DOI: 10.1002/pul2.12322

RESEARCH ARTICLE

Pulmonary Circulation Open Access | PVRI Pulmonary Vascular Research Institute | WILEY

Pulmonary embolism induces pneumonia-like lung injury beyond pulmonary infarction

Yue Wang[1] | **Bo Liu**[2,3] | **Chuming Zhou**[1] | **Yuan Wang**[1] | **Jianing Miao**[2] | **Li Zhao**[1]

[1]Department of Pulmonary and Critical Care Medicine, Shengjing Hospital of China Medical University, Shenyang, China

[2]Medical Research Center, Shengjing Hospital of China Medical University, Shenyang, China

[3]Liaoning Key Laboratory of Research and Application of Animal Models for Environmental and Metabolic Diseases, Shengjing Hospital of China Medical University, Shenyang, China

Correspondence
Li Zhao, Department of Pulmonary and Critical Care Medicine, Shengjing Hospital of China Medical University, Shenyang 110000, China.
Email: lzhaoli@163.com

Funding information
National Natural Science Foundation of China, Grant/Award Number: 82170047

Abstract

Patients with pulmonary embolism (PE) commonly manifest concomitant "pneumonia," which is generally believed to be either a cause (infection) or a consequence (infarction) of PE. This study aimed to clarify the relationship between PE and "pneumonia-like" lesions beyond pulmonary infection and infarction. Chest computed tomography (CT) images of patients with PE and deep vein thrombosis (DVT) were retrospectively analyzed to compare the incidence of pneumonia lesions. The pathological damage and wet/dry ratio of lung tissues were observed in PE rats and PE plasma-injected rats. In total, 793 and 914 inpatients were enrolled in the PE and DVT groups, respectively. Pneumonia lesions were observed in 36.9% and 26.3% of patients in the PE and DVT groups, respectively ($p < 0.0001$). Among PE rats, 33.3% exhibited focal severe lung injury, which closely resembled the pathological damage of community-acquired pneumonia. The wet/dry ratio was significantly higher in the PE group than in the PE-control group (4.98 ± 0.08 vs. 4.39 ± 0.06, $p < 0.0001$). Among PE plasma-injected rats, individuals with focal proven lung injury were found at all experimental points, with an incidence of 27.6%. The lung wet/dry ratio was significantly higher in the PE plasma group than in the PE-control plasma group at 1 and 2 h postinjection (5.02 ± 0.12 vs. 4.61 ± 0.06 and 4.76 ± 0.16 vs. 4.34 ± 0.09, respectively; $p < 0.05$). In conclusion, the manifestation of pneumonia lesions in chest CT images was higher among PE patients than among DVT patients. Plasma of PE rats could induce focal pneumonia-like lung injury in healthy rats.

KEYWORDS
computed tomography image, deep vein thrombosis, lung injury

Yue Wang, Bo Liu, and Chuming Zhou contributed equally to this study.

INTRODUCTION

Pulmonary embolism (PE) is a common disease with high mortality.[1,2] Pathogenic microbial infection is an important risk factor for PE.[3] Since the thromboembolus that causes PE originates from deep vein thrombosis (DVT), the incidence of pulmonary infection should theoretically be similar between DVT and PE. However, extant data have indicated that patients with pneumonia had a 7.9-fold higher risk of PE but only a 3.0-fold higher risk of DVT,[4] although patients with urinary tract infection had similar risks of DVT and PE.[3] Given that pulmonary infarction in PE might be incorrectly accounted for as "pneumonia," resulting in false positives to raise the "pneumonia" incidence, should the "pneumonia" incidence in PE be so high? It is generally believed that pulmonary infarction in PE involves the occlusion of distal pulmonary arterioles due to thromboembolic blocking, resulting in ischemia, hemorrhage, and eventually necrosis of the corresponding lung parenchyma.[5] However, lung parenchyma damage caused by pulmonary infarction is rarely observed in precapillary pulmonary hypertension, which typically presents as pulmonary arteriolar occlusion in pathology.[6] This implies that the incidence of pulmonary infarction might not be so high even if patients with PE develop pulmonary arteriolar occlusion. We assume that patients with PE coexisting with pneumonia might have other confounding factors.

Extensive evidence indicates that various inflammatory factors are activated and released in acute PE, including key pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin (IL)−6, and IL-8.[7,8] These inflammatory factors can also causally contribute to acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) in susceptible patients,[9] manifesting as pulmonary interstitial and alveolar exudation with ground-glass opacities (GGOs), reticular GGOs, mixed GGOs, patchy opacities, or consolidation in chest computed tomography (CT) images. Cases in which these imaging findings are localized to the lungs can be difficult to differentiate from pneumonia.[10] Furthermore, the common clinical symptoms of patients with acute PE are similar to those of patients with pneumonia, which often include chest pain, breathlessness, and fever.[11] Thus, according to the simplicity principle of initial diagnosis, patients with the aforementioned clinical symptoms who present with exudative lesions on chest CT images are more likely to be diagnosed with community-acquired pneumonia (CAP).[12,13] However, if pneumonia-like lung injury induced by inflammatory cytokines does indeed occur in acute PE, then a subset of patients with PE may be misdiagnosed with CAP, leading to treatment delays and even an increased risk of death.

