SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PhD)

**DIAGNOSIS OF PULMONARY EMBOLISM WITH**

**CT ANGIOGRAPHY IN OVERWEIGHT AND OBESE PATIENTS**

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# Diagnosis of pulmonary embolism with CT angiography in overweight and obese patients

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The Examination takes place at Department of Preventive Medicine, Faculty of Public Health, University of Debrecen on 9th of June 2015, at 11 a.m.

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The PhD Defense takes place at the Lecture Hall of Bldg. A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen on 9th of June 2015, at 1 p.m.

## I. Introduction

Acute pulmonary embolism (PE) is the third most common cause of cardiovascular mortality after ischemic heart diseases and stroke in developed Western countries. Untreated PE is fatal in up to 30 % of patients, but the mortality rate is 2-10 % even with timely diagnosis and treatment. Therefore it is very important to diagnose PE quickly and accurately. The nonspecific clinical signs and symptoms of PE make its diagnosis more difficult. In the past decade many different rules were described, which help assessing the clinical probability of PE. The most widely used clinical prediction rules are the Wells and Geneva score and their modified and simplified variations. Diagnostic algorithms and guidelines based on clinical probability combined with D-dimer-test and various imaging methods (echocardiography, compression ultrasonography of the deep veins of the lower limbs, invasive catheter pulmonary angiography, ventilation – perfusion scintigraphy, pulmonary CT angiography (PCTA)) support the correct diagnosis. Except for some special clinical situations (pregnancy, known adverse reaction to contrast material and renal failure) pulmonary CT angiography is suggested in patients with high clinical probability or elevated D-dimer level.

### 1. The role of pulmonary CT angiography in the diagnosis of PE

Multidetector CT imaging after intravenous contrast material administration depicts pulmonary arteries to the subsegmental level with high diagnostic confidence. PCTA just completely replaced invasive catheter pulmonary angiography and ventilation-perfusion scintigraphy as first line imaging tool. The major studies found sensitivity and specificity of PCTA between 80 and 100 %. The predictive value of PCTA significantly depends on the clinical probability of PE. The specificity and positive prognostic value of PCTA is also influenced by the position of emboli in the

pulmonary arterial tree. The clinical relevance and necessity of treatment of isolated, subsegmental emboli is highly controversial as anticoagulation therapy can increase mortality due to bleeding complications.

2. Optimization of PCTA: reduction of radiation and iodinated contrast material dose at low kilovoltage

About 25 % of the population's radiation exposure is attributed to diagnostic CT examinations in Western industrial countries. The stochastic effect of ionizing x-ray radiation can induce cancer and lymphoma decades after the CT examination. The probability of cancer induction increases with the cumulative dose over the whole life time. In this regard children, young adults and pregnant are the most compromised whereas radiation exposure induced cancer is a less important issue in the elderly. More importantly, elderly patients are at increased risk to develop iodinated contrast medium induced nephropathy (CIN) because they more often have dehydration, diabetes, impaired renal function or other predisposing factors.

From the various dose reduction techniques the use of low CT tube energy came into focus because of its simplicity and efficacy. Reduction of tube energy decreases radiation exposure because dose is proportional to the second power of tube energy. Moreover, attenuation in the vessels enhanced by iodinated contrast material increases because the tube voltage approaches the absorption maximum of iodine (33.2 keV). The higher iodine signal can compensate for the inevitably increased image noise, resulting in a constant contrast-to-noise ratio.

The low tube voltage protocol is especially favourable in the chest because of the low x-ray absorption of the air-filled lungs. Former studies show that 30-40 % reduced radiation dose and 25 % lower contrast material volume can be achieved in patients weighing less than 100 kg without deterioration of image quality and diagnostic

accuracy of PCTA. The reduced amount of iodine is expected to decrease the probability of CIN, making low tube voltage PCTA beneficial also in elderly patients.

