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CHAPTER 6

The association of deep-vein thrombosis load and severity of arterial obstruction in patients with pulmonary embolism

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ABSTRACT

Background

Pulmonary embolism (PE) originates from a thrombus elsewhere in the body. The aim of our study was to assess whether the extent of the remaining thrombus is related to PE severity.

Design and methods

56 CT scan-confirmed PE patients were enrolled in the study. Obstruction severity was quantified on CT by the Qanadli score, which includes the number of affected arteries and a weighting factor for the degree of obstruction of each pulmonary artery. Furthermore, we measured right ventricle (RV) and left ventricle (LV) diameter and calculated the RV/LV ratio as a second marker for PE severity. We used total body Magnetic Resonance Direct Thrombus Imaging to assess the extent of DVT, expressed as the number of occluded veins and thrombus length.

Results

Mean age of patients was 50 years (range 18-75). Mean Qanadli score was 20% (range 3-50). In 25 PE patients (45%), a thrombus was present on MRI. Median thrombus length was 21 cm (range 3-106). Obstruction in the lungs was more severe in those with DVT than in patients without demonstrable DVT. Also, increasing thrombus length and number of occluded veins were positively related to pulmonary obstruction.

Conclusions

Our results show that the severity of PE was related to DVT status and its extent as measured on MRI.

INTRODUCTION

Pulmonary embolism (PE) has an incidence of 0.5 per 1000 person-years, and is one of the common causes of cardiovascular death.[1] The mortality rate of acute PE (10% at one month, 15% at three months), exceeds the mortality rate of acute myocardial infarction.[1,2,206]

There are several methods to quantify the severity of a PE, such as clinical characteristics (i.e. hemodynamic instability), biomarkers (such as Brain Natriuretic Peptide (BNP) and pro-BNP) and imaging. The latter includes the right ventricle/left ventricle diameter ratio (RV/LV ratio) to assess right cardiac failure measured on CT pulmonary angiography (CTPA), and embolus load according to the method of Qanadli.[207] The Qanadli obstruction score has been designed as a PE severity index based on images obtained by CTPA scanning. Embolus load in pulmonary arteries affects right ventricular dilatation and even more so, predicts patient outcome and mortality.[208] A RV/LV ratio larger than one has been shown to be predictive for mortality at three months.[99]

What remains controversial, is whether the presence and extent of deep-vein thrombosis (DVT), affects PE severity.[10,11,209,210] Therefore, we aimed to assess whether thrombus extent, represented by thrombus length and the number of occluded veins measured on MRI, is related to PE severity. PE severity was assessed in two ways: as pulmonary vascular obstruction and as RV/LV ratio.

Another question that remains unanswered is why in PE patients that were systematically screened for DVT with compression ultrasonography or contrast venography, no thrombus was found in 20 to 50%.[11,210] In a necropsy study, 40% of PE patients had no DVT detected during the postmortem examination.[192] This leads to questioning whether all 'PEs' are indeed emboli from a DVT in the extremities. Recent studies suggested that not all dots seen on a CTPA are clots and concluded that in PEs without a concomitant DVT on ultrasonography, mostly subsegmental PE was seen.[193,211,212] Therefore, we assessed all CT images of PE patients to quantify whether the emboli were only present in a large artery, i.e. central PE, or in more peripheral arteries, segmental and subsegmental. We hypothesized that a local origin of a pulmonary clot would be more likely to give small, (sub)segmental clots than one that embolized from a DVT.

DESIGN AND METHODS

Patient enrollment

From November 2008 until July 2010, 56 consecutively diagnosed PE patients from the Leiden University Medical Center were enrolled in the study. Approval for this study was obtained from the Medical Ethics Committee of the Leiden University Medical Center. All participants provided written informed consent according to the Helsinki declaration.

Inclusion criteria were age above 18 years, a first PE, and a CTPA confirmed diagnosis. Exclusion criteria were inability to give informed consent, a history of DVT, and contraindications to undergo MRI scanning. Contraindications were the presence of a pacemaker, claustrophobia, and high body weight impeding fit within the diameter of the gantry. Patients were asked to undergo a total body MRDTI scan within one week after diagnosis.