We thus hypothesized that PE causes vascular endothelial damage resulting in extensive release of inflammatory factors, leading to focal lung injury in susceptible individuals and the appearance of pneumonia-like findings. In view of this hypothesis, the present study analyzed chest CT images from a large sample of patients with PE or DVT to clarify the differences in the incidence of pneumonia lesions between the two groups. In addition, an animal model was established to verify whether PE rat plasma can lead to pneumonia-like lung injury in healthy rats.

METHODS

Patient screening

Researchers were performed in the Hospital Information System (HIS) and digital scientific research platform of Shengjing Hospital of China Medical University using the following keywords: "pulmonary embolism," "pulmonary thromboembolism," "pulmonary arterial thromboembolism," "PE," "PTE," "deep vein thrombosis," "vein thrombosis," and "DVT" to screen for hospitalized patients with a confirmed diagnosis of acute PE or DVT between January 2012 and September 2021. The inclusion criteria for the PE group were as follows: (1) patients aged ≥ 18 years and (2) CT pulmonary angiography findings consistent with acute PE.[14] The exclusion criteria for the PE group were as follows: (1) concomitant chest trauma; (2) multiple pulmonary metastatic foci; (3) left ventricular dysfunction; and (4) confirmed ALI. The inclusion criteria for the DVT group were as follows: (1) patients aged ≥ 18 years and (2) findings of ultrasonography of the lower extremity veins consistent with DVT.[15,16] The exclusion criteria for the DVT group were as follows: (1) concomitant chest trauma; (2) multiple pulmonary metastatic foci; (3) left ventricular dysfunction; (4) confirmed ALI; and (5) concomitant PE. We used the hospital's electronic registry to gather baseline information on demographics and comorbidities. The study was approved by the Ethical Committee of Shengjing Hospital of China Medical University (approval permit number: 2021PS859K).

CT evaluation of pneumonia

CT findings of pneumonia included light patchy opacity, GGO, reticular GGO, mixed GGO, patchy opacity, or consolidation (Figure 1).[17] Two trained researchers independently analyzed the CT images of the selected

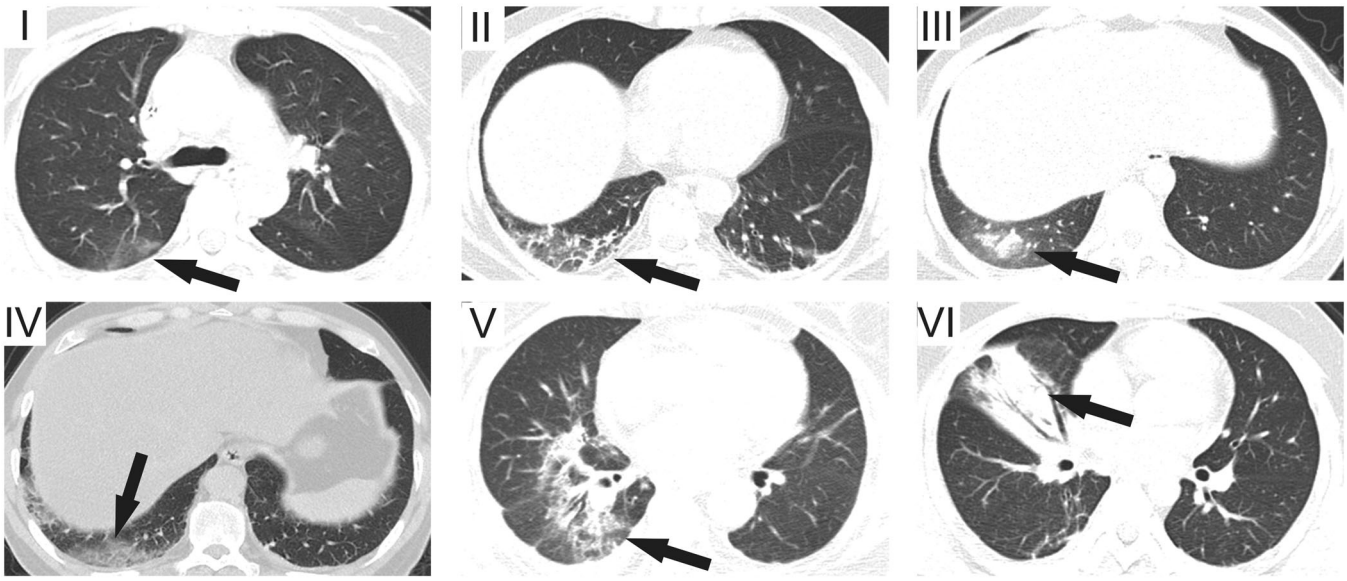

FIGURE 1 Pneumonia lesions in lung computed tomographic (CT) image. (I) Light patchy opacities; (II) reticular ground-glass opacities (GGOs); (III) mixed GGOs; (IV) GGOs; (V) patchy opacities; (VI) consolidation. "→" indicates pneumonia lesions.

patients based on the present study criteria. The researchers were only informed of the imaging number and were not allowed to view the mediastinal window. The date of CT examination was from 2 weeks before to 5 days after the diagnosis of PE or DVT. Patients in the DVT group who did not receive chest CT during the scheduled period were analyzed separately.