## 3. Diagnosis of PE in obese patients: limitations of physical examinations and PCTA

Obesity is an independent risk factor for PE. There are several reasons for increased risk of venous thromboembolism (VTE) in overweight and obese patients such as venous stasis with immobilization, raised intra-abdominal pressure, reduced venous blood flow velocity increased coagulation activity and decreased fibrinolytic activity. Obese patients often present with dyspnoea, tachycardia, hypoxemia and elevated D-dimer level even without PE. Although PCTA is the primary imaging tool to exclude acute PE also in obese patients, high image noise, lower iodine attenuation resulting from x-ray beam hardening and decreased spatial resolution because of larger field of view due to large body size hamper PE detection.  Though decreased image quality may be compensated by elevating the tube current or high voltage of x-ray or by increasing slice thickness of the reconstructed images but those measures are associated with increased radiation exposure, reduced vessel attenuation or decreased spatial resolution.

PCTA with 100 kVp tube voltage is becoming more widespread, replacing the former routine protocols using 120 or 140 kVp. The 100 kVp PCTA protocol is usually restricted to patients weighing no more than 80-100 kg due to worries about decreasing CNR and diagnostic confidence to exclude PE in most centres. Since obese patients are at increased risk for developing PE, it is important to develop specially adapted low-dose protocols for them in order to provide lower radiation exposure at an acceptable image quality and diagnostic accuracy. We are not aware of any investigation on these issues in the literature.

<u>4. Aims</u>

In our retrospective analysis we aimed to answer the following questions:

1. How do the body weight (BW) and body mass index (BMI) influence the diagnostic accuracy of PCTA?

2. Does the diagnostic accuracy of PCTA on a composite reference standard deteriorate at higher body weight?

3. Have BW >100 kg and BMI >30 kg/m$^2$ any effect on the specificity, sensitivity and diagnostic accuracy of the three general radiologists, who evaluated PCTA images?

4. Are there significant differences in the prevalence of PE between the patients with BW above and below 100 kg or between obese and no obese patients?

5. Are there any differences the vessel attenuation, image noise and CNR between patient groups >100 kg, 100-125 kg and >125 kg with the 100 kVp PCTA protocol? Is there any difference in diagnostic confidence and subjective image quality between these patient groups?

6. Is image quality with the reduced -dose 100 kVp PCTA protocol sufficient in patients with high body weight and body mass index? What are the causes for reduced image quality?

7. Do image quality parameters better correlate with body weight or body mass index?

8. Are there significant differences between patient groups in terms of radiation exposure or figure of merit, characterizing improvement of objective image quality per increase in radiation dose?

## II. Patients and methods

### II. A. Diagnostic accuracy of PCTA in patients with high body weight

<u>1. Patients</u>

All patients (123 subjects, 94 males and 29 females, mean age 57.8 years) who underwent PCTA to exclude PE, between September 2007 and April 2011 University Hospital Bern, Switzerland and had a BW ≥100 kg, were entered into our retrospective analysis. The control group consisted of 114 patients (81 males and 33 females, mean age 59.2 years) weighing 75 to 99 kg who were examined with the same 100 kVp PCTA protocol between September 2008 and April 2011. These subjects participated in a subgroup of the Reduced Dose in Pulmonary Embolism Diagnosis (REDOPED) trial, which was a prospective single-center randomized study performed in the same institute with more than 500 patients.

We used BW as discriminative parameter to define the patient collective because – based on former investigations- it had been found to correlate with image quality in CTPA better than BMI. However, we also analyzed our data based on the patients' BMI, since many institutions still adapt CTPA protocols to this parameter.

All patients with BW below 100 kg, who participated in REDOPED study gave written informed consent. Members of the ≥100 kg group gave oral consent during the follow-up. The Ethics Committee of University of Bern approved the study protocol.

<u>2. Clinical data and diagnostic tests</u>

The simplified revised Geneva score was used to assess clinical probability of PE. The threshold of D-dimer tests (ELISA, VIDAS©, bioMérieux, Marcy l'Etoile, France) was 500 ng/ml. Additional imaging modalities (compression sonography with color

Doppler of the lower limb veins and ventilation–perfusion (V/Q) scanning) were performed only if indicated.

## 3. CT protocol

Patients were examined with the 16-row CT scanner (Somatom Sensation 16, Siemens Medical, Forchheim, Germany) using automatic real-time modulation of the tube current (CareDose4D, Siemens). The parameters of data collection (16 × 0.75 mm collimation, 0.5 s tube rotation time and 1.15 pitch) were same in all patients. All patients in the control group and 102 patients from 123 patients with ≥100 kg group were examined 100 kVp tube voltage protocol at 100 mAs tube current. 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. During the PCTA 100 ml contrast medium (CM) with 300 mg/ml iodine concentration was injected intravenously at a rate of 4 ml/s, using an injector in all patients. Followed by 20 ml 0.9 % NaCl solution at the same flow. The image acquisition was started 4 s after reaching 100 HU in the main pulmonary trunk. Transversal images were reconstructed at 5 and 1 mm using filtered back projection and smooth reconstruction kernel.

