Computed Tomography Angiography Findings in Pulmonary Embolism Patients Vary Following Thrombolytic Treatment

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ABSTRACT: **Background:** Pulmonary embolism (PE) is the third most frequently occurring cardiovascular disease. However, the clinical presentation in patients with PE is variable.

Objectives: To evaluate the prevalence of radiological findings detected in contrast-enhanced computed tomography angiography (CTA) and their significance in patients with PE; and to assess whether the CTA findings differed in patients receiving tissue plasminogen activator (tPA) therapy from those who did not.

Methods: We retrospectively reviewed CTA scans of 186 patients diagnosed with acute PE. Incidental findings on CTA scan were assessed, including mediastinal and parenchymal lymph nodes, pleural effusion, space-occupying lesions, consolidations, emphysema, and pericardial effusion.

Results: Patients receiving tPA (19.9%) were less likely to have pleural effusion (29.7% vs. 50.3%, $P = 0.024$). Other CTA findings did not differ between the tPA and non-tPA groups, including lung infiltrates (40.5% vs. 38.9, $P = 0.857$), space-occupying lesions (5.4% vs. 6.7%, $P = 1$), pericardial effusion (8.1% vs. 8.7%, $P = 1$), emphysema (21.6% vs. 17.4%, $P = 0.557$), lung (18.9% vs. 24.2%, $P = 0.498$), and mediastinal (24.3% vs. 25.5%, $P = 0.883$) lymph nodes, respectively.

Conclusion: The prevalence of pleural effusion (unilateral or bilateral) was higher in patients not treated with tPA. Therefore, in patients with a borderline condition, the presence of pleural effusion could support the decision not to give tPA treatment.

IMAJ 2019; 21: 203–207

KEY WORDS: computed tomography angiography (CTA), pleural effusion, pulmonary embolism (PE), prognostic features, respiratory medicine

Venous thromboembolism (VTE) encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE) [1]. It is the third most frequent cardiovascular disease, with an annual incidence of 100–200 per 100,000 inhabitants [2,3]. The clinical presentation varies greatly – from an incidental finding in asymptomatic patients [3] to sudden cardiac death in others [4,5]. Hence, it is of great importance to diagnose PE and to assess its severity since thrombolytic therapy is usually given only to the massive PE cases, while the anticoagulant treatment is usually given to the sub-massive ones.

The PE severity index (PESI) score is based on clinical parameters and is a useful prognostic tool for assessing the 30-day mortality risk in patients with PE [6]. However, it is composed entirely of clinical parameters (e.g., age, gender, malignancy, congestive heart failure, chronic pulmonary disease, tachycardia, blood pressure, etc.).

Computed tomography angiography (CTA) has emerged as the gold standard for PE diagnosis [7]. The CTA allows evaluation of lung parenchyma and the pleural space. As a result, incidental findings such as consolidations, atelectasis, pleural and pericardial effusions, enlarged lymph nodes, and space-occupying lesions [8] might appear in CTA scans regardless of a PE diagnosis. Nevertheless, little is known about the relation between these radiological findings and PE severity using the common parameters.

Qanadli et al. [9] proposed a CT severity index score to evaluate PE severity according to these parameters (i.e., the PE obstruction index). The score was defined as an assessment of clot burden and correlated well with pulmonary angiography indices. Various trials [10-12] found correlations between the proposed score and the clinical outcomes in patients with PE. Others investigated pleuro-parenchymal findings in these patients [13]. Recently, Atasoy et al. [14], whose work included patients with non-severe PE (without hemodynamic compromise), found that the presence of parenchymal findings plus a high PESI score correlated with poor prognosis. Moreover, they

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examined clinical and radiological parameters associated with 1-month mortality in patients with mild (hemodynamically stable) PE. They found that the sPESI score, consolidations, and peripheral wedge-shaped opacities were significantly related to mortality, while the cardiovascular CT parameters and the clot burden were not. Hence, in the hemodynamically stable patients, PE severity assessment is based upon a combination of the PESI score, cardiac troponin, and right ventricular (RV) function.