Rat model and specimen collection

The animal experiments were approved by the Institutional Animal Ethics Committee (IAEC) of Shengjing Hospital of China Medical University (approval permit number: 2020PS580K). Healthy 7-week-old male Sprague Dawley rats weighing 210–230 g purchased from Beijing HFK Bioscience Co. Ltd. were housed in cages under specific pathogen-free conditions. Food and water were provided ad libitum.

At least five rats per group per timepoint were randomly assigned to the PE, PE-control (PE-con), PE plasma, and PE-con plasma groups. To establish PE model, the rats were anesthetized intraperitoneally with 20% urethane at a dosage of 1400 mg/kg. The bilateral jugular veins were dissected. The right jugular vein was cannulated with a catheter connected to a pressure transducer, which was carefully inserted into the right ventricle to monitor right ventricular pressure. A needle for clots infusion was inserted into the left jugular vein. The clots were prepared 1 day before the operation. Blood was drawn from the rat tail vein and filled with a 0.5 mm diameter catheter, allowing natural coagulation to form thromboembolus. The rats were infused with 20 autologous clots $1 \times 1 \times 2$ mm in size slowly over 5 min. A right ventricular pressure increase exceeding 10 mmHg above baseline pressure after clots infusion was considered as acute PE.[18,19] For few rats, supplementary clots were infused to take the right ventricular pressure exceeding that level. Not eligible for further experiment if the increase of right ventricular pressure did not reach 10 mmHg after the supplemental clot injection. The PE-con group was injected with an equal volume of normal saline instead of clots.

Two hours after PE and PE-con model establishment, blood was collected from the abdominal aorta. PE or PE-con plasma were isolated via centrifugation and stored at −80°C. Healthy rats were injected via the tail vein with 1 mL of plasma from the PE or PE-con groups to establish the groups of PE plasma or PE-con plasma. Lung tissues were histologically assessed at 2 h for the PE and PE-con groups, and at 0.5, 1, 2, 4, and 8 h for the PE plasma and PE-con plasma groups, respectively.

Histological assessment

Based on the American Thoracic Society (ATS) assessment method for ALI in animal models,[20] images were acquired using light microscopy under ×400, ×200, and ×40 magnification. Under a ×400 high-power field, at least 20 fields of view were randomly selected while avoiding the predominance of the lumen of large airways or vessels to ensure that >50% of each field was occupied by lung alveoli. The mean value for overall lung injury

scores was recorded as the total lung injury score (see Supplementary Table S1). The score in the most severe lung injury region was recorded as the highest lung injury score to determine whether focal lung injury occurred. The scale with the highest lung injury score >0.50, 0.70, or ≤0.30 was considered as proven lung injury, severe lung injury, or normal lungs, respectively.[21]

Measurement of lung fluid content

The accessory lobe of the right lung was carefully excised, and the wet weight was measured. Lung tissue was placed in a 60°C hot-air oven and dried for 72 h, followed by measurement of dry weight. The wet/dry ratio was calculated to evaluate the degree of pulmonary edema.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 8.01 and IBM SPSS Statistics 24.0. The Grubbs test was used for outliers, and two datapoints of the wet/dry ratio were rejected at the $\alpha = 0.05$ significance level. All continuous values are expressed as the mean ± SEM. Data were assessed for normality by the Shapiro–Wilk test. Student's t test was used to compare mean differences of normally distributed values. The Mann–Whitney U test was used for skewed distributions. Binary variables were compared using the χ^2 test and Fisher's exact test. Data were considered statistically significant at two-tailed $p < 0.05$.

RESULTS

Comparison of pneumonia lesion incidence between the PE and DVT groups

After screening, 793 and 1773 eligible patients were enrolled in the PE and DVT groups, respectively. Among these, 859 patients (48.4%) in the DVT group were unavailable to obtain chest CT images. A total of 793 patients in the PE group and 914 patients in the DVT group were focused in this study. Table 1 shows the baseline clinical characteristics of the study patients. There was no statistical difference between PE and DVT groups regarding gender, age, nonrespiratory infectious diseases, cancers, and common chronic medical diseases. Significant differences were observed between PE and DVT groups in terms of connective tissue disease, trauma, and surgery.

TABLE 1 Baseline clinical characteristics.

Characteristics	PE ($n = 793$)	DVT ($n = 914$)	p
Gender			0.121
Male	369 (46.5)	460 (50.3)	
Female	424 (53.5)	454 (49.7)	
Mean age, years (SD)	62.6 (14.1)	63.9 (15.0)	0.081
Hospital time, days (SD)	18.3 (15.8)	24.9 (35.1)	<0.0001
Nonrespiratory infectious disease	99 (12.5)	103 (11.3)	0.453
Chronic lung disease	48 (6.1)	49 (5.4)	0.600
Chronic cardiovascular disease	327 (41.2)	378 (41.4)	0.961
Chronic hematological disease	66 (8.3)	60 (6.6)	0.194
Chronic digestive disease	116 (14.6)	106 (11.6)	0.063
Chronic renal disease	60 (7.6)	82 (9.0)	0.334
Metabolic disease	228 (28.8)	264 (28.9)	0.957
Connective tissue disease	13 (1.6)	52 (5.7)	<0.0001
Cancers	220 (27.7)	219 (24.0)	0.075
Trauma and surgery	157 (19.8)	278 (30.4)	<0.0001

Note: Data are n (%) unless otherwise indicated.