## 4. Analysis of PCTA

Three general radiologists with CT experience of 4 years, 9 years and 15 years evaluated the diagnostic accuracy of all PCTAs. The readers who were blinded to all clinical data, were asked to detect or exclude PE to the second subsegmental level of pulmonary arteries on the randomized 237 PCTA exams. 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

## 5. Follow-up.

The follow-up of the patients was performed by a trained study nurse with several years' experience who searched electronic patient records for new admissions to our hospital within 90 days after PCTA. Patients were interviewed by telephone 3 to 12 months after PCTA and asked for any clinical signs and symptoms suggesting PE or deep venous thrombosis during the 90 days after initial PCTA.

## 6. Reference standard PCTA diagnosis

The radiological reference standard for PCTA was established by a chest radiologist with CT experience of 13 years. He knew the original written reports but not the results of additional imaging and follow-up. In cases of doubt, equivocal PCTAs were shown to a second chest radiologist with CT experience of 10 years and decisions were made by consensus.

## 7. Composite clinical reference standard

We used a composite standard of reference, which was established in accordance with the guidelines of the European Society of Cardiology, which included pretest probability (low, intermediate and high based on the simplified revised Geneva score), the reference PCTA diagnosis, results on additional imaging and 90-day follow-up. The final decision about whether PE was present in a patient or not was made from the composite reference standard.

## 8.Statistical analysis

The gender in patient groups was compared by chi-square test and the age of patients between the groups was compared by using the Mann–Whitney U test.

Prevalence of PE and performance of the 3 independent radiologists were evaluated on the basis of the composite reference standard diagnosis. The exact binomial 95 % confidence interval (CI) was calculated for sensitivity, specificity, accuracy, and positive and negative predictive values. Differences in the prevalence and 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 between patients grouped by BW (<100 kg and ≥100 kg) and BMI (BMI <30 kg/m$^2$ and > 30 kg/m$^2$ i.e. obese and non-obese patients), respectively. Statistical tests were performed by using Statistica software (StatSoft Inc., Tulsa, OK) , StatPages web site (http://statpages.org/ctab2x2.html) and MedCalc software (MedCalc, Mariakerke, Belgium). Values of p< 0.05 were considered statistically significant.

## II. B. Image quality of reduced dose 100 kVp PCTA in patients with high body weight

### 1.Patients

From the image quality analysis we had to discard the 21 patients with ≥100 kg who received PCTA using a tube energy of 120 kVp, because different kVp values achieve completely different image impressions (lower image noise and decreased density in the enhanced vessels at 120 kVp) The control group's characteristics were the same as described at II.A.1. Thus, 216 patients' PCTAs were evaluated in the image quality comparison study.

## 2. Analysis of objective image quality

Attenuation was measured on the 1mm thick transverse images in the main pulmonary artery ($HU_{vessel}$) and in the paraspinal muscles ($HU_{backgr.}$) in areas of at least on 100 mm$^2$. Three measurements per patient were performed and the mean was used for further calculations. The standard deviations of the attenuation in the main pulmonary artery were used as image noise. The contrast noise ratio (CNR) was computed as usual: CNR = ($HU_{vessel}$ – $HU_{backgr.}$) / noise.

## 3. Analysis of subjective image quality and diagnostic confidence

The subjective image quality was evaluated by three same radiologists described at II.A.4. The readers evaluated the subjective image quality on the 1 mm thick transverse images on a five-grade scale (1 - bad, no diagnosis possible; 2 - poor, diagnostic confidence significantly reduced; 3 - moderate, but sufficient for diagnosis; 4 - good; 5 -excellent). The cause of reduced image quality (image noise; incorrect bolus timing; artefacts from patient motion, breathing, or pulsation; other cause) was given in all cases with quality grades of 1 and 2. Observers also reported their diagnostic confidence to detect or exclude PE (1 - possible diagnosis; 2 – probable diagnosis; 3 - definite diagnosis, i.e., low, medium and high confidence).