CTPA

CTPA was performed in the same hospital for all 56 patients. CT scans were performed on either a 16-slice CT scanner, a 64-slice CT scanner or on the 320-slice Aquilion One dynamic volume CT scanner (Aquilion 16CFX, Aquilion 64, Aquilion 320; Toshiba Medical Systems, Otawara, Japan). Both ECG-triggered and -untriggered acquisitions were included in the study, this was described on the study form. Data acquisition was done every 0.5 mm and images were reconstructed to a thickness of 3 mm. For every CT scan, the observers documented the degree of technical adequacy. The score ranged from 1 (technically inadequate) to 4 (technically adequate); via 2 (technically poor), and 3 (technically moderate). In addition, observers had the possibility to describe specific reasons for images to be of inadequate technical quality, such as poor arterial opacification or breathing artifacts. As in the original article by Qanadli, images were assessed only in the transversal plane, meaning that no 3D reconstructions were performed.

The CTPA scans were scored according to the CT index by Qanadli et al.[207] by two independent observers (E.M.C.V. and S.F.). The Qanadli index includes not only the number of affected arteries, but also a weighting factor for the degree of obstruction of each vessel, i.e. partial or complete. The score is based on:

- Pulmonary arterial anatomy of 10 segmental arteries right and 10 left
- Complete obstruction = 2 points, partial = 1 point
- Maximum total CT obstruction index = 40, maximum of 20 points per lung.
- Percentage of vascular obstruction per patient: (patient score/40) x 100

In addition, the RV/LV ratio was calculated for all PE patients. A ratio of >1.0 was considered indicative for right ventricle dysfunction.[99,213] Measurements of RV/LV diameter ratio were independently performed on axial pulmonary CTPA images by the two observers on the same day they determined the CTPA obstruction score. The short axis of the right ventricle was measured from inner wall to inner wall at the widest point at the level of the tricuspid valve, typically in the basal third of the ventricle. The short axis of the left ventricle was measured from inner wall to inner wall at the widest point at the level of the mitral valve, also typically in the basal third of the ventricle as described by Chae et al.[214]

MRDTI scan

A validated, relatively new technique in diagnosing DVT is Magnetic Resonance Direct Thrombus Imaging (MRDTI).[13,125,189] It is a non-invasive technique without the need of contrast or radiation. Thrombosis can be objectively made visible from calf veins up to subclavian veins. Unlike other imaging techniques (e.g. contrast venography) MRDTI shows the thrombus itself and suppresses the background. The mechanism of MRDTI is based on the transformation of hemoglobin into methemoglobin when a thrombus is formed. Using a T1-weighted 3D gradient echo sequence, the methemoglobin in the thrombus gives a high signal that disappears after about 6 months.[125] Kelly et al. found a sensitivity of 98% and a specificity of 96% for MRDTI compared to ultrasound/venography in 101 patients with symptomatic DVT.[13]

The MRDTI scanning protocol has been described in more detail elsewhere.[190] In brief, patients underwent a total-body 1.5 Tesla MRI scan without contrast enhancement. The extent of DVT was quantified on MRDTI images in two ways. First, the number of occluded veins was counted and the anatomical location described. Second, the length of the occluded veins was measured in centimeters on MR images in the coronal plane. Two radiologists, both with more than 3 years of MRI experience (A.S. and C.J.v.R.), scored the MRDTI scans together by means of consensus. Both observers were blinded to CTPA findings.

Analyses

Mean PE obstruction scores from the two observers were calculated for the number of affected veins on MRDTI images to determine if there was a relation between PE severity and the extent of thrombus in the legs. Extensiveness of thrombi was also described by measuring thrombus length in centimeters. Furthermore, the presence of proximal versus distal thrombosis on MRDTI images was related to mean PE obstruction scores. Proximal involved all veins above and including the popliteal veins. Distal involved the calf veins. In addition, these three estimates of thrombus extent were calculated with RV/LV ratio as an outcome. Vital status was ascertained through community registries at three months after PE diagnosis.

Linear regression analyses were performed, including number of occluded veins and thrombus length as independent variables, and Qanadli score as outcome. Regression coefficients for each analysis were presented with their 95% confidence intervals (CIs). For the outcome RV/LV ratio, we used the clinical cut off for an RV/LV ratio larger than one, versus below or equal to one. We performed logistic regression analyses with the number of occluded veins and thrombus length as independent variables. Odds ratios were presented with 95% CIs.

To evaluate agreement between the two radiologists that performed the Qanadli scores, we calculated the limits of agreement according to the method of Bland-Altman.

Two limits of agreement are depicted around the mean, and 95% of measurements are expected to be in between these limits (the mean of the differences plus or minus 2 SD).[179] Cohen's Kappa was calculated for RV/LV ratio, with one as the cut off value.