Among the 793 patients in the PE group, there were 293 patients combined pneumonia lesions on CT images, compared to 240 patients in the DVT group of 914 patients. The incidence of pneumonia lesions on CT images was significantly higher in the PE group (36.9%) compared to the DVT group (26.3%) ($p < 0.0001$) (Table 2). Previous studies have suggested that chronic lung disease, chronic digestive disease, trauma, and tumors could induce pulmonary inflammation.[22–25] In our study, only connective tissue disease, trauma, and surgery exhibited significantly higher incidence rates in the DVT group compared to the PE group. Nevertheless, this difference does not provide an explanation for the higher rate of pneumonia lesions observed in the PE group, which could potentially be attributed to PE.

Rat PE model establishment

After injection of the thromboembolus, an immediate rise in right ventricular pressure of >10 mmHg was observed. At 2 h after injection, cyanosis was observed on the lips of PE rats. Lung tissue dissection revealed

TABLE 2 Comparison of pneumonia lesion incidence between the PE and DVT groups.

Groups	Pneumonia lesion findings	No pneumonia lesion findings	*p*
PE ($n = 793$)	293 (36.9)	500 (63.1)	<0.0001
DVT ($n = 914$)	240 (26.3)	674 (73.7)	

Note: Data are *n* (%). The incidence of pneumonia lesions on computed tomographic (CT) images was compared between the pulmonary embolism (PE) group and the deep vein thrombosis (DVT) group, $p < 0.0001$.

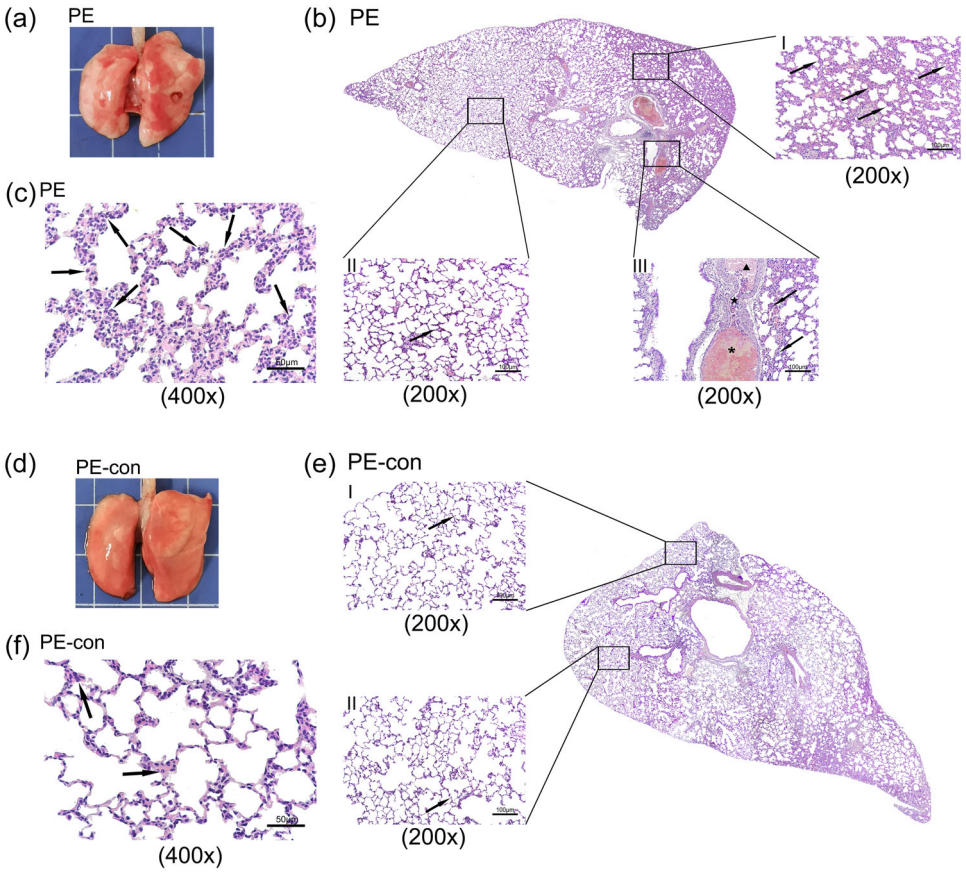

FIGURE 2 Lung injury in rat pulmonary embolism (PE) models. Panels (a) and (d) were the gross specimens of lung tissues in the PE and PE-con groups, respectively; (b, c) and (e, f) showed hematoxylin-eosin staining of the lung tissues. Compared to those of the control group (d–f), the lung tissues of rat PE models exhibited focal damage (a–c). Significant thickening of the alveolar wall, accompanied by a large amount of neutrophil infiltration, a small amount of neutrophil migration into the alveolar space, and occasional fibrin exudation forming fibrin chains or hyaline membranes, was observed (b, c). A thromboembolus was observed in the pulmonary artery (b-III). Panels (b) and (e) are mosaic images; "→" indicates neutrophils in the alveolar wall; "▲" indicates red blood cells; "★" indicates intravascular neutrophils; "✻" indicates the thromboembolus. The numbers in brackets are the image magnification.

thromboembolism of the pulmonary artery, indicating successful establishment of the rat PE model (see Supplementary Figure S1).

