

# Diagnosing Pulmonary Embolism With Computed Tomography Pulmonary Angiography

## *Diagnostic Accuracy of a Reduced Scan Range*

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**Purpose:** Computed tomography pulmonary angiography (CT-PA) is frequently used in the diagnostic workup of pulmonary embolism (PE), even in highly radiosensitive patient populations. This study aims to assess CT-PA with reduced z-axis coverage (compared with a standard scan range covering the entire lung) for its sensitivity for detecting PE and its potential to reduce the radiation dose.

**Materials and Methods:** We retrospectively analyzed 602 consecutive CT-PA scans with definite or possible PE reported. A reduced scan range was defined based on the topogram, where the cranial slice was set at the top of the aortic arch and the caudal slice at the top of the lower hemidiaphragm. Locations of emboli in relation to the reduced scan range were recorded.

**Results:** We included 513 CT-PA scans with definite acute PE in statistical analysis. Patients' median age was 66 (52 to 77) years, 46% were female. Median dose length product was 270.8 (111.3 to 503.9) mGy\*cm. Comparing the original and reduced scan ranges, the mean scan length was significantly reduced by 48.0±8.6% (26.8±3.0 vs. 13.9±2.6 cm,  $P < 0.001$ ). Single emboli outside the reduced range in addition to emboli within were found in 15 scans (2.9%), while only 1 scan (0.2%) had an embolus outside the reduced range and none within it. The resulting sensitivity of CT-PA with reduced scan range was 99.81% (95% confidence interval: 98.74%-99.99%) for detecting any PE.

**Conclusion:** A reduced scan length in CT-PA, as defined above, would substantially decrease radiation dose while maintaining diagnostic accuracy for detecting PE.

**Key Words:** pulmonary embolism, computed tomography, pulmonary angiography, radiation dose, sensitivity

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The authors declare no conflict of interest.

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Pulmonary embolism (PE) is a potentially lethal condition with an incidence of 99/100,000/year in the general population.<sup>1</sup> Early diagnosis is important to enable timely initiation of treatment, usually based on anticoagulation or, in case of hemodynamic instability, thrombolysis.

The most commonly applied tool to diagnose or exclude PE is computed tomography pulmonary angiography (CT-PA), as it is widely available, quick, and accurate. CT-PA has thus become a frequent examination.<sup>2</sup> Diagnostic yield, however, is often low but can be improved using preselection strategies including appropriate risk scores and D-dimer cutoffs.<sup>3</sup> Despite the comparatively low amount of radiation applied with modern scanners, radiation exposure is still a concern in susceptible populations. Limiting radiation dose is of particular importance not only in children, but also in young adults, especially women, as the highly radiosensitive breast tissue is located within the scan field. CT-PA may even be indicated in the vulnerable population of pregnant patients.<sup>4</sup> Especially in these populations, it is important to reduce the radiation dose applied during CT-PA to an absolute minimum, while at the same time maintaining high diagnostic accuracy.

Radiation dose of CT-PA depends on several factors, including patient size, scanner type, available reconstruction algorithms (such as iterative reconstruction), and specific protocol adjustments (helical or volume CT, kV settings, tube current modulation, and accepted signal-to-noise ratio).<sup>5</sup> Another and often underestimated factor is scan length. While as per standard protocol the entire lung is usually included within a CT-PA scan, the most apical and basal parts of the acquired volume often do not contain pulmonary vasculature at a caliber large enough to be assessable with CT-PA. The clinical relevance of possibly detected subsegmental PE in these lung regions has yet to be conclusively settled.<sup>6,7</sup>

Previous studies suggested that reducing the scan range in CT-PA could significantly lower the radiation dose.<sup>8–12</sup> However, most of these studies had relatively low numbers of positive scans, and thus knowledge regarding the accuracy of reduced range CT-PA is still limited.

This study aimed to investigate the sensitivity for detecting PE and the potential for radiation dose reduction of CT-PA with reduced z-axis coverage relative to a standard scan range covering the entire lung.

## MATERIALS AND METHODS

In this retrospective study, the reports of all consecutive CT-PA examinations performed at the Division of

**TABLE 1.** Standard Scan Parameters of CT Pulmonary Angiography on the 3 CT Scanners Used

	<b>Aquilion 64</b>	<b>Revolution CT</b>	<b>SOMATOM Force</b>
Tube voltage (kV)	120	100 (kV Assist)	100 (Care kV)
Tube current (mA)	Automatic exposure control (SureExposure)	Automatic exposure control (SmartmA)	Automatic exposure control (CareDose)
Collimation (mm)	32	80	115.2
Pitch factor	0.828	0.992	1.2
Rotation time (s)	0.5	0.35	0.25

The standard protocols include an anteroposterior (all scanners) and lateral (only Aquilion 64 and Revolution CT) topogram, a contrast bolus equivalent to 40 mL at an iodine concentration of 400 mg/mL with an injection rate of 4 mL/s, bolus tracking in the pulmonary trunk and helical scan in a craniocaudal direction.