Finally, we studied all patients with and without a DVT on MRI, and specified their location of PE as either central PE, or peripheral PE. Central was defined as a saddle embolus or an embolus in either the right or the left pulmonary artery. Peripheral PE was defined as all PEs that were not central, and contained emboli in segmental or subsegmental arteries. If patients had a central PE, the Qanadli scoring method stopped by definition, instead of measuring possible segmental or subsegmental defects. This is because of the idea that more proximal vessels are leading in the obstruction score and determine its maximum. For this analysis we only included patients on which the radiologists fully agreed regarding the level of PE, i.e. PE confined to the (sub)segmental level or central PE.

RESULTS

We enrolled 56 patients with a CTPA proven PE in the study. Mean age was 50 years (range 18 to 75). There were more male participants in the study than female participants, in a ratio of two to one. The baseline characteristics of all patients are presented in Table 1. The duration of complaints varied between 0 to 105 days. One out of four patients had an active malignancy at the time of PE diagnosis. We assessed whether patients received the PE diagnosis during hospitalization, and this was the case in 25% of patients. In these 56 patients, the mean duration from CT to MRI was 5.6 days (range 1-10). Overall, 47 patients underwent the MRI scan within 7 days, and 9 patients underwent the MRI between day 7 and day 10.

MRI results are shown in Table 2. In 25 patients (45%), a thrombus was found on MR images. Most thrombi were present in the left lower extremity (68%). 40% of patients had a DVT in a single vein, whereas 60% had two or more veins filled with thrombus. Median thrombus length on MRI was 21 cm, ranging from 3 to 106 cm. 9 of these 25 patients had an isolated distal thrombosis of the calf veins (including 3 with superficial vein thrombosis), versus 16 with a proximal DVT.

37 CTs (66%) were performed on the 64-slice CT scanner and 18 (32%) on the 320-slice CT scanner. One CT (2%) was performed on the 16-slice CT scanner. There was only one patient that had an ECG-triggered CT scan. Radiologist A had a mean technical adequacy score of 3.6 (range 2-4) and radiologist B also had a mean of 3.6 (range 1-4). As a reason for technical inadequacy in the only patient with a score of 1, poor arterial opacification was given.

The median Qanadli obstruction score in these patients was 17% (interquartile range (IQR) 9-29). For radiologist A, the median obstruction score was 18% (IQR 10-35), whereas radiologist B had a median score of 13% (IQR 8-23).

Table 1. Baseline characteristics of PE patients

	PE patients N=56
Age (mean in years, range)	50 (18-75)
Sex	
male	37 (66%)
female	19 (34%)
BMI (mean in kg/m^2, range)	26 (16-37)
In hospital patients at the time of diagnosis	14 (25%)
Duration of complaints (median in days, range)	2 (0-105)
Presence of malignancy	15 (27%)
Time from diagnosis to MRI (mean in days, range)	5.6 (1-10)

Table 2. MRDTI data for the PE patients

	Total N=56 n (%)
No thrombus on MRI	31 (55)
Thrombus present on MRI	25 (45)
Right leg DVT	5 (20)
Left leg DVT	17 (68)
Bilateral DVT	3 (12)
1 vein	10 (40)
2 veins	5 (20)
3 veins	2 (8)
4 veins	3 (12)
5 veins	4 (16)
6 or more veins	1 (4)
Proximal DVT	16 (64)
Distal DVT	9 (36)

The median RV/LV ratio was 0.87 (IQR 0.80-1.0) for both radiologists. Radiologist A had a median ratio of 0.88 (IQR 0.80-1.0) and radiologist B had a median ratio of 0.85 (IQR 0.75-0.99). 12 patients (21%) had a RV/LV ratio larger than 1, meaning enlargement of the right ventricle indicative of a decrease in right heart function. Patients with a RV/LV ratio above one had an over 2-fold higher median Qanadli score (33%, IQR 12-49) than those with a RV/LV ratio smaller than or equal to one (14%, IQR 8-23).

Table 3 shows the Qanadli scores (of two radiologists combined) for patients with (29%, IQR 17-37) and without a thrombus on MRI (10%, IQR 6-21). For the group of PEs with a thrombus on MRI, further comparisons were made of Qanadli scores with thrombus characteristics. Qanadli scores were 2-fold higher for patients with a thrombus length above 10 cm versus below or equal to 10 cm, and for a thrombus present in 2 or more veins as compared to in one vein only. Patients with proximal thrombi had a median Qanadli score of 31% (IQR 24-42), whereas patients with distal thrombi had a Qanadli score of 17% (IQR 14-29). Similar results were found when radiologist A and B were assessed separately (see Appendix). A linear regression model with the number of occluded veins and the Qanadli score as outcome resulted in a regression coefficient of 4.5 (95% CI 2.7-6.4), which implies an increase of 4.5 points in Qanadli score per extra occluded vein on MRI. The regression coefficient for thrombus length was 0.28 (95% CI 0.12-0.43), meaning an increase of 0.28 in Qanadli score per added centimeter thrombus length.