Proved lung injury in rat PE models

Gross specimen examination revealed spotted patterns on the surface of lung tissues of individuals in the PE group, whereas the lung tissues of the PE-con group were uniformly pink (Figure 2a,d). Haematoxylin-eosin (HE) staining revealed focal pathological damage in the PE group, with the majority of injury sites located at the lung periphery (Figure 2b). Significant thickening of the alveolar wall was observed at these sites with a large amount of inflammatory cell infiltration (predominantly neutrophils), some neutrophils migrating into the alveolar space, and occasional fibrin exudation forming fibrin

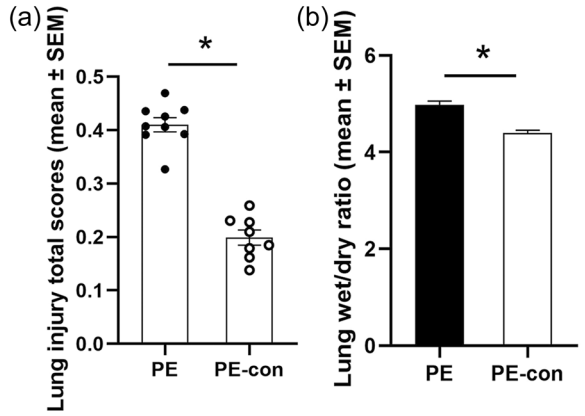

FIGURE 3 Lung injury scores (a) and lung wet/dry ratio (b). Compared to the pulmonary embolism control (PE-con) group, the PE group exhibited a significantly higher total lung injury score (a) and wet/dry ratio (b). *$p < 0.0001$.

TABLE 3 Degree of lung injury in PE rats and PE-con rats.

	Highest lung injury scores			
Groups	**≤0.30**	**0.51–0.70**	**>0.70**	***p***
PE ($n = 9$)	0	5 (55.6)	3 (33.3)	<0.0001
PE-con ($n = 8$)	5 (62.5)	0	0	

Note: Data are *n* (%). The incidence of proven lung injury (highest lung injury score > 0.50) was compared between the pulmonary embolism (PE) group and the PE-control (con) group, $p < 0.0001$.

chains or hyaline membranes (Figure 2c). The lung in PE-con group was characterized by thin alveolar walls with few neutrophils (Figure 2e,f). These observations suggested the occurrence of focal lung injury in PE rats,[20] which was also similar to CAP pathological damage.[26] The total lung injury score was significantly higher in the PE group than in the PE-con group (0.41 ± 0.01 vs. 0.20 ± 0.01, $p < 0.0001$) (Figure 3a). In the PE group, 88.9% (8/9) of rats exhibited proven lung injury (highest lung injury score > 0.50), of which 33.3% had severe lung injury (highest lung injury score > 0.70) and 1/9 had a highest lung injury score of 0.50. In the PE-con group, none of the rats had proven lung injury (5/8 had a highest lung injury score ≤ 0.30, and 3/8 had a highest lung injury score of 0.37–0.48). The difference between the two groups was statistically significant ($p < 0.0001$) (Table 3). None of the rats showed alveolar hemorrhage or lung tissue necrosis in either group. The wet/dry ratio was significantly higher in the PE group than in the PE-con group (4.98 ± 0.08 vs. 4.39 ± 0.06, $p < 0.0001$) (Figure 3b), implying more exudate in the lungs of PE rats.

Plasma of PE rats induced proved lung injury in the healthy

At 0.5, 1, 2, 4, and 8 h after healthy rats were infused with plasma from the PE rats (PE plasma group) or PE-con rats (PE-con plasma group), the gross lung tissue specimens exhibited similar findings to those of the PE and PE-con groups (Figure 4a,b,d,e). In the PE plasma group, focal pathological damage was observed at every experimental point individually (Figure 4c), and most injury sites were located at the periphery of lung tissues (Figure 4b). Similar to PE rats, these injury sites manifested as significant thickening of the alveolar wall, accompanied by neutrophil infiltration and occasional formation of fibrin chains or hyaline membranes (Figure 4b,c). None of the rats in the PE-con plasma group exhibited this damage (Figure 4e,f). The total lung injury score was significantly higher in the PE plasma group than in the PE-con plasma group at 0.5 and 4 h ($p < 0.05$) (0.29 ± 0.03 vs. 0.19 ± 0.01 and 0.28 ± 0.03 vs. 0.17 ± 0.01, respectively) (Figure 5a). In the PE plasma group, proven lung injury (highest lung injury score > 0.50) was observed in 8/29 (27.6%) rats, one of which exhibited severe lung injury (highest lung injury score = 0.82). In the PE-con plasma group, none of the rats had proven lung injury (30.0% had a highest lung injury score ≤ 0.30, and 70.0% had a highest lung injury score of 0.32–0.48). The difference between the two groups was statistically significant ($p < 0.05$) (Table 4). None of the rats showed alveolar hemorrhage or lung tissue necrosis in either group. The wet/dry ratio was significantly higher in the PE plasma group than in the PE-con plasma group at 1 and 2 h (5.02 ± 0.12 vs. 4.61 ± 0.06 and 4.76 ± 0.16 vs. 4.34 ± 0.09, respectively; $p < 0.05$) (Figure 5b), implying more lung exudate in the PE plasma group.