## 4. Analysis of patient radiation exposure

The size-specific dose estimates ($SSDE_s$), computed by multiplying volume CT dose index ($CTDI_{vol}$) by a correction factor, were used to assess patient exposure. The correction factor was defined by the reference diameter of the chest, which was calculated as the square root of the product of the anteroposterior and lateral chest diameters. The effective dose was estimated by multiplying the dose length product by an organ-specific correction factor of 0.016 mSv/mGycm. A figure of merit (FOM)

was calculated to better discern changes in objective image quality as a function of radiation dose in various BW groups: FOM = $CNR^2$/ SSDE.

<u>5. Statistical analysis</u>

Objective and subjective image-quality parameters, dose values, and diagnostic confidence were compared between 3 different BW subgroups (75-99 kg, 100-125 kg, > 125 kg) by using the Kruskal- Wallis test and Turkey-Kramer test. In a second step, the same comparisons were made between the following BMI groups: BMI <25 kg/m$^2$ (underweight or normal weight), BMI = 25-30 kg/m$^2$ (overweight), BMI >30 kg/m$^2$ (obese). The effect of BW on vessel attenuation, noise and on diagnostic confidence was investigated with a logistic ordinal regression model. The same regression analysis was performed also in a second model, where BW was replaced by BMI. The linear regression method was used to identify whether BW, BMI, or effective diameter of the chest had the greatest effect on objective quality parameters (i.e., vessel attenuation, noise, and CNR). Interobserver agreement was assessed by Cohen's kappa statistics and the Kendall coefficient of concordance. Statistical test was performed by using the same softwares described at II.A.8.

## III.  Results

**III. A. Diagnostic accuracy of PCTA in patients with high body weight**

<u>1.Patients</u>

There was no significant difference between the patients weighing above and below 100 kg with respect to sex (male/female ratio: 81/33 and 94/29, p=0.377), age

(59.2±15.8 years and 57.8±14.8 years, p=0.478) and outpatient ratio (54/114 [47 %] and 52/123 [42 %], p=0.437), respectively.

A previous VTE (17/116 [15 %] vs. 5/114 [4 %], p=0.012) and a slightly elevated heart rate (49/109 [45 %] vs. 25/98 [29 %], p=0.004) was more frequent in patients weighing ≥100 kg compared to the 75-99 kg group. The clinical probability of PE did not differ between the BW groups. A high pretest probability was found in only 2 % of patients. The mean dose-length product, given by the CT unit, was 232 mGy cm ± 4 in the <100 kg group and 369 mGy cm±14 in the ≥100 kg group, respectively (p <0.001). This difference was not only attributable to the BW but also to the use of 120 kVp not 100 kVp CT tube voltage in 21 patients in the ≥100 kg group.

Based on BMI 15 patients from 93 non-obese subjects had normal weight, (BMI= 18.5-24.9 kg/m$^2$) and 78 patients were overweight (BMI=25-29.9 kg/m$^2$). One hundred forty four patients were obese (BMI ≥30 kg/m$^2$). We did not find any significant different between the obese and non-obese groups with respect to age (p=0.163) and outpatient ratio (p=0.593), but there were significantly more obese female (47/144), than non-obese (14/93, p=0.002). A moderate elevated heart rate was more frequent in obese patients (53/128 [41 %] vs. 21/79 [27 %], p=0.037), whereas a heart rate above 95/min was more frequent in non-obese subjects (33/128 [26 %] respectively 31/79 [39 %], p=0.046).

2. Follow-up and composite reference diagnosis

No VTE related deaths were registered during the 90-day follow-up period. In four patients in each BW group with a low to intermediate pretest probability the CTPA showed segmental or subsegmental PE, but the composite reference diagnosis was indeterminate.  Four patients had no revised, simplified Geneva score. In one of those patients, CTPA and V/Q scanning showed lobar PE, fulfilling the diagnosis of PE on the

reference standard; the other three subjects had an indeterminate reference diagnosis. Thus, 226 patients from 237 subjects had a definite composite reference diagnosis, 38 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).

The prevalence of PE was 20.2 % in non-obese patients and 14.6 % in obese group (OR: 1.483, 95 % CI: 0.695-3.163, p=0.28).