General Radiology, Department of Radiology, Medical University of Graz between April 2017 and December 2019 were searched for a definite or possible diagnosis of PE. These scans were then reanalyzed according to the pre-specified protocol set out below. Scans were included in statistical analysis if they covered the entire lung and were positive for acute PE. For all analyses related to radiation dose and incidental findings, scans with an extended range were excluded. The study was approved by the Institutional Review Board (internal reference number 32-333ex19/20), which waived the requirement for patients' informed consent. Study data are available from the corresponding author on reasonable request.

### CT-PA

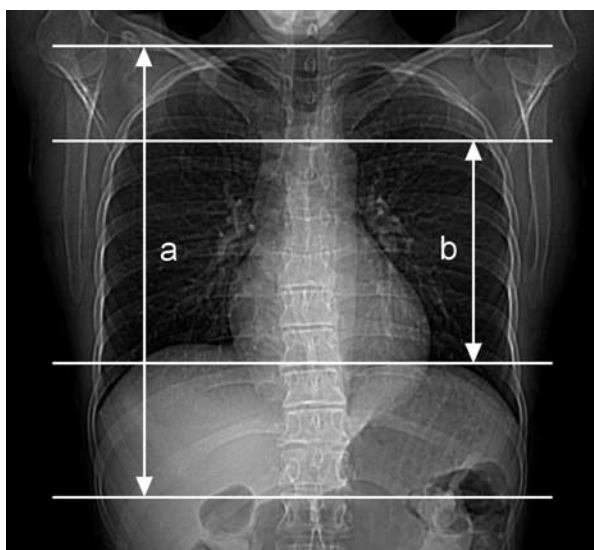
CT-PA, including acquisition of an anteroposterior topogram, bolus tracking in the pulmonary trunk, and helical scanning in a craniocaudal direction, was performed on 3 different scanners: Aquilion 64 (Canon Medical Systems, Otawara, Tochigi, Japan—previously Toshiba Medical Systems), Revolution CT (GE Healthcare, Waukesha, WI), and SOMATOM Force (Siemens Healthineers, Erlangen, Germany). Table 1 lists the standard scan

parameters. Modifications to the standard protocols were possible at the discretion of the operating technician.

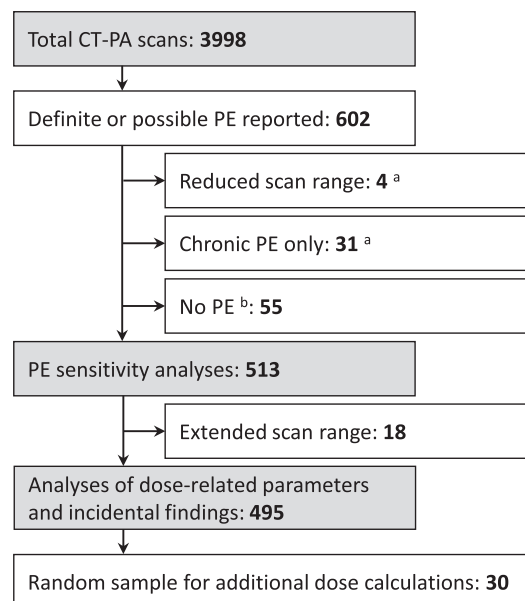
### Image Analysis

A reduced  $z$ -axis scan range was defined and measured on the anteroposterior topogram, ranging from the cranial edge of the aortic arch to the top of the more inferior hemidiaphragm (Fig. 1). Pulmonary emboli and incidental findings that were entirely above or below the defined scan range were classified as missed. In addition, the slice position of the most proximal embolus was recorded, separately for emboli above and below the main pulmonary artery bifurcation. This allowed for estimation of sensitivities according to different positions of cranial and caudal range boundaries.

PE was defined as a sharply delineated contrast filling defect in a pulmonary artery. The finding was verified in other reconstruction planes. Apparently reduced intravascular contrast was correlated to breathing or pulsation artifacts and not diagnosed as PE if likely explained by these artifacts. An embolus was considered chronic in the presence of certain morphologic features (web-like or band-like, thin and wall adherent, calcified).<sup>13</sup> PE was classified according to the most proximal thrombus as central (pulmonary trunk and



**FIGURE 1.** Scan range boundaries: Original (a) and reduced (b)  $z$ -axis coverage on an exemplary topogram. The cranial boundary slice is set at the upper edge of the aortic knob and the caudal boundary slice at the top of the lower hemidiaphragm.



**FIGURE 2.** Flowchart of included and excluded patients. <sup>a</sup>One scan with both reduced range and chronic PE only. <sup>b</sup>Reported findings likely explained by artifacts.