Thrombolytic therapy is widely accepted for massive pulmonary embolism (PE) due to the high mortality risk associated with standard anticoagulation alone [15]. Its role in sub-massive PE, however, has remained controversial.

The prevalence of incidental findings in patients treated with primary reperfusion therapy compared with those who did not receive such treatment has yet to be examined. In this study, we assessed the prevalence of radiological findings in CTA and their significance in patients with PE according to whether or not they received thrombolytic (tPA) therapy.

PATIENTS AND METHODS

STUDY GROUP

The retrospective study group consisted of 204 patients aged 18 years and older. Patients recruited to the study were those diagnosed with PE at Meir Medical Center from June 2009 to July 2015. The diagnosis was based on CTA in 186 of the cases and on ventilation/perfusion scans in 18. Only patients diagnosed through the CTA scan were included.

DATA COLLECTION

Epidemiological parameters retrieved from the electronic medical records included age and gender; background diseases including malignancy; previous VTE; chronic heart, lung or kidney diseases; immunosuppression; diabetes, alcoholism, and cirrhosis. Clinical parameters (blood pressure, oxygen saturation, heart rate, and need for mechanical ventilation), laboratory data [creatine phosphokinase (CPK) and troponin levels] and imaging parameters (i.e., CTA and echocardiography) were also recorded.

CT ANGIOGRAPHY

Radiological assessment included right and left ventricular diameter, right-to-left ventricular diameter ratio, pulmonary artery diameter, ventricular septum protuberance, and inferior vena cava contrast reflux. For the purpose of this study, each CTA was evaluated independently by two radiologists. CT parameters were collected using multiplanar reformatted four-chamber views from the pulmonary CTA data. Incidental findings on the CTA scan including mediastinal and parenchymal lymph nodes, pleural effusion with size and type (transudate/exudate), space-occupying lesions, consolidations, emphysema, and pericardial effusion were evaluated.

ECHO-DOPPLER STUDY

Cardiology assessment included right ventricular size and function. Pulmonary arterial pressure (PAP) was calculated as the sum of the tricuspid regurgitation gradient and estimated right atrial pressure. Maximum tricuspid regurgitation velocity (taken from all available views) was measured by continuous-wave Doppler echocardiography to evaluate the pressure gradient from the right ventricle to the right atrium.

THROMBOLYSIS PROTOCOL

Thrombolysis treatment consisted of intravenous (IV) administration of 100 mg thrombolytic therapy (tPA) (alteplase, Actilyse ®, Boehringer Ingelheim, GmBH), consisting of a 10 mg bolus followed by a continuous dose of 90 mg for 2 hours.

Patients were considered for tPA treatment based on the clinical discretion of the attending physician in our department. Treatment criteria routinely included right heart failure and the existence of refractory symptoms or present/developing respiratory or hemodynamic failure.

STATISTICAL ANALYSIS

Results were expressed as mean ± SD for continuous variables. Qualitative data were expressed as percentage of patients. Nominal variables were compared using Pearson's chi-square or Fisher's exact test, each when appropriate. Continuous outcome variables were compared using Student's *t*-test. Statistical significance was defined as $P < 0.05$. Statistical analysis was performed using SPSS, version 18.0 (SPSS Inc., Chicago, IL USA).

ETHICAL AND IRB APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal informed consent was not required; however, an Institutional Review Board (IRB) approved this study.

RESULTS

TPA AND NON-TPA RECEIVING PATIENTS ARE CLINICALLY SIMILAR

The study screened 204 patients diagnosed with PE. Diagnosis was based on either CTA or ventilation/perfusion scans. However, only the patients diagnosed based on CTA were eventually included in the study (n=189). Three patients with contraindication for tPA were excluded. Mean age was 66.3 ± 16.5 years (range 20–92). These patients were divided into two groups: those who received tPA treatment (n=37) and those who did not (n=149). Patient demographics, clinical characteristics and co-morbidities of the two groups are summarized in Table 1. Interestingly, except for age, which

Table 1. Demographic and medical history data for PE patients with and without tPA treatment