3. Reference PCTA

Compared with the composite reference standard, the reference CTPA diagnosis reached a sensitivity of 94,4 % and 95,0 %, a specificity of 97,8 % and 97,9 %, and a diagnostic 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. Results were very similar also in non-obese and obese patients, where the sensitivity was 94.4 % and 95 %, the specificity was 97.1 % and 98.3 %, and the diagnostic accuracy was 96.6 % and 97.8 %, respectively (p=1.0 for all comparisons).

4. PCTA results by three independent radiologist

The mean specificity of three radiologists was very similar in both BW groups. Although the mean sensitivity seemed to differ between the patient groups, the variation was not statistically significant. The mean accuracy was 91.5 % in patients with <100 kg and 89.9 %, in subjects with ≥100 kg (OR: 1.207; 95 % CI: 0.451 to 3.255; P= 0.495). Similarly we did not find any significant difference in diagnostic indices between the various BMI groups. The difference in the mean sensitivity did not reach statistical significance (68.5 % in non-obese patients and 81.7 % in obese subjects, p=0.548) while mean specificity (95.3 % vs. 92.9 %) and diagnostic accuracy (89.9 % vs. 91.2 %) were virtually the same in both BMI groups. The accuracy was 80/89 in

the non-obese group and 125/137 in obese patients (OR: 0.853, 95 % CI: 0.317 to 2.319 p=0.816).

## III. B. Image quality of reduced dose 100 kVp PCTA in patients with high body weight

### 1. Patients

Eighty eight patients from 102 subjects, who were examined with 100 kVp PCTA, weighed 100-125 kg (mean age 59.2±14.1 years) and 14 patients had BW >125 kg (mean age 52.7±16.7 years). The maximum BW was 150 kg. Based on BMI 58 % of patients (125/216) were obese.

### 2. Image quality and diagnostic confidence in various BW groups

Attenuation in the main pulmonary artery was higher in the 75-99 kg group (349±98 HU) compared with patients weighing ≥100 kg (p=0.007 and 0.03), but there was no significant difference between the 100-125 kg (300±80 HU) and >125 kg (265±78 HU) subgroups (p=0.892). The CNR was also significantly higher in the 75-99 kg subgroup (8.17±2.56), than in the other patient groups (6.77±2.33 and 4.88±1.76, p <0.001 and p=0.046, respectively). SSDE was significantly lower in the 75-99 kg subgroup (7.25±1.4 mGy) than at higher BWs (p < 0.006), there was no difference between the 100-125 kg (9.75±3.3 mGy) and >125 kg subgroups (10.63±3.9 mGy, p=1.0).

The estimated effective dose was 3.7± 0.7 mSv in patients weighing 75-99 kg, 5 ±1.2 mSv in the 100-125 kg subgroup and 6.2±2.3 mSv in the >125 kg subgroup, respectively . As expected, the FOM decreased as BW increased (75-99 kg: 10.34±6.3, 100-125 kg: 5.37±3.5 and >125 kg: 2.61±1.6, p <0.001 and p=0.045). Subjective image quality and diagnostic confidence were not different between the BW subgroups (p between 0.225 and 1.0).

3. Image quality and diagnostic confidence in various BMI groups

The CNR was significantly lower in patients with BMI >30 kg/m$^2$ (median: 6.4; quartile range [5.1; 8.1]) than in the other BMI groups (7.9 [6.1, 9.8] and 8.2 [7.4, 10.2], respectively; p=0.006 and p=0.004). Patient exposure, characterized by SSDE, was higher (8.4 [7.1, 10.3] mGy vs. 6.9 [6.4, 7.1] mGy vs. 7.0 [6.2, 8.0] mGy; p <0.001), whereas the FOM was significantly lower (5.2 [2.9, 8.8] vs. 9.8 [8.3, 15.3] vs. 8.4 [5.2, 14.1];p <0.001) in obese patients compared with normal weight or overweight patients. Subjective image quality was significantly worse in obese patients (3.7 [3.3; 4.3]) than in normal weight subjects (4.3 [4.0, 4.3] p=0.025), with no difference for the other BMI subgroups. Diagnostic confidence was not different among all three BMI groups (normal weight: 2.7 [2.3, 3.0], overweight: 3.0 [2.7, 3.0] and obese patients: 3.0 [2.7, 3.0], p=0.105).