**TABLE 2.** Characteristics of the Cohort

Patients (n = 499)	
Age (y)	66 (52-77)
Female	227 (45.5)
BMI (kg/m <sup>2</sup> )	27.7 ± 5.6
Effective chest diameter (cm)	29.2 ± 3.4
History of malignancy	94 (18.8)
Hospitalized at referral	107 (21.4)
Scans (n = 513)*	
HU in pulmonary artery	407.2 ± 124.9
Significant artifacts†	37 (7.2)
Most proximal PE	
Central	152 (29.6)
Proximal lobar	94 (18.3)
Distal lobar	75 (14.6)
Segmental	113 (22.0)
Subsegmental	79 (15.4)

\*Fourteen patients were referred for CT-PA twice.

†Artifacts affecting the assessment of pulmonary artery branches proximal to a subsegmental level.

Numbers are mean ± SD, median (interquartile range) or percentage (absolute numbers).

Effective diameter = √(anteroposterior diameter × transverse diameter).

BMI indicates body mass index; HU, Hounsfield units.

main pulmonary arteries until branching into lobar arteries), proximal lobar (until first runoff of a segmental artery), distal lobar (until final branching into segmental arteries), segmental (until first branching of a segmental artery), or subsegmental.

Incidental findings outside the reduced range were classified as follows: likely benign (eg, incidental nodules <6 mm or calcified nodules, adrenal lesions with density <10 Hounsfield units, thyroid nodules <1.5 cm, hepatic cysts, postoperative findings, cholecystolithiasis, benign but with potential clinical significance (eg, pneumonia, pleural effusion, pericardial effusion, ascites, pneumothorax), equivocal (eg, incidental nodules 6 to 10 mm,<sup>14</sup> other adrenal lesions, solid hepatic lesions, enlarged lymph nodes), and likely malignant (eg, larger nodules and masses, bone lesions of suspicious morphology).

Each scan was independently analyzed by one of the study readers (consultant radiologists and radiology residents

with a minimum experience in thoracic radiology of 3 y): J.S. (consultant, 6 years' experience), E.N. (consultant, 7 years' experience), A.-K.K.-B. (resident, 3 years' experience), J.S. (resident, 5 years' experience), M.J. (resident, 4 years' experience), E.J. (consultant, 6 years' experience), C.R. (resident, 4 years' experience), M.E. (consultant, 6 years' experience), N.S. (resident, 4 years' experience), G.A. (consultant, 8 years' experience). Analyses were supervised by J.S. who second read at least all findings that were equivocal or divergent from original reports. The readers were not blinded to the original reports.

**Estimates of Radiation Dose**

The CT dose index (CTDI) and dose length product (DLP) of the scans were recorded as dose estimates. Effective dose was calculated via a conversion factor (0.0145).<sup>15</sup> Scan length reduction served as an approximation for radiation dose savings.

In a random subset of 30 scans, additional dose calculations were performed to account for effects of tube current modulation in addition to the comparison of scan length between original and reduced range scans. Tube current (mA) was extracted per slice from the DICOM metadata and summed up over the respective scan length. Only scan length and mA differ significantly between the standard and reduced ranges, and because the percent dose reduction is a ratio, other constant variables (eg, tube voltage) influencing DLP calculation are largely factored out. Thus, comparing the sum of mA per slice between scan ranges can provide an estimate of dose reduction comparable to DLP decrease.

In an additional cohort of 20 patients, we calculated CTDI and DLP reduction by planning both a full and a reduced CT-PA scan on chest topograms and recording the respective prescan estimated CTDI and DLP provided by the scanner. These data were available only from 2 scanners (Revolution CT and SOMATOM Force).

**Statistics**

Parameters were presented as mean ± SD, median (interquartile range), or percentage (absolute numbers). Statistical tests were performed in SPSS version 26.0.0.1 (IBM, Armonk, NY). Sensitivity was calculated with

