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Expression and Correlation of Hypoxia-Inducible Factor-1α (HIF-1α) with Pulmonary Artery Remodeling and Right Ventricular Hypertrophy in Experimental Pulmonary Embolism

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

AE 1 **Wenjuan Liu**
AEF 2 **Yimei Zhang**
BC 1 **Liwen Lu**
BC 3 **Liling Wang**
CD 4 **Mingxin Chen**
DF 5 **Tianyou Hu**

1 Department of Respiratory Medicine, Shanghai Jiaotong University Affiliated Sixth People's Hospital South Campus, Shanghai Fengxian District Central Hospital, Shanghai, P.R. China
2 Department of Respiratory Medicine, First Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, P.R. China
3 Department of Emergency, Medical Ward, First Clinical Medical College, Harbin, Heilongjiang, P.R. China
4 Department of Respiratory Medicine, First Clinical Medical College, Harbin, Heilongjiang, P.R. China
5 The Medical College of Jiamusi University, Jiamusi, Heilongjiang, P.R. China

Corresponding Authors: Wenjuan Liu, e-mail: WenjuanLiuwjlj@163.com, Yimei Zhang, e-mail: yimeizhangymzy@163.com
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Background: We investigated the expression of HIF-1α (hypoxia-inducible factor-1α) and its correlations with pulmonary artery remodeling and right ventricular hypertrophy in PE (pulmonary embolism) rats.

Material/Methods: After the PE rat model was established, the dynamic changes of mPAP (mean pulmonary artery pressure), PAMT (relative medial thickness of small pulmonary arteries), WA/TA (vessel wall area/total area), and RVHI (right ventricular hypertrophy index) were detected. Then, histomorphology of pulmonary vascular was observed, followed by HIF-1α mRNA and protein for pulmonary artery and right ventricle were checked via *in situ* hybridization and immunohistochemistry, respectively. The correlations between HIF-1α and mPAP, PAMT, WA/TA, and RVHI were analyzed.

Results: The mPAP level increased from the initial time to 12 weeks of PE and reached the peak at 12 weeks. After 4 weeks of PE, PAMT increased compared with the initial control group ($p<0.05$), and increased further after 8 weeks and 12 weeks. Changes of the vessel WA/TA were the same as PAMT. Compared with the initial control group, RVHI increased at 8 weeks ($p<0.05$) and 12 weeks of PE ($p<0.01$). HIF-1α mRNA and protein were positively correlated with mPAP, PAMT, and WA/TA in pulmonary arteries. HIF-1α mRNA and protein were positively correlated with mPAP, PAMT, WA/TA, and RVHI in right ventricles ($p<0.01$).

Conclusions: HIF-1α mRNA and protein are expressed in the pulmonary artery and right ventricular of PE rats, and HIF-1α may correlate with pulmonary artery remodeling and right ventricular hypertrophy in rats with PE.

MeSH Keywords: **Lung Abscess • Hypoxia-Inducible Factor-Proline Dioxygenases • Hypertrophy, Right Ventricular • Airway Remodeling • Cell Hypoxia**

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Background

Pulmonary embolism (PE) is an important cardiopulmonary disease, with an annual incidence rate of 1 per 1000 individuals, hospitalizing approximately 150,000 Americans each year [1]. It may lead to acute life-threatening but potentially reversible right ventricular failure via occluding the pulmonary arterial bed [2]. One of the consequences of PE is arterial hypoxemia [3], which leads to substantial pulmonary vascular remodeling and further results in pulmonary hypertension and right ventricular hypertrophy, and finally right heart failure and death [4].

Hypoxia-inducible factor-1α (HIF-1α) is a specific transcription factor for cells to adapt to the hypoxia response [5,6] by regulating the oxygen homeostasis, vascular remodeling, and other biological processes [4]. HIF-1α plays an important role in hypoxia signal transmission [7]. In a low oxygen environment, HIF-1α is expressed in various cells of pulmonary tissue, such as alveolar, bronchial epithelial cells, and endothelial cells [6,8]. In smooth muscle cells, HIF-1α knockdown inhibits hypoxia-induced proliferation [9], which suggests that HIF-1α may be associated with pulmonary vascular remodeling. In addition, in vascular smooth muscle, HIF-1α regulates pulmonary hypertension in chronic hypoxia [10]. However, much is yet to be determined regarding the role of HIF-1α in the development of pulmonary hypertension in PE, and the accompanying vascular remodeling is not completely understood.