Variable	No tPA	tPA	*P* value
Age	65 ± 16	72 ± 16	0.033
Gender (male)	60 (40.3%)	15 (44.1%)	0.680
Prior VTE	34 (22.8%)	12 (35.3%)	0.130
Known malignancy	44 (29.5%)	9 (26.5%)	0.723
Diabetes	34 (22.8%)	13 (38.2%)	0.063
Chronic lung disease	21 (14.1%)	8 (23.5%)	0.174
Atrial fibrillation	21 (14.1%)	2 (5.9%)	0.192
Chronic heart disease	46 (30.9%)	13 (38.2%)	0.407
Chronic kidney disease	14 (9.4%)	5 (14.7%)	0.360
Obstructive sleep apnea	2 (1.3%)	1 (2.9%)	0.508
Obesity	21 (14.1%)	1 (2.9%)	0.071
Stroke	28 (18.8%)	4 (11.8%)	0.330
Active smokers	33 (22.1%)	3 (8.8%)	0.078
Neuromuscular disease	12 (8.1%)	6 (17.6%)	0.09
Dementia/Depression	27 (18.1%)	10 (29.4%)	0.139
Known hypercoagulability	8 (5.4%)	2 (5.9%)	0.905
Hypertension	66 (44.3%)	19 (55.9%)	0.222
Collagen vascular disease	5 (3.4%)	3 (8.8%)	0.159
Thyroid disease	12 (10.4%)	3 (9.1%)	0.822

was higher in the tPA group ($P = 0.033$), there were no significant differences between the groups.

tPA-RECEIVING PATIENTS DIFFER IN LABORATORY FINDINGS RESULTS

As a next step, we compared the simplified PESI (sPESI) score [16], oxygen saturation, blood pressure, heart rate, as well as the troponin and CPK levels of those who received tPA vs. those who did not [Table 2]. We found that a greater proportion of patients receiving tPA had a significantly higher sPESI score ($P = 0.004$). Additionally, they had lower oxygen saturation ($P < 0.001$), higher heart rate ($P < 0.001$), and were less hemodynamically stable upon admission ($P < 0.001$). In addition, RV diameter, RV/LV ratio, and septal deviation were all significantly higher in patients receiving tPA ($P < 0.001$). The rate of RV dysfunction per echocardiography was 2.5 times higher among the tPA-treated patients ($P < 0.001$). Additional parameters are listed in Table 2. These findings highlight significant differences in the CT and echocardiographic findings, as well as in physical examination and laboratory findings of patients who received tPA treatment in comparison to those who did not.

COMPARISON OF CTA FINDINGS ACCORDING TO TPA TREATMENT

In order to determine whether there is a relation between tPA treatment and differences in CTA findings, we compared the CTA findings of the two groups. Indeed, patients receiving tPA were shown to be less likely to have pleural effusion ($P = 0.024$) [Table 3]. However, there were no additional statistically significant differences between the tPA and non-tPA groups regarding other CT findings, including lung infiltrates, space-occupying lesions, pericardial effusion, emphysema, and lung or mediastinal lymph nodes.

Table 2. Laboratory findings according to tPA treatment

Physical exam & laboratory data at admission			
Variable	**No tPA**	**tPA**	***P* value**
sPESI (high risk*)	93 (62.4%)	30 (88.2%)	0.004
Oxygen saturation	92 ± 5	87 ± 6	‹ 0.001
Systolic blood pressure	125 ± 20	119 ± 25	0.186
Heart rate	92.6 ± 13.7	103.35 ± 20.9	‹ 0.001
Hemodynamic instability during admission	7 (5%)	8 (24%)	‹ 0.001
Troponin	33.1 ± 75.5	35.6 ± 87	0.879
CPK	399.3 ± 1576	257 ± 617	0.644
CT findings			
RV diameter	39.7 ± 7.9	49.3 ± 6.1	‹ 0.001
LV diameter	37.4 ± 7.5	29.5 ± 9.6	‹ 0.001
RV/LV ratio	1.1 ± 0.36	1.86 ± 0.7	‹ 0.001
Septal deviation	0.79 ± 0.83	1.59 ± 0.7	‹ 0.001
PA diameter	29.5 ± 5.0	30.9 ± 3.9	0.126
Echocardiographic findings			
RV dysfunction	32.4%	84.4%	‹ 0.001
SPAP	45.9 ± 14	55.4 ± 17	0.005
LV under-filling	8.6%	38.5%	‹ 0.001
TR regurgitation	48.0%	68.0%	0.073

