA reliably detects PE in the lobar and main pulmonary artery (third row from the top), but requires further testing in cases of segmental filling defects (fourth and fifth rows from the top). ‡ CTPA needs additional imaging for definite diagnosis in cases of subsegmental PE irrespective of pretest probability and in cases of negative CTPA results when clinical probability is high. § In cases of positive ultrasonography or PE-related death within 90-day follow-up, negative CTPA with low clinical probability was regarded as a false negative. || In cases of positive V/Q scan with negative CTPA and low clinical probability,
therapy is not warranted according to the guidelines. # In cases of conflicting results on CTPA and on additional imaging, the result of the method showing PE or deep venous thrombosis was regarded as true when the pretest probability was intermediate or high. CTPA = computed tomography pulmonary angiography; PE = pulmonary embolism; CUS = compression ultrasonography with color coded Doppler of the lower extremity veins; FP = false positive; TP = true positive; TN = true negative; FN = false negative; V/Q = ventilation-perfusion lung scintigraphy.

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Results

Patients

The maximum BW was 150 kg and the highest BMI was 53.3 kg/m$^2$ in our patient collective. There was no significant difference between the BW groups with respect to age, sex and outpatient ratio (Table 2). A previous VTE and a slightly elevated heart rate was more frequent in patients weighing #100 kg ($P = 0.012$ and 0.004, respectively). The clinical probability of PE did not differ between the BW groups. A high pretest probability was found in only 2% of patients.

Follow-up and composite reference diagnosis

No VTE and no PE-related deaths were registered during the 90-day follow-up period. From a total of 237 patients, 226 had a definite composite reference diagnosis: 38 patients had PE and 188 had no PE. The prevalence of PE was 16.4% in the <100 kg group and 17.2% in the #100 kg group (OR, 0.939; 95% CI, 0.442 to 1.994; $P = 1.0$).

Performance of CTPA

Compared with the composite reference standard, the reference CTPA diagnosis, established by the non-blinded chest radiologist, reached a sensitivity of 94.4% and 95.0%, a specificity of 97.8% and 97.9%, and an accuracy of 97.2% and 97.4% (OR, 0.947; 95% CI, 0.187 to 4.795; $P = 0.947$) in the <100 kg group and in the #100 kg group, respectively (Fig. 1). Results were very similar in non-obese and obese patients. A subgroup analysis in the #100 kg group showed no significant difference in the number of correct diagnoses in patients examined with 100 kV (99 of 101) and those examined with 120 kV tube voltage (14 of 15; OR, 3.536; 95% CI, 0.118 to 55.451; $P = 0.342$; Fig. 2).

CTPA results by three blinded readers

Although the difference in the mean sensitivity of three independent readers seemed to be evident, it did not reach statistical significance (Table 3). The interreader agreement was substantial with a mean weighted kappa value of 0.698 (range, 0.636-0.796). The mean accuracy was 91.5% and 89.9%, in each BW group, respectively (OR, 1.207; 95% CI, 0.451 to 3.255; $P = 0.495$). Comparisons between non-obese (BMI <30 kg/m$^2$) and obese (BMI #30 kg/m$^2$) patients did not yield any significant difference either.
Table 2: Demographic and clinical data of the study population grouped by body weight. † Elevated D-dimer was defined as a plasma level >500 ng/mL. ‡ The score includes eight variables, giving 1 point to each except for heart rate. Patients with heart rates of 95 beats per min or more receive 2 points. § Clinical probability was based on the simplified revised Geneva score. || No score was calculated when four or more parameters could not be assessed # Statistically significant difference SD = standard deviation; DVT = deep venous thrombosis; PE = pulmonary embolism

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Fig. 2: One millimeter thick transverse slices from CTPA at 100 kVp in a patient weighing 90 kg (A) and 150 kg (B) with multiple filling defects (arrows) in the pulmonary arteries. The image quality allows a confident diagnosis in both cases.

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Table 3: Performance of three independent readers with CTPA in both body weight groups. Only patients with definite composite reference diagnosis are shown. Data below readers' identification is CT experience in years. Values for TP, FP, TN and FN are numbers of patients. Numbers in parentheses are 95% confidence intervals. Differences in means between the study groups were not significant for all parameters. TP = true positive; FP = false positive; TN = true negative; FN = false negative; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; PPV = positive predictive value; NPV = negative predictive value.

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Conclusions

Our results suggest that accuracy of CTPA in detecting or excluding PE is not significantly different in patients with a BW of 75-99 kg and a BW of >100 kg. Neither did we find any significant difference between non-obese and obese patients. The applied composite reference standard was robust, as no VTE and PE-related death occurred in the 90-day follow-up among patients with a negative standard reference diagnosis. To the best of our knowledge, this is the first study that analyzes performance of CTPA in patients with high BW or obesity. The performance of the reference CTPA diagnosis was very high and virtually the same in all patient groups.

There are several explanations for how obesity might increase PE risk. Increased intraabdominal pressure and stasis in the lower extremity veins, hypercoagulability, decreased fibrinolytic activity, leptin, chronic inflammation, estrogen and progesterone have been discussed as possible associations [4]. Analysis of large national and international patient registries and prospective cohort studies showed that increasing BMI is associated with an increasing risk of VTE, the correlation being higher for women than for men. Remarkably, the prevalence of PE in our composite reference standard tended to be lower in patients with obesity or high BW, although the difference was not statistically significant. This finding contradicts the results from large cohort studies. One possible explanation is that more patients with a BW of >100 kg received prophylactic anticoagulant therapy in our collective than did subjects with a lower BW. This notion is supported by the higher rate of former VTE in the history of the BW >100 kg group.

We used BW as a selective factor to define the patient collective because it had been found to correlate with image quality in CTPA better than BMI [9]. Thus, technical parameters of CTPA are tailored to BW and not to BMI to sustain diagnostic image quality in our institute. The lower BW limit of 75 kg for inclusion of patients in the study was somewhat arbitrary and based on our former clinical experience showing that image quality is sometimes compromised above this BW. We note that data from the REDOPED trial show no significant difference in the prevalence of PE between the BW ranges of 75-99 kg and of <75 kg (44 of 237 vs 47 of 264; OR, 0.950; 95% CI, 0.588 to 1.534; P = 0.908). Thus, extending our analysis to patients weighing <75 kg would not have influenced the results.

Limitations of our investigation are:

- This was a retrospective study with rather low statistical power
- The composite reference standard incorporates CTPA results (incorporation bias). However, performance of CTPA as standalone method did not reveal any difference in the patients groups either.
• We used a 16-row detector CT scanner with a conventional image reconstruction algorithm in the study. Noise reduction, in particular the use of iterative image reconstruction techniques, can further improve image quality.

• Both the experience of and the results from the three readers assessing CTPAs were inhomogeneous.

In conclusion, the diagnostic accuracy of CTPA was not significantly different in our patients weighing 75-99 kg or ≥100 kg. Our results suggest that CTPA can confidently rule PE in or out in obese patients. Since the rate of patients with obesity and suspected PE is expected to rise, we propose further studies on larger patient collectives to address this problem.
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