4. The effect of the patients size on the image quality and diagnostic confidence

BW had a significant effect on objective image-quality parameters such as vessel attenuation (beta: -0.238; p < 0.001), noise (beta: 0.299; p =0.0016), and CNR (beta: -- -0.507; p< 0.001). Between BMI and effective chest diameter there was no significant effect (p=>0.05). Both vessel attenuation (Z=-8.452, p<0.001) and noise (Z=4.489, p<0.001) had a significant effect on subjective image quality and diagnostic confidence. The regression analysis did not prove any significant relationship between the subjective image quality and BW or BMI, but there was near significantly correlation between the subjective image quality and BW (p=0.078, Z= -1.765).

<u>5. Inter-reader agreement and causes for diminished image quality</u>

The mean weighted kappa-value for the ratings given for subjective image quality by the three independent readers was less than zero (kappa= -0.233) indicating no agreement, whereas the Kendall coefficient of concordance was 0.363. For the diagnostic confidence, the mean weighted kappa was 0.324 indicating fair agreement between the readers. The mean subjective image quality over the three readers was poor in five patients (4 %) in the 75-99 kg group; in seven patients (7 %) in the 100-125 kg group; and in four patients (18 %) in the >125 kg group. The number of CTPA images of poor quality was significantly higher in the >125 kg group compared with the 75-99 kg group (p=0.033), and was not different from the 100-125 kg group (p= 0.108). The cause for diminished quality was given as high image noise (50 %), suboptimal bolus timing (38 %), and movement or respiratory artefacts (12 %). No PCTA had a bad subjective image quality on the average rating, so no patient had to be excluded from the study.

## **IV. Discussion**

To our knowledge these are the first investigations on diagnostic accuracy of PCTA and on image quality and diagnostic confidence of 100 kVp PCTA protocol in patients with high body weight.

Our results show that there is no significant difference between patients below 100 kg and above 100 kg in the diagnostic accuracy of PCTA, which is the gold standard imaging tool to detect or exclude of PE. We neither found any significant difference between obese and non-obese patients in this respect. Despite reduction of CNR, a measure of objective image quality, the 100 kVp CPTA protocol provided similar subjective image quality and diagnostic confidence to detect PE in patients weighing >100 kg, as in the 75-99 kg BW range. Diagnostic confidence in normal, overweight and obese patients was not significantly different either. These data suggest that the

100 kVp PCTA can be used safely in the surveyed BW range, which was 75-150 kg, although the number of patients weighing 125-150 kg was low, which inevitably reduced the statistical power for this comparison.

The prevalence of PE based on our composite reference standard diagnosis tended to be lower in patients with obesity than in non-obese patients. Although the difference was not significant, this finding contradicts the results from large cohort studies reporting higher PE prevalence with increasing bodyweight. One possible explanation is that presumably a larger proportion of patients with a BW of $\geq$100 kg received prophylactic anticoagulant therapy, which is supported by the higher rate of former VTE in the history of higher BW group. However, we did not collect data on the therapy in the patients. We note that 4patients in each body group with segmental and subsegmental PE in the reference PCTA were excluded from the prevalence calculation because of an indeterminate diagnosis on the composite reference standard. We suppose that the real prevalence of PE could be somewhat higher in the examined population, than the calculated values.

Sensitivity, specificity and diagnostic accuracy of the reference PCTA on the composite reference diagnosis was very high with 94.4-97.8 % and was virtually the same in all patient groups. The average diagnostic performance of three independent radiologists, who evaluated the PCTA images, was not significantly different between the various patient groups, although sensitivity tended to be higher in patients with high BW and BMI with a near constant accuracy. These inhomogeneities can be explained on the one hand by the various experience levels and preferences of radiologists, on the other hand by the considerable uncertainty of the calculated sensitivity with a wide 95 % CI. The low agreement between the three readers with respect to subjective image quality can be explained by the radiologists' different subjective preferences, which can be particularly expressed in the case of colleagues from different institutions with various training skills.

