Lung Infarction Following Pulmonary Embolism: A Comparative Study on Clinical Conditions and CT Findings to Identify Predisposing Factors

Prädisponierende Faktoren postembolischer Lungeninfarkte: eine Vergleichsanalyse von klinischen und computertomografischen Befunden.

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Zusammenfassung

Zielsetzung: Ziel der vorgelegten Arbeit war es, begünstigende Faktoren für das Auftreten eines Infarktes zu finden.
Material und Methoden: Hierzu erfolgte eine retrospektive Analyse von 154 Patienten, bei denen zwischen Januar 2009 und Dezember 2012 anhand einer computertomografischen Untersuchung (Toshiba Aquilion 64) eine Lungenembolie diagnostiziert worden war. Die Schwere der klinischen Symptomatik wurde in 4 Gruppen unterteilt, die embolische Thrombuslast mittels eines modifizierten Miller-Scores quantifiziert. Wir korrelierten das Infarktauftreten mit verschiedenen möglichen prädisponierenden Faktoren wie demografischen Daten, Thrombuslast, dem Abstand zwischen kompletter Gefäßverlegung und der Pleura und computertomografischen Zeichen von kardialer Stauung, chronischer Bronchitis oder Emphysem.
Ergebnisse: Die computertomografische Untersuchung zeigte 78 Infarktzonen bei 45/154 (29,2 %) Patienten, wobei diese signifikant häufiger die rechte Lunge betrafen ($p < 0{,}001$). Es zeigten sich weder Korrelationen zwischen einer Infarktbildung und dem Vorliegen einer malignen Begleitdiagnose ($r = -0{,}069$), computertomografischen Zeichen der chronischen Bronchitis ($r = -0{,}109$) oder Linksherzinsuffizienz ($r = -0{,}076$), der Thrombuslast ($r = 0{,}176$) noch der Schwere der klinischen Symptomatik ($r = -0{,}024$). Eine allenfalls ganz schwache Korrelation zeigte sich zwischen Infarktauftreten und dem Lebensalter ($r = -0{,}199$). Unsere Ergebnisse belegten andererseits eine moderate negative Korrelation zwischen der Distanz von kompletter Gefäßverlegung und der abhängigen Pleura ($r = -0{,}504$).
Schlussfolgerung: Unsere Ergebnisse zeigen, dass weder Linksherzinsuffizienz oder die absolute Thrombuslast Hauptfaktoren für eine Infarktbildung sind; diese scheint hingegen im Wesentli-

Abstract

Purpose: The aim of this study was to identify factors predisposing to lung infarction in patients with pulmonary embolism (PE).
Materials and Methods: We performed a retrospective analysis on 154 patients with the final diagnosis of PE being examined between January 2009 and December 2012 by means of a Toshiba Aquilion 64 CT scanner. The severity of clinical symptoms was defined by means of a clinical index with 4 classes. The pulmonary clot load was quantified using a modified severity index of PE as proposed by Miller. We correlated several potential predictors of pulmonary infarction such as demographic data, pulmonary clot burden, distance of total vascular obstruction and pleura, the presence of cardiac congestion, signs of chronic bronchitis or emphysema with the occurrence of pulmonary infarction.
Results: Computed tomography revealed 78 areas of pulmonary infarction in 45/154 (29.2 %) patients. The presence of infarction was significantly higher in the right lung than in the left lung ($p < 0.001$). We found no correlation between pulmonary infarction and the presence of accompanying malignant diseases ($r = -0.069$), signs of chronic bronchitis ($r = -0.109$), cardiac congestion ($r = -0.076$), the quantified clot burden score ($r = 0.176$), and the severity of symptoms ($r = -0.024$). Only a very weak negative correlation between the presence of infarction and age ($r = -0.199$) was seen. However, we could demonstrate a moderate negative correlation between the distance of total vascular occlusion and the occurrence of infarction ($r = -0.504$).
Conclusion: Neither cardiac congestion nor the degree of pulmonary vascular obstruction are main factors predisposing to pulmonary infarction in patients with PE. It seems that a peripheral total vascular obstruction more often results in infarction than even massive central clot burden.