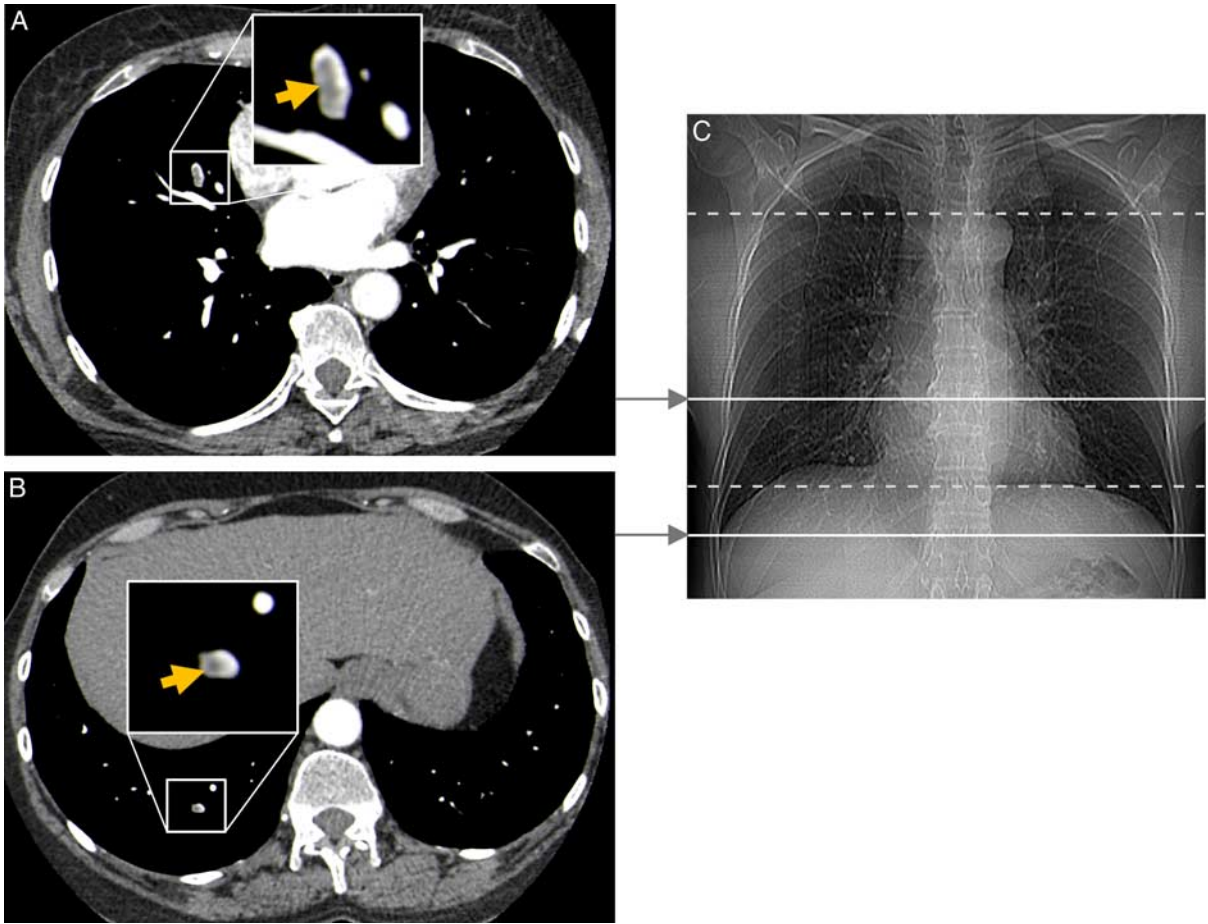
**TABLE 3.** Scan Length and Dose Estimates

	Scanner 1 (Aquilion 64)	Scanner 2 (Revolution CT)	Scanner 3 (SOMATOM Force)	All Scanners
Study cohort	n = 297	n = 152	n = 46	n = 495
Original scan length (cm)	27.1 ± 3.0 <sup>b</sup>	26.4 ± 2.9	25.6 ± 3.3 <sup>b</sup>	26.8 ± 3.0
Reduced scan length (cm)	14.5 ± 2.5 <sup>ab</sup>	13.1 ± 2.3 <sup>a</sup>	12.4 ± 2.2 <sup>b</sup>	13.9 ± 2.6
Delta scan length (%)	-46.3 ± 8.2 <sup>ab</sup>	-50.3 ± 8.7 <sup>a</sup>	-51.3 ± 8.5 <sup>b</sup>	-48.0 ± 8.6
Original CTDI (mGy)	21.3 ± 8.8 <sup>ab</sup>	3.6 ± 2.2 <sup>ac</sup>	5.5 ± 3.3 <sup>bc</sup>	14.4 ± 11.0
Original DLP (mGy*cm)	473.1 ± 236.9 <sup>ab</sup>	121.0 ± 77.1 <sup>ac</sup>	179.6 ± 106.5 <sup>bc</sup>	338.0 ± 253.5
Original effective dose (mSv)	6.9 ± 3.5 <sup>ab</sup>	1.8 ± 1.1 <sup>ac</sup>	2.6 ± 1.6 <sup>bc</sup>	4.9 ± 3.7
Random sample	n = 10	n = 10	n = 10	n = 30
Delta ΣmA (%)	-48.4 ± 13.8	-58.7 ± 9.3	-61.7 ± 17.3	-56.3 ± 14.6
Prescan dose estimates	—	n = 10	n = 10	n = 20
Delta scan length (%)	—	-44.1 ± 4.7	-47.0 ± 3.6	-45.5 ± 4.3
Delta CTDI (%)	—	-6.2 ± 23.0	-24.4 ± 8.5	-15.3 ± 19.3
Delta DLP (%)	—	-45.6 ± 8.4	-50.6 ± 9.9	-48.1 ± 9.3

Numbers are mean ± SD. All parameters from the helical scan only (ie, without topogram or bolus tracking).