Patients with PE tend to be older and have multiple medical problems such as chronic lung disease, trauma, and so forth, which complicated the etiology of pulmonary inflammation. In contrast to patients with PE, the young rats with no comorbidities were used to animal study, thereby minimizing confounding factors that contribute to lung inflammation. The only reason for PE plasma group showing pneumonia-like lung injury should be the infusion of PE plasma. Certain specific molecule induced by acute PE could trigger pneumonia-like lung injury.

DISCUSSION

PE and DVT share common risk factors, including pulmonary infection.[27] The underlying mechanisms may involve inflammation-induced vascular endothelial

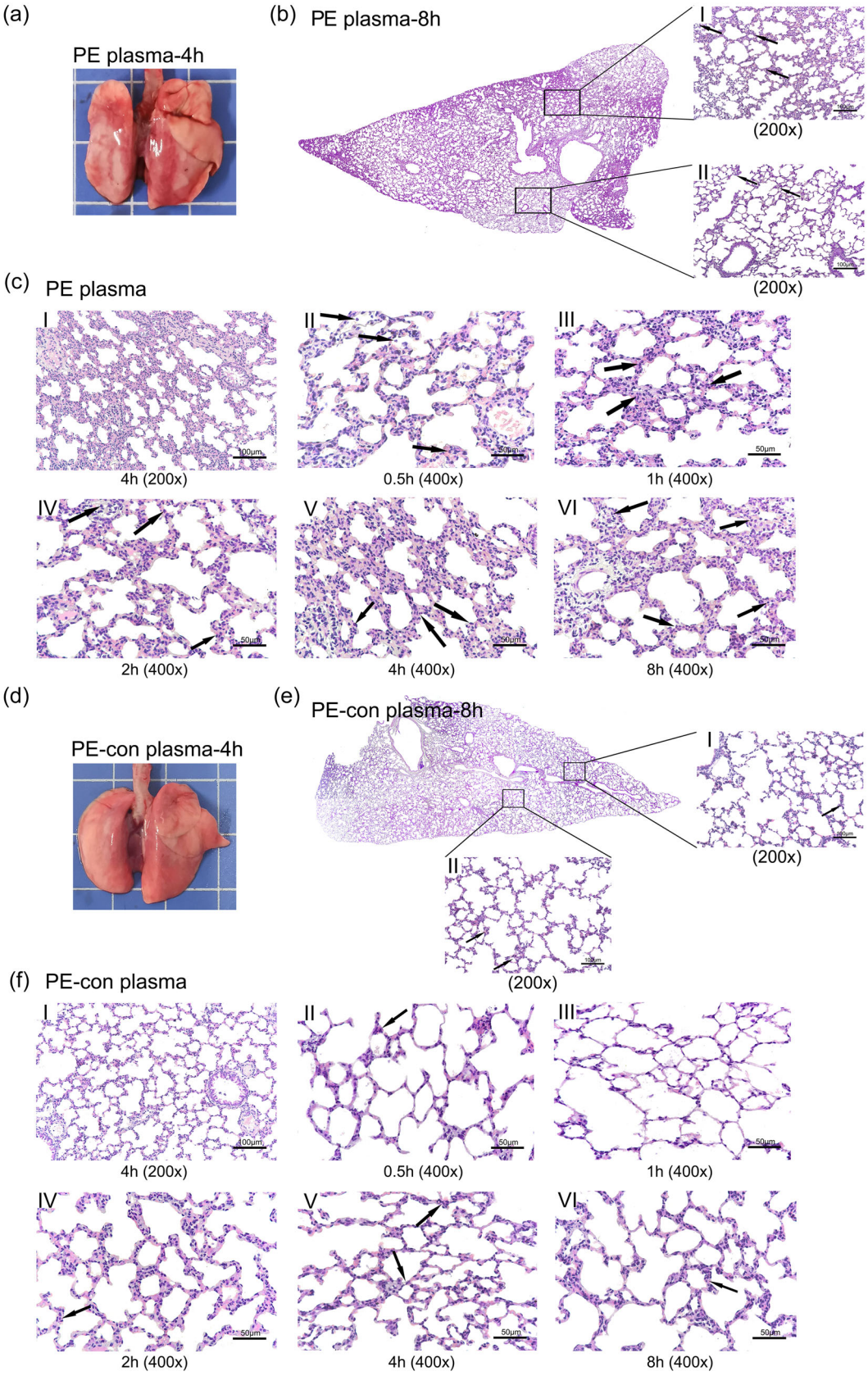

FIGURE 4 (See caption on next page).