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chen durch die weit periphere Lage des thromboembolischen Verschlusses determiniert zu werden.

Kernaussagen:

- Die weit periphere Lage des thromboembolischen Verschlusses ist der wichtigste pathophysiologischen Faktor in der Infarktentwicklung.

Key points:

- A peripheral location of vascular occlusion is the main factor predisposing to pulmonary infarction.

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Introduction

Pulmonary artery embolism (PE) is the third most frequent cardiovascular disorder potentially leading to death [1, 2]. Besides acute right heart failure, lung infarction is a major complication of PE. Since the lung has a second blood supply through the bronchial arteries, occlusion of a pulmonary artery usually does not produce tissue necrosis. Nevertheless, the development of acute lung infarction is frequent and may be observed in up to 60% of autopsies following fatal PE [2]. The conditions resulting in lung infarction are not yet definitely understood and are discussed controversially [3]. The most popular hypothesis is that the development of pulmonary infarction is favored by left heart failure. Therefore, it was been repeatedly postulated that in cases of cardiac congestion the forward feed of the bronchial arteries is insufficient to supply the obstructed area due to increased pulmonary circulatory pressure and necrosis occurs after blood flow stagnation [4–6]. Other cited predisposing conditions are accompanying pneumonia [6], presence of sepsis [4], malignant disease [5], and advanced age [7]. In addition, high clot burden has also been made responsible for pulmonary infarction [8, 9].

Because modern multi-slice computed tomography (MSCT) scanners are widely available and permit rapid acquisition of a thin-slice dataset even in breathless patients, CT pulmonary angiography (CTPA) is nowadays considered the reference standard in acute pulmonary embolism [10]. However, in contrast to the diagnosis of pulmonary embolism, the literature contains minimal information about the role of CTPA in the diagnosis and attendant circumstances of lung infarction.

The aim of this study was to identify conditions that might predict the development of lung infarction by means of an analysis of the medical records and chest CT of patients with PE. We hypothesized that pulmonary infarction is associated with the location and degree of vascular obstruction rather than accompanying illnesses such as cardiac congestion or malignant disease.

Materials and Methods

We performed a retrospective analysis on all patients being examined in our CT unit between January 2009 and December 2012 with a final diagnosis of PE. These patients were recruited by means of a computer-aided search of our radiological information system (gap-it, ISOFT Corporation, Mannheim, Germany). The criteria for inclusion were the presence of PE on chest CT and complete clinical documentation in the electronic health records needed for classification of the severity of the symptoms as well as underlying diseases. Exclusion criteria were incomplete clinical documentation, low quality of CT examination (e.g. due to movement artifacts), loss of lung segments due to resection or other severe alterations of the pulmonary architecture (e.g. post-specific changes). Finally 154 patients were included in the evaluation.

MSCT was carried out using a Toshiba Aquilion 64 (Toshiba Medical Systems, Tokyo, Japan) CT scanner. Images were obtained in full inspiration using a 64 × 0.75 mm slice collimation with a tube voltage of 120 kV. The tube current (mA) was adjusted in relation to patient attenuation by means of the Sure Exposure® mode (Toshiba Medical Systems). The reconstruction slice thickness was 2–5 mm. During MSCT 100–120 ml of 300 mg or 400mgI/l contrast medium (Imeron®, Altana, Koblenz, Germany) were generally administered intravenously at a rate of 2–3 ml/s with a power injector followed by a 30 ml normal saline "chaser". Scan reading was performed consentaneously by two experienced radiologists using standard software (Cedara I-SoftView™ 6.3, Cedara Software Co. Ltd., Shanghai, PR China). Analysis was performed on at least two reconstruction planes (usually axial and coronal reconstruction). The readers quantified the pulmonary clot load using a modified severity index as proposed by Miller et al. [11] as follows: An embolus in a segmental artery is given a score of 1 if complete occlusion is present. Partial occlusion was weighted as 0.5 points (approximately half of the lumen occluded) or 0.25 (small filling defect surrounded by contrast media). Consequently, on the assumption of 10 segmental branches of the right PA and 9 segmental branches of the left PA, the maximal obstruction index is 19. In addition, the readers measured the distance between a complete occlusion of any segmental artery and the pleura.