Prescan dose estimates were calculated on topograms of 20 different patients (not part of the main study cohort). In the study cohort, Games-Howell post-hoc analysis revealed significant differences between scanners 1 and 2 (<sup>a</sup>), 1 and 3 (<sup>b</sup>), and 2 and 3 (<sup>c</sup>).

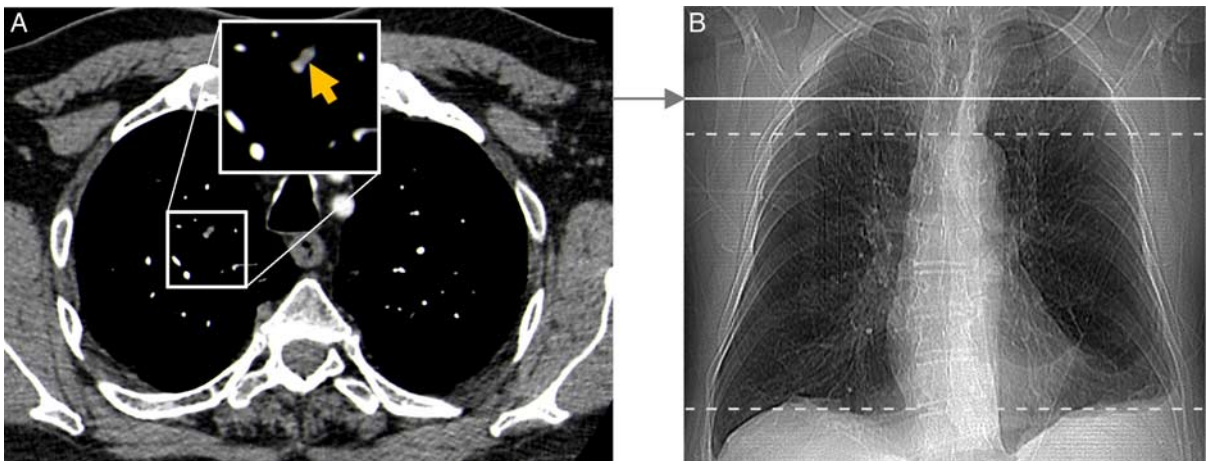
ΣmA indicates sum of mA extracted per slice over the respective scan range (this estimate takes dose modulation into account, but not overranging) calculated in a subset of the main study cohort (random sample).



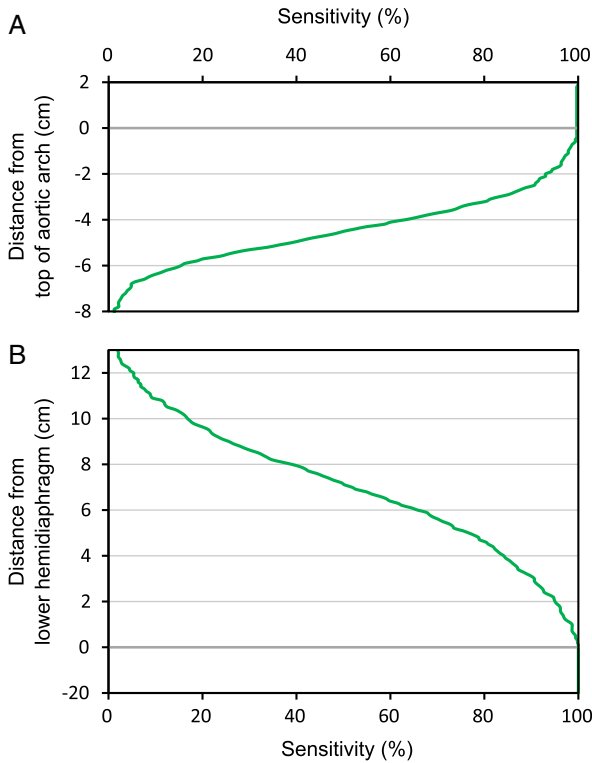
**FIGURE 3.** Example of a case with both emboli within and outside the reduced range. Boundary slices of the reduced range are indicated with dashed lines in C. A, Segmental embolus in the medial segment of the middle lobe (arrow), located within the reduced range (reference line in C). B, Subsegmental embolus in the posterobasal segment of the right lower lobe (arrow), located outside the reduced range (reference line in C). [full color online](#)

standard CT-PA as the reference standard, and the confidence interval was calculated using the score method with continuity correction.<sup>16</sup> Scanners were compared with the

Welch analysis of variance and Games-Howell post hoc analysis. A *P*-value of <0.05 was regarded as statistically significant. A random sample of 10 cases per scanner was



**FIGURE 4.** Example of a case with an isolated embolus outside the reduced range. Boundary slices of the reduced range are indicated with dashed lines in B. A, Subsegmental embolus in the apical segment of the right upper lobe (arrow), located outside the reduced range (reference line in B). [full color online](#)



**FIGURE 5.** Estimated sensitivities of different boundary slice positions. Estimated sensitivity is based on the location of the most proximal thrombus end. A, Sensitivities of the cranial boundary slice to detect emboli at or above the pulmonary artery bifurcation. B, Sensitivities of the caudal boundary slice to detect emboli at or below the pulmonary artery bifurcation.

drawn automatically using SPSS. Euler diagrams were created in R version 3.5.1 (The R Foundation for Statistical Computing, Vienna, Austria) using the eulerr package.