Data analysis of the 100 kVp PCTA protocol showed that objective image quality parameters as vessel attenuation and CNR were dependent on patient BW but not on BMI. In contrast, subjective image quality and diagnostic confidence were influenced neither by BMI nor by BW. An interesting and important result was that subjective image quality was more dependent on vessel attenuation than on noise. This can explain the worldwide increasing success of low voltage PCTA protocols. It seems that higher vessel signal at reduced tube voltage can effectively compensate for increased noise and thus, even a decreased CNR does not significantly deteriorate the diagnostic confidence and subjective quality of those reduced dose PCTA protocols.

Many of our patients weighing ≥100kg were examined with 100 kVp PCTA, which is rather unusual in this BW group, although it provides dose reduction of ca. 30-50 % compared with the still widespread 120-140 kVp protocols. Our study proved that PCTA at relatively low dose is feasible in this high BW group with no significant deterioration of subjective image quality, diagnostic confidence or accuracy. We used SSDE to characterize patient dose, which not only reflects the technical parameters, such as $CTDI_{vol}$ or DLP provided by the CT unit, but it also considers patient size.

The main limitation of our investigation is its retrospective nature and the relatively low number of patients, especially in the >125 kg subgroup. Although we did not find significant differences for the investigated parameters in patients with higher BW or BMI, we cannot definitively exclude the possibility of such differences in larger sample sizes. The 100 kVp PCTA protocol was not compared with higher tube energies and no data were obtained on the BW limit at which the tube voltage should be increased to 120-140 kVp in order to provide diagnostic image quality. A further limitation was the rahter outdated MDCT technology with a 16-row detector and a conventional image reconstruction algorithm used in the study. We note that a former investigation comparing 4- and 64-row multidetector PCTA found no significant difference in the detection rate of central, segmental and subsegmental PE, i.e., more detector rows do not mean higher sensitivity automatically. Moreover,

the therapeutic consequence of subsegmental PE is controversial. Thus, we think that the number of detector rows of the CT unit had no significant effect on our results. We also note that noise reduction, in particular the use of iterative image reconstruction techniques, can further improve image quality, especially in overweight or obese patients. Further studies are necessary to decide whether reduced image noise can improve the diagnostic confidence and accuracy of PCTA or whether 100 kVp CT tube voltage is feasible in patients with higher BW.


Conclusions and implementation of the results in  practice

1. PCTA seems to reliably diagnose or exclude PE in patients with BWs up to 150 kg, because sensitivity, specificity and diagnostic accuracy of PCTA was not significantly different between patients weighing 75-99 kg and 100-150 kg.


2. Accuracy of reference PCTA compared with the composite reference standard was high with 97 %, there was no difference between the patients groups.


3. Accuracy of the radiologists was not significantly different neither inter individually nor between the patient groups.


4. The prevalence of PE was not significantly different between neither the patients with 75-99 kg and ≥100 kg nor the obese and non-obese patients. The ratio of females was higher in obese patients than in the non-obese group.


5. The low tube voltage 100 kVp PCTA protocol provides adequate subjective image quality and diagnostic accuracy to exclude PE up to 150 kg despite the decreasing contrast noise ratio at higher BW. Although we neither found any difference in patients with 125-150 kg, the number of patients was too low for a safe conclusion.

6. No patient was excluded from the study because of bad subjective image quality. The number of PCTA examinations with poor image quality was significantly higher in the >125 kg group compared with the other BW groups. The cause for diminished quality was high image noise in 50 % of cases.

7. The vessel attenuation and noise had a significant effect on subjective image quality and diagnostic confidence. BW but not BMI had a significant effect on objective image quality parameters. We did not find any significant relationship between the subjective image quality parameters and BW or BMI.

8. Patients' dose, characterized by SSDE, was lower in the <100 kg group than at higher body weights. The figure of merit, which represented the improvement in objective image quality per dose increment, was lower as BW increased.

Based on our retrospective analysis we expect that PCTA with 100 kVp tube voltage will replace the currently widespread protocols using 120-140 kVp to exclude PE in patients weighing up to 125 kg. We think that modern CT technology (e.g. the use of noise reducing image reconstruction algorithms) can further expand the application field of reduced dose PCTA in patients with high body weight.