Following the recommendations of Revel et al. [12], lung infarction was only considered present when CT showed a more or less homogenous consolidation or a well-defined area of ground glass opacity in a lung segment depending on an occluded pulmonary artery (**Fig. 1**). Consequently, the readers performed a per-segment correlation with CT angiography and infarctions were only rated as such if there was a corresponding embolus. Above this the readers evaluated different cardiovascular parameters such as the measurement of the RV/LV ratio (RV dysfunction was defined as > 1) or the presence of cardiac congestion.

The thickening of bronchial walls as a sign of chronic bronchitis was classified as moderate or severe compared with the representative HRCT images of airway wall thickness as published by Awadh et al. [13]. The presence of areas of abnormally low attenuation (less than –900HU) compared with the surrounding tissue was regarded as a sign of emphysema. Centrilobular emphysema was defined as round areas of low attenuation up to 1 cm in diameter within a homogenous background of normal lung parenchyma, while panlobular emphysema was defined as large and extensive areas of uniform low attenuation.

We performed an analysis of the electronic health records of our hospital (SolutionsCentre®, ISOFT Corporation, Mannheim, Germany) in order to document the indications for CT, the severity of clinical symptoms and the presence of accompanying illnesses. The severity of clinical symptoms was defined by means of a clin-

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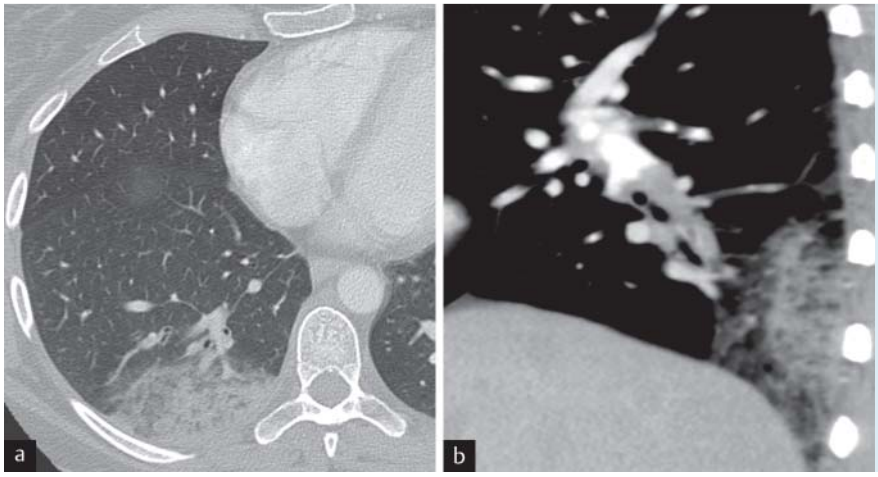

Fig. 1 **a** 32-year-old female suffering from acute dyspnea, thoracic pain and elevated D-dimers. Lung infarction was considered present because MSCT (64 × 0.75 mm slice collimation, tube voltage 120 kV) shows triangular opacity in the right lower lobe (W2000, C -500HE). **b** The sagittal reconstruction shows (W 400HE, C 40HE) almost complete obstruction of the segmental artery.