**RESULTS**

From a total of 3998 consecutive CT-PA scans, 602 scans with reported possible or definite PE were analyzed. Of those, 513 scans (in 499 patients) had definite acute PE in

CT-PA (12.8% positivity rate) and were included in statistical analyses (Fig. 2). Median age was 66 (52 to 77) years, and 45.5% were female; detailed characteristics are listed in Table 2.

**Reduction of Radiation Dose**

After excluding extended range scans, in the remaining 495 scans’ median DLP (helical scan) was 270.8 (111.3 to 503.9) mGy\*cm. Comparison of the original and reduced scan ranges showed that the mean scan length would be reduced significantly by  $48.0 \pm 8.6\%$  ( $26.8 \pm 3.0$  vs.  $13.9 \pm 2.6$  cm,  $P < 0.001$ ). In the analysis of prescan dose estimates calculated on topograms of 20 additional patients the estimated DLP was similarly reduced by  $48.1 \pm 9.3\%$  ( $124.8 \pm 55.0$  vs.  $64.4 \pm 31.0$  mGy\*cm,  $P < 0.001$ ) when applying a reduced scan range (Table 3).

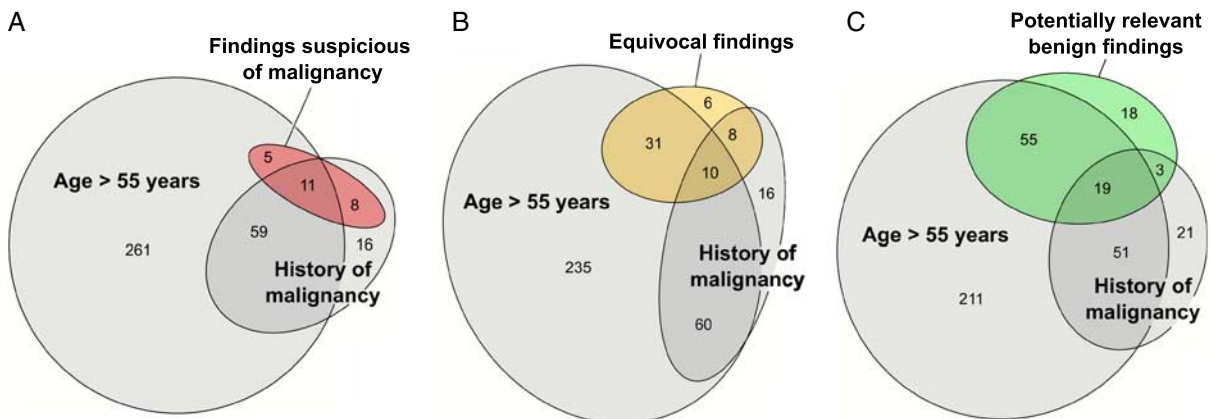
**Detection of PE**

Fifteen scans (2.9%) showed single emboli that were completely outside of the reduced range in addition to emboli within the reduced range (example in Fig. 3). Only 1 scan (0.2%) had no emboli within the reduced range. In this scan a single, subsegmental embolus in the apical segment of the right upper lobe was detected, which would have been missed in a reduced range scan (Fig. 4). The resulting sensitivity of CT-PA with the reduced scan range was 99.81% (95% confidence interval: 98.74%-99.99%) for detecting any PE.