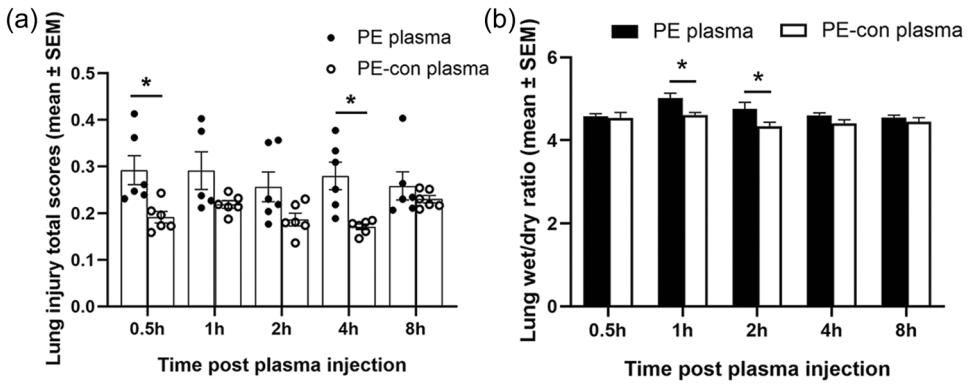

FIGURE 5 Lung injury scores (a) and lung wet/dry ratio (b). Compared to the pulmonary embolism-control (PE-con) plasma group at the corresponding time points, the PE plasma group exhibited significant increases in total lung injury score (a) at 0.5 and 4 h after plasma injection and significant increases in the wet/dry ratio at 1 and 2 h after plasma injection (b), $*p < 0.05$.

TABLE 4 Degree of acute lung injury in the PE plasma and PE-con plasma groups.

		Hours postplasma injection				
Group scores		**0.5**	**1**	**2**	**4**	**8**
PE plasma	$n = 29$*	$n = 6$	$n = 5$	$n = 6$	$n = 6$	$n = 6$
≤0.30	1 (3.4)	0	0	0	0	1 (16.7)
0.51–0.70	7 (24.1)	2 (33.3)	2 (40.0)	2 (33.3)	1 (16.7)	0
>0.70	1 (3.4)	0	0	0	0	1 (16.7)
PE-con plasma	$n = 30$*	$n = 6$	$n = 6$	$n = 6$	$n = 6$	$n = 6$
≤0.30	9 (30.0)	1 (16.7)	2 (33.3)	2 (33.3)	4 (66.7)	0
0.51–0.70	0	0	0	0	0	0
>0.70	0	0	0	0	0	0

Note: Data are *n* (%).

*All rats in the pulmonary embolism (PE) plasma group or PE-control (con) plasma group. The incidence of proven lung injury (highest lung injury score > 0.50) was compared between the PE plasma group and the PE-con plasma group, $p < 0.05$.

dysfunction.[28] Our study demonstrated that the incidence of PE or DVT with comorbid pneumonia based on CT images was 36.9% or 26.3%, respectively, and this difference was statistically significant. Similar conclusions were drawn by other studies regarding the inconsistency in pneumonia incidence between PE and DVT.[4] In the present study, appropriate CT images were unavailable for 48.4% of patients with DVT to evaluate for pneumonia. This may have led to a bias in the DVT group. However, given that chest CT scans are predominantly driven by respiratory symptoms, including pneumonia, patients without CT images might be less likely to have pneumonia than those with chest CT scans. Since PE and DVT share common risk factors, pneumonia as a

FIGURE 4 Pulmonary embolism (PE) plasma induced pneumonia-like lung injury in healthy rats. Panels (a) and (d) were the gross specimens of lung tissues in the PE plasma and PE-control (con) plasma groups at 4 h after plasma injection, respectively. Panels (b, c) and (e, f) depict hematoxylin-eosin staining of the lung tissues. In the PE plasma group, focal damage was observed at all experimental points (b, c), manifesting as significant thickening of the alveolar wall, accompanied by a large amount of neutrophil infiltration, a small amount of neutrophil migration into the alveolar space, and occasional fibrin exudation forming fibrin chains or hyaline membranes. None of the rats in the PE-con plasma group exhibited these changes (e, f). Panels (b) and (e) are mosaic images; "→" indicates neutrophils; the numbers in brackets are the image magnification.

trigger should theoretically have a similar incidence among both PE and DVT groups. A higher incidence of pneumonia lesions on CT images in PE than in DVT implies the involvement of other confounding factors. We realized that pulmonary infarction might be incorrectly accounted for as "pneumonia," resulting in false positives in the PE group. However, we did not find any PE rats showing alveolar hemorrhage or lung tissue necrosis in the present study.