Thrombus extent had no consistent effect on RV/LV ratio (see Table 3). We found no dose-response effect for the number of occluded veins, as we did for Qanadli score. Thrombi of more than 10 cm had a higher median RV/LV ratio (0.94, IQR 0.85-1.30) than thrombi below or equal to 10 cm (0.88, IQR 0.77-1.18). For number of occluded veins, we found an OR of 1.1 (95% CI 0.79-1.6) for patients with a RV/LV ratio larger than one versus below or equal to one. For thrombus length the OR was 1.0 (95% CI 0.97-1.0). Overall, we found no increased risk of thrombus extent on a RV/LV ratio larger than one, versus below or equal to one.

Of the 56 enrolled patients, two patients died within the first 3 months (4%). Both patients had a proximal DVT in 2 or more veins, with a thrombus length of more than 10 cm.

We assessed agreement in Qanadli score between the two radiologists and found a mean difference of 5.64 with SD 8.49. This made that the 95% limits of agreement ranged from -11.0 to 22.3. Cohen's Kappa for RV/LV ratio above one versus below or equal to one was 0.6 (i.e. moderate agreement).

To answer the question on central versus peripheral PE and the presence of DVT, we included all patients that the radiologists fully agreed on according to the definition of central and peripheral PE. This left 44 patients (79%) out of the total of 56. 4 out of 44 (9%) patients had a central PE, and 40 out of 44 had a peripheral PE (91%). Of those with central PE, 3 out of 4 patients (75%) had a DVT on MRI. Of the 40 patients with peripheral PE, 19 (48%) had a DVT on MRI (see Table 4).

The rows in Table 4 illustrate the location of PE by DVT status on MRI. Of the 22 patients without DVT, only one had a central PE (5%). The other 21 patients had a non-central PE (95%). In the 22 patients with DVT on MRI, a central PE was found in 3 (14%), whereas a peripheral PE was present in 19 (86%).

As for the side of PE, the right lung was affected in 9 patients (16%), while PE in the left lung was seen in 3 (5%). 42 patients had a bilateral PE (75%) and 2 (4%) had a saddle embolism.

Table 3. Thrombus extent on MRI related to Qanadli obstruction score, RV/LV ratio, and mortality at 3 months after CTPA as measures of PE severity.

	N= 56	Qanadli score (median (%), IQR)	RV/LV ratio (median, IQR)	Deceased at 3 months N (%)
0 veins occluded	31	10 (6-21)	0.86 (0.80-0.93)	-
1 vein occluded	10	17 (11-27)	0.95 (0.77-1.21)	-
≥ 2 veins occluded	15	31 (24-42)	0.92 (0.85-1.30)	2 (13)
Thrombus length ≤ 10 cm	11	16 (9-34)	0.88 (0.77-1.18)	-
Thrombus length > 10 cm	14	31 (24-39)	0.94 (0.85-1.30)	2 (14)
Distal DVT (calf veins)	9	17 (14-29)	0.95 (0.79-1.14)	-
Proximal DVT	16	31 (24-42)	0.88 (0.79-1.29)	2 (13)

IQR: interquartile range

Table 4. Central versus non-central (segmental and subsegmental) PE in 44 patients related to DVT status on MRI

DVT status on MRI	PE location Central N (%)	Non-central N (%)
PE without DVT N=22	1 (5%)	21 (95%) segmental 17 (77%) subsegmental 4 (18%)
PE with DVT N=22	3 (14%)	19 (86%) segmental 12 (54%) subsegmental 7 (32%)
Total N=44*	4 (9%)	40 (91%) segmental 29 (66%) subsegmental 11 (25%)

(* PE location divided into three levels: central, segmental and subsegmental. Both radiologists agreed on the levels of occlusion in 44 patients.)

DISCUSSION

We studied 56 PE patients to assess whether peripheral thrombus extent on MRI was related to the severity of pulmonary arterial obstruction on CT. Our main finding was that Qanadli score was related to DVT extent on MR images. The extent of DVT was quantified in several ways, and findings were consistent for the number of affected veins, thrombus length, and location of DVT (proximal versus distal). Moreover, we found a dose-response relation for the number of veins and the severity of PE, expressed as Qanadli score.