Abb. 1 **a** 32 jährige Patientin mit acuter Dyspnoe, Thoraxschmerz und erhöhten D-Dimeren. Computertomografischer Nachweis (MSCT 64 × 0,75 mm slice collimation, tube voltage 120 kV) einer triangulären Verschattung im rechten Unterlappen als Ausdruck eines Lungeninfarktes (W2000, C -500HE). **b** Die sagittale Rekonstruktion (W 400HE, C 40HE) zeigt einen nahezu kompletten Verschluss der entsprechenden Segmentarterie.

ical index with 4 classes as proposed by Grosser [14] as follows: class 1: discrete symptoms, normal blood pressure; class 2: distinct symptoms (dyspnea, pain, hemoptysis, etc.), moderate hypotension; class 3: distinct symptoms, hypotension; class 4: circulatory shock. The clinical course of the patients was evaluated until discharge from the hospital.

Statistics

Descriptive data were presented as means with SD in the case of normal distribution or median and range if normal distribution tested negative. Categorical data were given as counts and percentages. Chi-square test, Fischer's exact test or Spearman's coefficient of rank correlation were initially performed with patient characteristics and CT findings as predictors of infarction (yes or no) as well as the number of infarcted segments. A Spearman's coefficient (r) of 0.99 – 0.8 was considered to indicate very strong correlation, 0.79 – 0.6 strong correlation, 0.59 – 0.4 moderate correlation and 0.39 – 0.2 weak correlation. Analyses were performed using a specialized computer algorithm (MedCalc© Software, Mariakerke, Belgium). Significance was set at a P-value of less than 0.05.

The present study was approved by the ethics committee of our university and was HIPAA compliant. Patient informed consent was not felt to be necessary by the ethics committee.

Results

In total 154 patients with pulmonary embolism were included in our study. The mean age of all patients was 68.45 +/- 15.85 years (median: 74 years, range: 21 – 92 years) with a predominance of the female gender (65 [42.2 %] male, 89 [57.8 %] female).

Common indications for performing a CT examination of the chest CT were dyspnea (91/154, i. e. 59.1 %) or elevated D-dimers (41/154, i. e. 26.6 %). In 36/154 (23.4 %) cases the finding of pulmonary embolism was incidental. Discrete clinical symptoms with normal blood pressure (Grosser I) were seen in 47 (30.5 %) patients. 84 (54.5 %) patients showed dyspnea, pain and hemoptysis with moderate hypotension (Grosser II). A Grosser stage III (distinct symptoms with hypotension) was documented in 13 (8.4 %) patients. 10 (6.5 %) patients showed circulatory shock (Grosser IV), and 4 of them died. So the 30-day mortality was 2.6 %.

Accompanying diseases

The chart review of the 154 included patients revealed concomitant cardiovascular diseases in 95 cases (61.7 %). In these patients arterial hypertension (55/95, i. e. 57.9 %) and coronary heart disease (24/95, i. e. 25.3 %) were most often documented. Accompanying malignancy was reported in 57/154 (37.0 %). In 35/154 (22.7 %) patients CT revealed congestion, and cardiac failure with pulmonary edema was observed in only two patients (1.3 %). In 91/154 (59.1 %) patients CT revealed signs of chronic bronchitis or emphysema.

Infarction

CT revealed 78 areas of pulmonary infarction in 45/154 (29.2 %) patients. The mean age of these patients was 63.2 +/- 18.35 years (median: 66.0 years, range: 22 – 94 years). Compared with the entire PE population, the patients with infarction showed a more balanced gender ratio (female 23 [51.1 %], male 22 [48.9 %]), but this difference was not significant (p = 0.536).

The most common CT finding of infarction was the presence of a triangular consolidation of lung parenchyma (50.0 %). CT showed a segmental ground-glass pattern in 35.9 % of cases. Hampton's sign was seen in 14.1 % of cases.

Most often infarction occurred in the segments S5 R (12/78, 15.4 %), S9 R (17/78, 21.8 %) and S10 R (11/78, 14.1 %). Therefore, in total, more than half of all infarctions were demonstrated in only three segments of the right lung. In the left lung only 16 infarctions (20.5 %) were observed in 12 patients. The presence of infarction in the right lung was significantly higher than in the left lung (p < 0.001).