In the present study, we designed an animal experiment involving the injection of plasma from PE rats into healthy rats. Our findings revealed that some recipients of PE plasma showed focal pathological damage of proven lung injury (predominantly distributed at the lung periphery), which was observed at all experimental points after PE plasma injections. The total incidence of proven lung injury in the PE plasma group was 27.6%, of which 3.4% was severe lung injury, manifesting as significant thickening of the alveolar wall accompanied by a large amount of neutrophil infiltration, a small amount of neutrophil migration into the alveolar space, and occasional fibrin exudation. None of the rats were found to have alveolar hemorrhage or lung tissue necrosis in the PE group or PE plasma group. It is well known that PE may produce numerous cytokines and chemokines, such as interferon-γ, IL-6, IL-8, IL-9, IL-10, IL-1β, chemokine ligand 2, IL-17A, transforming growth factor-β, and TNF-α,[7] many of which are also major inflammatory cytokines inducing ALI/ARDS.[9,29] Given that ARDS is inducible by extrapulmonary diseases, the lungs of susceptible individuals are target organs of systemic inflammatory factors. Animal experiments have demonstrated that the simulation of PE via the injection of polystyrene microspheres into the jugular vein (circulatory system) resulted in extensive recruitment of chemokines in lung tissues and bronchoalveolar lavage fluid (respiratory tract).[30] These findings imply that the lungs of susceptible rats were indeed the target organs of the systemic inflammatory response induced by PE. Unfortunately, even if we do repeat previous experiments and confirm an increased level in some of these inflammatory cytokines in our PE model rats, we still cannot confirm they are correlated to ALI or not. However, determining which specific inflammatory cytokines are responsible for the lung injury is beyond the scope of this study's objectives. Collectively, these events resulted in similar pneumonia-like pathological damage and might also correspond to the findings of GGO,[26] mixed GGO and reticular GGO observed in chest CT images.[31] Unlike the diffuse pathological damage of classic ALI/ARDS, PE-induced lung injury had a focal distribution, which more closely resembled the distribution of lesions in patients with CAP. Therefore, the results of these animal experiments suggest that the possibility of PE diagnosis should be considered when patients exhibit acute onset of symptoms such as chest tightness, breathlessness, chest pain, and/or fever, which are accompanied by pneumonia lesions predominantly distributed in the lung periphery in chest images. Given that the treatment strategies for CAP and PE completely differ and that the efficacy of CAP treatment requires evaluation after 72 h, misdiagnosis of pneumonia-like lesions caused by PE as CAP will result in a delay in PE diagnosis and may lead to adverse consequences. In addition, given that lung injury is caused by PE-induced systemic inflammatory responses and that heightened systemic inflammatory responses are a major factor contributing to poor PE prognosis,[32] fully recognizing that patients with PE may exhibit pneumonia-like lesions is essential to improving PE prognosis.

In our study, the researchers who reviewed images were well trained with the study criteria. They were blinded to PE status to minimize bias of the review results. To prevent overlooking patients in the early stages of pneumonia, patients with "mild" imaging findings were also included. Furthermore, to ensure that pneumonia might be a risk factor for venous thromboembolism, the time window for chest CT scans was defined as from 2 weeks before to 5 days after the diagnosis of PE or DVT. In the animal experiment, the PE plasma collection time (2 h after PE model establishment) was determined based on pilot data. The PE-con group received an equivalent volume of normal saline that was injected via the jugular vein, and plasma was collected at the same time point as that for the PE group for injection into the PE-con plasma group to eliminate the inflammatory effects caused by surgical trauma. The assessment method for animal models of lung injury was based on the recommendations of the ATS,[20] while the score thresholds for proven lung injury have been adopted in other studies.[21]

We acknowledge certain limitations of the present study. As the patient population was retrospectively evaluated, most DVT patients lacked chest CT images acquired during the appropriate time window, which affected the accuracy of pneumonia incidence. The purpose of this study was to observe the possibility of PE plasma-induced lung injury, and hence, only one experimental point was included to observe the pathological damage in both the PE group and PE-con group. This could have underpinned the lack of evidence of pulmonary infarction.

In conclusion, the manifestation of pneumonia lesions in chest CT images was higher among PE patients than among DVT patients. Most PE rats developed focal proven lung injury, and some exhibited severe lung injury,

manifesting as pneumonia-like interstitial and alveolar exudation predominantly distributed at the lung periphery. These injuries are associated with the presence of PE-induced pathogenic factors in the plasma, but further investigations are warranted to elucidate the underlying mechanisms.

AUTHOR CONTRIBUTIONS

Yue Wang and Li Zhao designed the study and drafted the manuscript. Yue Wang, Bo Liu, and Jianing Miao did the animal study. Yue Wang, Chuming Zhou, Yuan Wang, and Li Zhao did the patients screening and CT images evaluation. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

ACKNOWLEDGMENTS

We would like to thank Shuang Bai for technical assistance and Editage (www.editage.cn) for English language editing. This work was supported by the General Program (82170047 to LZ) from the National Natural Science Foundation of China. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data that support the findings of this study are available from the corresponding author (Li Zhao) upon reasonable request and with permission of Shengjing Hospital of China Medical University, Shenyang, China.

ETHICS STATEMENT

This study was approved by the Ethical Committee of Shengjing Hospital of China Medical University (approval permit number: 2021PS859K), and the Institutional Animal Ethics Committee (IAEC) of Shengjing Hospital of China Medical University (approval permit number: 2020PS580K).

ORCID

Yue Wang http://orcid.org/0000-0001-8673-6358

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Wang Y, Liu B, Zhou C, Wang Y, Miao J, Zhao L. Pulmonary embolism induces pneumonia-like lung injury beyond pulmonary infarction. Pulm Circ. 2023;13:e12322. https://doi.org/10.1002/pul2.12322