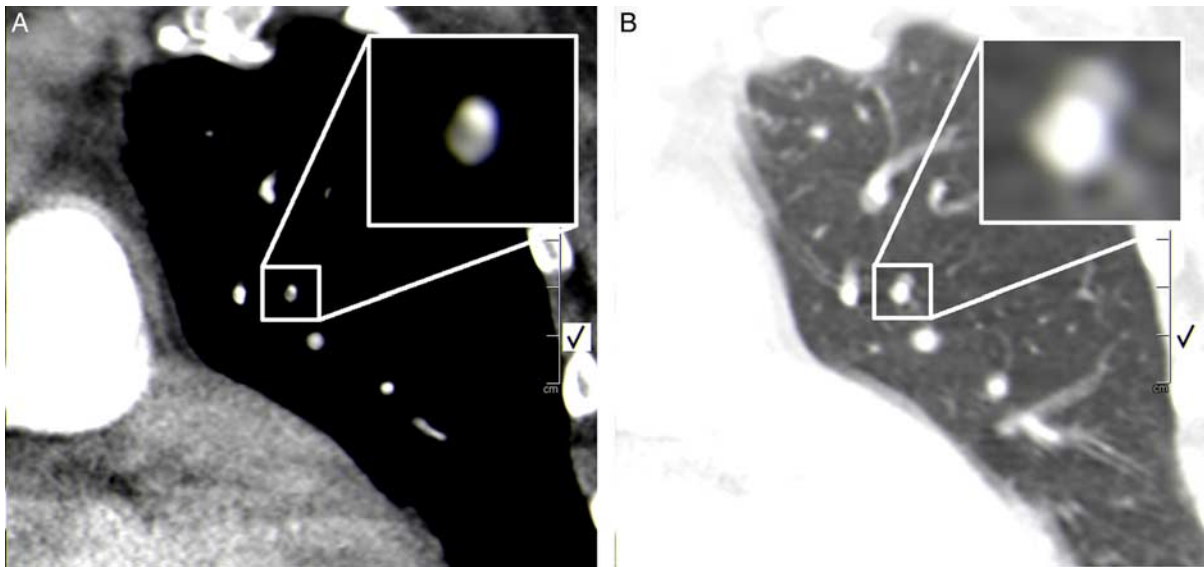
A more detailed analysis of thrombus location allowed additional estimation of sensitivities for PE at different positions of the cranial and caudal boundary slice. Putative sensitivities of different positions of the cranial boundary slice in relation to the upper edge of the aortic knob are displayed in Figure 5A; putative sensitivities of caudal boundary slice positions in relation to the lower hemidiaphragm are displayed in Figure 5B.

**Incidental Findings**

In addition to PE, incidental findings may also potentially be missed when scanning with a reduced range. Irrelevant benign findings were detected outside the reduced range in 181 (36.6%) scans, benign but potentially relevant findings in 95 (19.2%) scans, equivocal findings in 55 (11.1%) scans, and findings suspicious for malignancy in 24 (4.8%) scans. Multiple logistic regression including the



**FIGURE 6.** Missed incidental findings. Euler diagrams illustrating the frequency of incidental findings outside the reduced range (colored ellipses) in subgroups stratified by age and history of malignancy. Total n = 495. A, Findings suspicious of malignancy. B, Equivocal findings. C, Potentially relevant benign findings.



**FIGURE 7.** Example of a pulsation artifact that was initially reported as PE. A, Apparently reduced contrast in a subsegmental artery of the anterior segment of the left upper lobe. B, Using a lung window a doubled contour of the vessel becomes visible. This is a typical pulsation artifact that can explain the finding. full color online

independent variables such as age, sex, C-reactive protein, hospitalization, and history of malignancy showed prediction of missed relevant benign findings by age ( $P=0.004$ ), prediction of missed equivocal findings by history of malignancy ( $P=0.006$ ) and age ( $P=0.045$ ), and prediction of missed malignant findings by history of malignancy ( $P<0.001$ ). Considering the latter, only 7 scans (1.4%) had likely malignant findings outside the range that would prompt further investigation. In those, only 2 (0.4%) had no prior history of malignancy. Stratifying the cohort into those without a history of malignancy and age younger than 55 years resulted in no missed malignant findings in this subgroup (Fig. 6).

## DISCUSSION

Our study illustrates the potential of a shortened scan range in CT-PA for effectively reducing radiation exposure while causing no significant loss of sensitivity. We provide data that forms a basis for aiding the selection of an appropriate CT-PA protocol. Especially in radiosensitive populations, the use of CT-PA with a reduced scan range appears justified for the exclusion of PE.

Mean scan length was almost halved using the proposed boundaries at the upper edge of the aortic knob and the lower hemidiaphragm. Other studies have investigated the extent of scan length reduction with a variety of scan margin definitions. Using the top of the aortic arch and the lower border of the heart (which is generally more caudal than the top of the lower diaphragm), Kallen et al<sup>10</sup> could reduce the scan length by 37%, and Shahir et al<sup>11</sup> reduced the scan length by 43% with a similar approach in a cohort of pregnant patients. With a fixed scan length positioned in relation to the carina, Atalay et al<sup>8,17</sup> could reduce z-axis coverage by 47% to 49%.

Importantly, as an effect of overranging and tube current modulation, the applied radiation dose is not a strictly linear function of scan length. Tube current

modulation deliberately increases radiation dose at the shoulder and abdominal regions, sections that are in large part cut off by reducing the scan length. On the contrary, the relative contribution of overranging to total radiation dose increases with shorter scan length.<sup>18</sup> In our study, estimated radiation dose would be reduced by an average of 48%, which is substantial. A previous study<sup>11</sup> found an even larger reduction in DLP, which was, however, likely overestimated, because the calculations presented did not account for the effects of overranging on reported DLP. In comparison to the overall reduction of radiation exposure, the effect of a shorter scan length on the organ dose of the breast tissue may be less pronounced as the breast may be located entirely or partially inside the reduced scan range, depending on individual anatomy.