Correlation between clinical and CT findings and infarction

Univariate analysis (▶ **Table 1**) revealed a very weak negative correlation between presence of infarction and age (r = –0.199). Although no correlation was found between the assessment of the severity of the clinical symptoms in PE and infarction (r = –0.024), patients with infarction were significantly less often asymptomatic (p = 0.034). In this group patients demonstrated chest pain (12/45, 26.7 %) significantly more often (p = 0.019) than in the group without infarction (11/109, 10.1 %).

Patients with accompanying malignant diseases showed infarction in 15/57 (26.3 %) cases, and patients without malignancy in 30/97 (30.1 %) cases. This difference was not significant (p = 0.67, r = 0.069).

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Table 1 Univariate linear regression (outcome lung infarction) and patient characteristics in a cohort of 154 patients with pulmonary embolism; r = correlation coefficient (Spearman).

variable	all	without infarction	infarction	r	95 % confidence interval	p-value
age (years)	68.45 ± 15.84	70.6 ± 14.23	63.24 ± 18.34	–0.199	–0.3459 – 0.0417	0.014
male gender (n)	65	45	22	0.087	–0.0722 – 0.2418	0.282
severity of symptoms (mean score)	1.91 ± 0.80	1.77 ± 0.72	2.24 ± 0.90	–0.024	–0.1819 – 0.1342	0.762
pneumonia (mean)	0.14 ± 0.34	0.12 ± 0.32	0.18 ± 0.38	–0.047	–0.2039 – 0.1117	0.559
distance obstruction/ pleura (mm)	29.72 ± 15.22	34.61 ± 13.97	19.24 ± 12.32	–0.504	–0.6227 – 0.3629	0.000
cardiac congestion (mean)	0.28 ± 0.75	0.25 ± 0.43	0.18 ± 0.38	–0.076	–0.2313 – 0.0833	0.348
chronic bronchitis (mean)	1.03 ± 1.09	1.10 ± 1.09	0.87 ± 1.08	–0.109	–0.2623 – 0.0503	0.179
malignant disease (mean)	0.37 ± 0.48	0.39 ± 0.49	0.33 ± 0.47	–0.069	–0.0898 – 0.2250	0.391
thromboembolic burden (mean score)	5.25 ± 3.14	4.42 ± 3.89	5.26 ± 3.14	0.176	–0.0185 – 0.325	0.029

The CT assessment of different cardiac parameters regarding size and function revealed no correlation with the occurrence of infarction after embolism. This is also true for an increased RV/LV ratio (r = 0.082) and the presence of cardiac congestion (r = –0.076). There was no correlation between infarction and signs of chronic bronchitis (r = –0.109) as well as the clot burden score (r = 0.176).

Nevertheless, one major difference between the two groups was found by closer analysis of the location of the embolic burden: patients with infarction showed occlusion of distal vessels (mean distance between total obstruction and pleura 19.24 +/- 12.32 mm, median 15 mm) significantly more often than patients without development of infarction (mean distance between total obstruction and pleura 34.61 +/- 13.97 mm, median 33 mm). Thus, we found a moderate negative correlation between the maximal distance between the embolus and the dependent pleura and the occurrence of pulmonary infarction (r = –0.504).

Discussion

Sinner et al. already described CT findings of PE and infarction in 1978 [15]. Following the rapid technological evolution of CT, several attempts were made to correlate CT findings and clinical severity of PE [16 – 22]. In contrast to numerous publications on CT diagnosis and CT impact on risk stratification in cases of PE, there are only a few reports dealing with the findings of lung *infarction* in CT and subsequent implications [23 – 26]. This fact is somewhat surprising since pulmonary infarction is a frequently observed condition. The relative high incidence of pulmonary infarction (29.2 %) in our study group is in accordance with the literature.