Thrombus extent was not consistently related to RV/LV ratio in this study. We did see an association for thrombus length and RV/LV ratio. We had expected to see a positive association for all markers of thrombus extent with RV/LV ratio, as the latter was previously shown to be related to Qanadli score ($r = 0.66$[214] and $r = 0.49$[215]), however the correlation was not strong in these studies. In our study the r was similarly weak (0.56). There was no clear explanation for the absence of a stronger relation in our data.

The finding that PE severity is associated with a more extensive thrombus load does not support the hypothesis of frequent total embolization of a DVT to the pulmonary arteries. This has been proposed as an explanation for the failure to find DVT in a substantial proportion of patients with PE. In case of complete embolization, patients without a DVT would have a higher thrombus load in the lungs, and a higher percentage of obstruction (Qanadli score) than patients with a DVT. This is opposite to what we found (Table 3).

This is the first study that we know of that related thrombus extent, measured by a MRI technique, to the severity of PE quantified by Qanadli score and RV/LV ratio on CTPA. Our findings are in agreement with the findings of Girard and colleagues,[210] who performed bilateral contrast venography in 213 PE patients. To quantify pulmonary obstruction, they applied the Miller score (designed to assess PE on pulmonary angiography images). Mean pulmonary vascular obstruction in their study was lower in patients without DVT, than in patients with DVT (37.6 +/- 20.9% vs 48.4 +/- 21.7%; p = 0.007).[210]

Ouriel et al. assessed 885 DVT patients, of whom 32 were diagnosed with PE.[216] A DVT clot score was developed to quantify DVT severity. A higher DVT clot score was found in patients with a concomitant PE (mean 9.6; 95% CI 7.2-12.0), than in patients without a PE (mean 7.7; 95% CI 7.2-8.2). These data are not directly comparable to our data, but the main findings are in accordance to the idea that more extensive DVT leads to PE rather than less extensive DVT.

Different results were shown by Ghaye et al. in a study including 110 patients suspected of either PE or DVT.[209] In the PE group (n=66), 83% of patients was found to have a DVT. The mean Qanadli score in this study was 10%. This low score may have been due to the use of single-detector row CT scanners, which do not give enough detail to assess subsegmental arteries. DVT clot load, assessed on CT venography, was only weakly linked to PE clot load (Spearmans correlation coefficient of 0.5 for both DVT clot load scores correlated to the Qanadli score). We found no other studies that assessed both DVT thrombus extent and PE severity by the Qanadli score.

A cohort study from Spain showed that in PE patients a concomitant DVT was an independent predictor of death at 3 months after diagnosis.[11] The authors conclude by advising assessment of the DVT burden for further risk stratification of patients with acute PE. Accordingly, in our study we found that the presence of a DVT in PE patients was related to short term mortality at 3 months.

As for the question on whether the distribution of PE is related to DVT status, we found that of patients with a DVT on MRI 14% had central PE, and 86% had segmental or subsegmental PE. For PE patients without DVT on MRI, only 5% had central PE, and 95% had (sub)segmental PE. As the number of patients with central PE was small, we were reluctant to draw conclusions based on these data. In addition, if our hypothesis that stated "local PE is often seen in patients without a DVT of the legs" were to be confirmed, we had expected to find most patients without DVT in the subsegmental PE group, fewer in the segmental PE group and the least in the central PE group (i.e. an inverse dose-response relation). Our results showed that 77% of patients without a DVT had a segmental PE, and 18% had a subsegmental PE. In summary, the pattern of embolization to the lungs seemed to be unrelated to DVT status in this study.

This study has limitations. The agreement between radiologists on the Qanadli score was moderate, with the 95% limits of agreement ranging from -11 to 22. This moderate agreement could be due to the difference in CT assessment in the clinical setting, as compared to the study setting. To decide on treatment, the exact localization of PE is not relevant. In this study, it was important to describe PE location in great detail and that could be the reason for the wide spread in Qanadli obstruction scores of the two observers. From the radiologists' median Qanadli scores, we could interpret that radiologist A had systematically higher scores than radiologist B. (see Appendix)

Another limitation was that the analysis on central versus peripheral PE contained a small number of people. Due to differences in what the radiologists called segmental or subsegmental, not the entire patient group could be included in this analysis.

In conclusion, we found a positive association between the percentage of obstruction of the pulmonary arteries as a marker of PE severity, and the extent of DVT on MR images. The MRDTI technique is an easy and relatively fast imaging modality to assess DVT extent, including the calf veins. However, ultrasonography for the assessment of thrombus load might be an option. In the clinical setting, knowledge of the presence and extent of a DVT in a patient with PE could add information to a doctor's risk stratification analysis.