Not surprisingly, radiation dose varied widely between the different scanners used in our study.<sup>19</sup> The older generation scanner (Aquilion 64) applied 3 to 4 times the dose of the newer, latest-generation scanners (Revolution CT, SOMATOM Force) with optimized low-dose protocols and improved reconstruction techniques. Still, with a given hardware, we showed that significant dose reduction is possible by such simple means as optimizing the scan range.

Considering the therapeutic consequences, it is essential that CT-PA can distinguish between PE-positive and PE-negative patients. This decision requires the detection of at least 1 embolus, not necessarily all emboli present. Thus, as shown in our data, the rare occurrences of missed subsegmental emboli at the lung base or apex were mostly irrelevant, because additional emboli were present toward the center of the scan. Only in 1 scan a solitary subsegmental embolus was located outside the reduced scan range. Of note, the management of isolated subsegmental PE is still subject to debate, due to conflicting evidence on the benefits and harms of anticoagulation therapy in these cases.<sup>7,20,21</sup> Therefore, the relevance of such a finding is questionable. Moreover, subsegmental PE is frequently overdiagnosed in clinical practice due to overinterpretation of artifacts.<sup>22</sup> This is avoided in our study by a clear definition of acute PE and

consensus reading of equivocal findings. An example of an artefact that had been reported as PE is shown in Figure 7. Previous studies did not report any cases of missed PE diagnosis with their reduced z-axis scans; however, those studies were largely limited by comparatively low sample sizes.<sup>8–12,17</sup> Overall, the sensitivity of 99.81% we found with reduced z-axis coverage was excellent. An additional analysis of sensitivities of different boundary slice positions showed that the prespecified positions were appropriate and sensitivities continuously dropped as the boundaries moved toward the scan center.

An argument favoring the coverage of the entire lung is that a reduced scan range has the potential for missing incidental findings frequently found on CT-PA.<sup>23</sup> Although we found a relatively large prevalence of incidental findings outside the reduced range, most of these were of limited clinical relevance. Still, some were suggestive of malignancy or might have had potential clinical relevance. Therefore, to reduce the risk of missing pertinent findings in patients scanned with a reduced scan range, application of pre-selection criteria appears prudent. The simple criteria of age younger than 55 years and no history of malignancy enabled the exclusion of all scans with a potentially missed malignant finding. Benign findings classified as potentially relevant mostly included small pleural effusions or areas of pulmonary infarction at the lung bases. Additional similar findings (eg, other areas of pulmonary infarction) were often identified within the reduced scan range, meaning that the use of the reduced range in these cases had no impact on clinical management. A previous study that additionally included PE-negative scans found a much lower prevalence of pertinent findings outside a reduced scan range,<sup>17</sup> suggesting that the prevalence of such missed findings may be overestimated in our cohort. However, our study's focus was not on incidental findings but on the sensitivity for the detection of PE.

Concerning radiation dose with respect to incidental findings, some clinically inconclusive cases may still require a subsequent full range CT of the chest, which will result in an increased overall radiation exposure in these patients. Although the proportion of these additional scans cannot be evaluated from our retrospective data, we believe this would affect a minority of cases. Conversely, fewer incidental equivocal findings in reduced range scans may potentially lower the need for further imaging or follow-up examinations.

This is the largest study to date investigating the sensitivity for detecting PE of CT-PA with a reduced scan range, applying simple scan boundary definitions. Previous studies were too small to provide exact figures on sensitivity and did not report any missed emboli. We additionally highlighted differences in radiation dose between different scanner generations, including up-to-date technology. Limitations of the study included the retrospective nature of the analysis and the fact that all analyses were done on full range scans, which may have affected the classification of findings that appeared only in the volume at the boundary slice. However, slice definitions were clear and were per protocol defined on the topogram before analysis of actual CT data. The prevalence of incidental findings may be biased, as we analyzed only patients with PE, who may have a different prevalence of comorbidities compared with PE-negative patients. Our reported numbers for radiation dose reduction rely on estimates, as measurement of true dose differences would have required scanning patients twice with 2 different scan lengths. Still, the estimates used (prescan dose indices) are reasonably accurate.<sup>24</sup>

In conclusion, a reduced scan length in CT-PA ranging from the top of the aortic arch to the top of the lower hemidiaphragm would substantially decrease the scan's radiation dose while maintaining diagnostic accuracy for the detection of PE. This approach appears justified especially in young patients referred for CT-PA to rule out PE.

## ACKNOWLEDGMENTS

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