A preference of the right lower lobe in pulmonary infarction has already been reported by Montgomery [4] in 1965, but has also been mentioned in more recent publications [8, 26]. While Ohtsubo et al. [26] report 57 % and He et al. [8] 73 % of all infarctions to be located in the right lung, in our group the predominance of the right side was even more obvious (79.5 %). It was not an aim of our study to investigate possible reasons for this observation and it remains speculative whether an increased incidence of lung infarction in these areas is caused by hemodynamic factors. Aside from reflections about the location of pulmonary infarction, only a few publications deal with the pathogenesis of pulmonary infarction and most reported results are contrarious to our own findings.

First of all and in contrast to the widespread opinion that simultaneous left heart failure favors the development of pulmonary infarction [5, 9], we did not find any correlation between these conditions. Secondly, the hypothesis that concomitant malignancy is a predisposing condition not only for the occurrence of pulmonary embolism but also infarction [9] could not be confirmed by our results. Also the observation that pre-existing pulmonary infection may increase the likelihood for the development of pulmonary infarction [6] could not be supported by our results.

He et al. [8] correlated clinical and CT findings in a total of 74 patients with pulmonary embolism and 24 infarctions. The authors found a trend toward a higher mean clot burden in PE patients with infarction. Our own results cannot support this observation. Although we could not find any correlation between the severity of clinical symptoms (Grosser score) and the occurrence of infarction, patients with infarction presented significantly more often with chest pain. This observation may implicate a more peripheral location of the emboli resulting in painful pleural affection and may strengthen the assumption that infarction is more often present in the peripheral vascular occlusion. The idea that a vast peripheral vascular obstruction is a major condition of infarction development was already postulated by Karsner and Ghoreyeb in 1913 [27]. The authors demonstrated that complete obstruction of blood flow in the pulmonary arteries is followed by almost complete taking over of the circulation by the bronchial artery supply, but also that this mechanism does not occur when an embolism is present in a smaller branch of the pulmonary arteries. The authors assume that the physiological anastomoses between the two systems could be occluded by seeds about three millimeters in diameter [27]. Accordingly and as the result of a post-mortem autopsy, Tsao et al. [5] reported an increase in the occurrence of infarction in embolic occlusion of pulmonary vessels with a diameter of less than 3 mm. These observations are in accordance with our finding that shows a moderate negative correlation with the minimal distance between the total vascular obstruction and the dependent pleura.

Finally it remains unclear whether the very low negative correlation between infarction and age effectively implies that younger patients tend towards the development of infarction or not.

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Limitations

There were some limitations to our study. A major limitation of our study was that the sample size was small, thus limiting generalization of our results. Owing to the retrospective character of our investigation, the time point of imaging was not defined. Therefore, it is not absolutely certain that all infarctions are detected because some may have developed later. The demographic data of our patients showed some differences compared to other studies dealing with pulmonary embolism. Even though the high incidence of patients with accompanying malignant disease (37 %) is in relative accordance with White [28] (25 %), the percentage of surgical patients is obviously lower than reported by most other authors [1, 29]. The patients included in our study showed a relative high mean age (74 years), but this is in accordance with the clear increase of pulmonary embolism in patients older than 60 years [7, 29].

Conclusion

In contrast to the literature, we did not find clear correlations between the occurrence of lung infarction and diverse clinical conditions (age, presence of malignancy, etc.), CT signs of cardiac congestion, and the clot burden. The results of our study corroborate the theory that the vast peripheral location of an embolus beyond the physiological anastomoses between the pulmonary and bronchial arteries may be a crucial factor deciding whether an infarction occurs or not.

Clinical relevance

1. The radiological finding of pulmonary infarction in PE is frequent and important in differential diagnosis.
2. The degree of pulmonary vascular obstruction (clot burden) does not correlate with the frequency of pulmonary infarction.
3. Cardiac congestion is not a main factor predisposing to pulmonary infarction in patients with PE.
4. The crucial factor for infarction seems to be the peripheral location of an embolus beyond the physiological anastomoses between the pulmonary and bronchial arteries.

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