sPESI = simplified Pulmonary Embolism Severity Index (low risk defined as 0 points and high risk as 1 or more points, TR = tricuspid regurgitation, LV = left ventricle, RV = right ventricle, SPAP = systolic pulmonary artery pressure

Table 3. CTA-related findings according to tPA treatment

CTA findings	tPA (n=37)	No tPA (n=149)	*P* value
Pleural effusion	11 (29.7%)	75 (50.3%)	0.024
Space-occupying lesion	2 (5.4%)	10 (6.7%)	1.00
Consolidations	15 (40.5%)	58 (38.9%)	0.857
Pericardial effusion	3 (8.1%)	13 (8.7%)	1.00
Pleural lymph nodes	7 (18.9%)	36 (24.2%)	0.498
Mediastinal lymph nodes	9 (24.3%)	38 (25.5%)	0.883
Emphysema	8 (21.6%)	26 (17.4%)	0.557

DISCUSSION

Pulmonary embolism is the third most frequently occurring cardiovascular disease [17,18]. However, clinical presentation in patients with PE is variable [3-5]. Assessment of PE severity is essential for guiding treatment options, including the decision to administer thrombolytic treatment in severe cases [19-21]. In this study, we found that the absence of pleural effusion

indicates severe PE and the need for thrombolytic therapy.

To the best of our knowledge, this is the first study to assess the prevalence of related CTA findings in patients with acute PE treated with tPA compared to those not receiving tPA treatment. Most trials examined the frequency of incidental CTA findings in patients being evaluated for PE, which may prove useful in cases when the CT scan results are equivocal. However, there is sparse evidence regarding the correlation of PE severity and related CT findings. Moreover, PE severity is usually defined based on CT angiographic and not clinical parameters and may not necessarily correlate with disease severity.

In this study, we compared the group that received tPA treatment vs. those who did not. Assuming that patients on the tPA treatment represent a more severe disease, accompanied by hemodynamic instability, elevated cardiac biomarkers and RV dysfunction in echocardiography, the findings are very similar to those found by Karabulut and Kiroglu [22], although in their study the PE severity was defined based on the CTA severity index. As stated above, Atasoy et al. [14] found a prognostic correlation between clinical parameters plus CTA findings, including consolidations and wedge-shaped opacities (but not pleural effusion), and mortality. Thus, it appears that the clinical presentation in patients with PE has greater prognostic significance than the ancillary CT angiography findings.

Malignancy is also an important prognostic factor in patients with PE. Gussoni and co-authors [23] demonstrated that malignancy is associated with poor prognosis in the 3 months following diagnosis of PE. The RIETE investigation found that malignancy is a risk factor for bleeding during PE anticoagulation therapy. [24] In addition, there is evidence that D-dimer level, which is frequently used when diagnosing PE in patients considered at low risk, correlates with PE severity [25]. In this study, however, no difference was found in malignancy occurrence between patients who received the tPA treatment and those who did not.

The purpose of our study was to retrospectively identify related pleuro-parenchymal findings in the CTA scans that may correlate to disease severity. As shown in Table 3, the prevalence of pleuro-parenchymal findings in patients receiving thrombolysis was similar to that of patients not treated with tPA. However, we demonstrated the inverse correlation for the presence of pleural effusions (whether unilateral or bilateral) and the probability of tPA treatment. Previous studies [13,22] have shown that pleural effusions were not more frequent in patients with PE and those without. One possible explanation for the higher prevalence of pleural effusion in patients who ultimately were not treated with thrombolysis could be because at least some of the respiratory symptoms at presentation were due to pleural effusions, but not PE itself, while the latter may have not been considered severe according to clinical parameters. Another explanation is that pleural effusion, for unknown reasons, could represent a milder disease in patients with PE.