## V. Summary

We retrospectively analyzed pulmonary CT angiography (PCTA) as the first choice imaging tool to exclude pulmonary embolism (PE) in 237 patients. Our primary aims were to evaluate the diagnostic confidence of PCTA and to assess the image quality of a reduced dose 100 kVp tube voltage PCTA protocol in patients with high body weight (BW) or high body mass index (BMI). Our secondary aim was to analyze the association between image quality, diagnostic confidence and morphological parameters of the patients.

1. **Diagnostic accuracy of PCTA:**

   - There was no significant difference in sensitivity, specificity and diagnostic accuracy of PCTA between patients with 75-99 kg and 100-150 kg BW.

   - The accuracy of PCTA on a composite clinical reference standard was high, reaching 97% in all patient groups.

2. **Image quality and diagnostic confidence of the reduced dose 100 kVp PCTA protocol:**

   - Despite decreasing contrast- to- noise- ratio at higher body weights the reduced dose 100 kVp tube voltage PCTA protocol provided adequate subjective image quality and diagnostic accuracy to exclude PE up to a BW of 125 kg.

   - Although we did not find any difference between the 125-150 kg and other BW-subgroups, the low number of patients did not allow a reliable conclusion in this BW subgroup.

3. **Association between image quality, diagnostic confidence and morphological parameters of patients:**

   - Vessel attenuation and image noise had a significant effect on subjective image quality and diagnostic confidence.

- BW but not BMI had a significant effect on objective image quality. There was no significant correlation between the subjective image parameters and BW or BMI, respectively.

- Improvement in objective image quality per dose increment was lower as BW increased.

Our results show that PCTA provides very similar diagnostic accuracy in patients weighing 75-99 kg and ≥100 kg. The reduced dose 100 kVp PCTA protocol provides adequate subjective image quality and diagnostic confidence and thus, it appears to be appropriate to exclude PE in patients weighing up to 125kg.

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Doctoral School: Doctoral School of Health Sciences
Mtmt ID: 10048513

## List of publications related to the dissertation

1. **Megyeri, B.**, Christe, A., Schindera, S.T., Horkay, E., Sikula, J., Cullmann, J.L., Kollár, J., Heverhagen, J.T., Szűcs-Farkas, Z.: Diagnostic confidence and image quality of CT pulmonary angiography at 100 kVp in overweight and obese patients.
   *Clin. Radiol. 70* (1), 54-61, 2015.
   DOI: http://dx.doi.org/10.1016/j.crad.2014.09.014
   IF:1.663 (2013)

2. **Megyeri, B.**, Christe, A., Schindera, S.T., Horkay, E., Sikula, J., Cullmann, J.L., Kollár, J., Heverhagen, J.T., Szűcs-Farkas, Z.: Accuracy of computed tomography angiography in the detection of pulmonary embolism in patients with high body weight.
   *Eur. J. Intern. Med. 25* (8), 724-730, 2014.
   DOI: http://dx.doi.org/10.1016/j.ejim.2014.07.003
   IF:2.3 (2013)

## List of other publications

3. Szűcs-Farkas, Z., **Megyeri, B.**, Christe, A., Vock, P., Heverhagen, J.T., Schindera, S.T.: Prospective randomised comparison of diagnostic confidence and image quality with normal-dose and low-dose CT pulmonary angiography at various body weights.
   *Eur. Radiol. 24* (8), 1868-1877, 2014.
   DOI: http://dx.doi.org/10.1007/s00330-014-3208-8
   IF:4.338 (2013)

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4. Szűcs-Farkas, Z., Christe, A., **Megyeri, B.**, Rohacek, M., Vock, P., Nagy E. V., Heverhagen, J.T., Schindera, S.T.: Diagnostic accuracy of computed tomography pulmonary angiography with reduced radiation and contrast material dose : a prospective randomized clinical trial.
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5. Szűcs-Farkas, Z., Schick, A., Cullmann, J.L., Ebner, L., **Megyeri, B.**, Vock, P., Christe, A.: Comparison of dual-energy subtraction and electronic bone suppression combined with computer-aided detection on chest radiographs: Effect on human observers' performance in nodule detection.
*Am. J. Roentgenol. 200* (5), 1006-1013, 2013.
DOI: http://dx.doi.org/10.2214/AJR.12.8877
IF:2.744

Total IF of journals (all publications): 15,498
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The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of Web of Science, Scopus and Journal Citation Report (Impact Factor) databases.

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