LIMITATIONS

Our study has some limitations. The first is the retrospective analysis design, and the second the relatively small number of patients treated with tPA. However, we included all consecutive patients who were treated according to the common practice guidelines. Therefore, we believe the results reflect our true 5-year experience with these patients.

CONCLUSION

Our study aimed to evaluate CTA-related findings in patients diagnosed with acute PE, and their prevalence among patients who received tPA treatment and those who did not, in an attempt to identify additional parameters for tPA treatment. In fact, we suggest that the prevalence of pleural effusion (unilateral or bilateral) may be greater in patients not treated with tPA.

Acknowledgments

We thank Mrs. Nava Jelin for the statistical analyses and Ms. Faye Schreiber for the English editing.

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Capsule

Impact and timing of smoking cessation on reducing risk for rheumatoid arthritis

Analysis of two large prospective cohorts found that individuals who quit smoking and maintained their non-smoking status over a long duration of time had a decreased risk of developing seropositive rheumatoid arthritis (RA). Compared with recent quitters – those who stopped less than 5 years previously – women who quit smoking ≥ 30 years previously had a 37% decreased risk of being diagnosed with RA (HR 0.63, 95%CI 0.44–0.90), according to J.A. Sparks of Harvard Medical School in Boston, and colleagues. Nonetheless, a "modestly elevated" risk was still present 30 years after stopping smoking, with a hazard ratio of 1.25 (95%CI 1.02-1.53) for all RA and 1.30 (95%CI 1.01–1.68) for seropositive RA, which suggests that "in some individuals, the immune system may be permanently altered perhaps with resultant autoimmunity established once a threshold of smoking is reached and progression to RA occurring many years later" (**Liu** et al.). Smoking has been recognized as a potentially important risk factor for RA, and particularly for seropositive disease, meaning the presence of rheumatoid factor or anti-cyclic citrullinated peptide antibodies. Smoking's influence may result from local inflammation in the lung, promotion of citrullination, impaired T cell function, and the induction of pro-inflammatory cytokines, although the precise mechanisms have not been identified. However, whether smoking cessation can influence the risk of subsequent RA has been less certain. To address this question, the authors analyzed data from the Nurses' Health Study (1976–2014) which included 117,182 women, and the Nurses' Health Study II (1989–2015) which included 113,550. Participants completed biennial questionnaires on multiple aspects of sociodemographics, health, and lifestyle (including smoking). They identified 1528 incident cases of RA, of which 63.4% were seropositive, during more than 6 million person-years of follow-up, or up to 38 years. There were more smokers in the earlier cohort (18.8% current, 35.8% former) than in the latter group (13.4% current, 21.3% former). In both groups, smokers reported more alcohol consumption and sedentary behavior. After adjustment for multiple factors including age, cohort, body mass index, physical activity, parity/breastfeeding, and income, the overall hazard ratio for RA was 1.36 (95%CI 1.22–1.53) for past smokers and 1.46 (95%CI 1.26–1.70) for current smokers. The intensity of smoking also influenced risk. Compared with never-smokers, those currently smoking 25 or more cigarettes per day had a 92% increased risk for seropositive RA (HR 1.92, 95%CI 1.39–2.66). No increased RA risk was seen for women whose smoking history was less than 10 pack-years, but those with 10 to 20 pack-years of smoking were at elevated risk for all RA (HR 1.38, 95%CI 1.17–1.64) and seropositive RA (HR 1.54, 95%CI 1.25–1.89), although not for seronegative RA. Those whose smoking history exceeded 40 pack-years had a greater risk for all RA (HR 1.83, 95%CI 1.52–2.20) and a twofold greater risk for seropositive RA (HR 2.25, 95%CI 1.80–2.82). Again, there was no increased risk for seronegative disease, "suggesting that seropositive and seronegative RA may be distinct phenotypes with distinct risk factors," the investigators noted. Limitations of the study included its inclusion of primarily white, well-educated women and the self-report of smoking.

Arthritis Care Res 2019; doi:10.1002/acr.23837

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