In the present study, HIF-1α mRNA and protein expression for pulmonary artery and right ventricle were detected via *in situ* hybridization and immunohistochemistry, respectively. In addition, the correlations between HIF-1α expression and pulmonary artery remodeling and right ventricular hypertrophy after PE were investigated.

Material and Methods

Animals

A total of 80 male Wistar rats (220±10 g, 6–8 weeks) were provided by the Animal Experimental Center of the First Hospital of Harbin Medical University (Harbin, China). All animal procedures were approved by the Institutional Animal Care and Use Committee. Rats were randomly divided into 8 groups (10 in each group): initial control group, 6 experimental groups (3 days and 1, 2, 4, 8, 12 week(s) after modeling) and a terminal control group (12 weeks of modeling).

Pulmonary embolism (PE) model

Rats were anaesthetized by intraperitoneal injection of xylazine (3 mg/kg) and ketamine (70 mg kg). Then, PE was induced in anaesthetized rats by injecting polystyrene microspheres (1.3 million/100 g body weight, 25±1 μm; no. 7525A; Duke Scientific, Palo Alto, CA) into the right jugular vein, as previously described [11]. Animals in initial and terminal control received vehicle (0.01% Tween 20 at 0.16 ml/100 g body weight), but not microspheres. Surgical incisions were sealed with staples and animals recovered for the period indicated in each experimental group.

Detection of the mean pulmonary artery pressure (mPAP) and right ventricular hypertrophy index (RVHI) measurement

mPAP was detected as described previously [12]. After rats were anesthetized, a specially designed single-lumen catheter was inserted into the main pulmonary artery through the right jugular vein. Then, mPAP was detected using PowerLab monitoring equipment (AD Instruments Pty Ltd., Milford, MA).

Hearts were removed from anesthetized rats via midline thoracotomy and placed in ice-cold saline. Then, the right ventricle and left ventricle were isolated and weighed, and RVHI was calculated by determining the weight ratio of the right ventricle (RV) to left ventricle (LV) and interventricular septum (S) (RV/[LV+S]).

Histomorphological observation

Pulmonary tissues were cut from anesthetized rats, embedded in paraffin, and sectioned into 4-μm-thick sections. Then, sections were stained by Hematein-Eosin (HE) staining and mounted. Two random pulmonary tissue slices of each rat were selected and 5 random areas of 100–150 μm pulmonary arteries were analyzed using Motic Images Advanced 3.0 (Motic Instruments Inc., British Columbia, Canada). Pulmonary artery diameter, vascular lumen diameter, vascular lumen area, vessel wall area (WA), total area (TA), and medial thickness of pulmonary arteries were measured by use of Motic Images Advanced 3.0. The relative medial thickness of pulmonary arteries (PAMT) and WA/TA were calculated and recorded as the indexes of pulmonary artery remodeling.

In situ hybridization of HIF-1α

In situ hybridization was performed to measure HIF-1α mRNA according to the instructions of *in situ* hybridization detection kit (Boster Biological Technology Co., Wuhan, China). The sequences of probes against HIF-1α mRNA were: 5'-CAAAG CTCTG AGTAA TTCTT CACCCTGCAG-3'; 5'-ATCAT ATACG TGAAT GTGGCCTGTG CAGTG-3'; 5'-GTGAC AACTG ATCAA AGGAACGTAA TCGGA-3', which were designed according to the sequences of rat HIF-1α by Boster Biological Technology Co. Hybridization was carried out on serial paraffin-embedded lung tissue slices which were fixed by formalin (containing 0.1% diethyl pyrocarbonate). Briefly,

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sections were first digested with pepsin for 20 min at 37°C, and after prehybridization for 2 h, sections were incubated with digoxin-labelled single-stranded oligonucleotide probes for 16 h at 37°C (negative control was incubated with blank probes solution). After unbound probes were washed off, sections were incubated with rabbit antibodies against digoxin and with biotinylated goat anti-rabbit secondary antibodies, followed by incubated with streptavidin horseradish peroxidase (HRP). Then, sections were visualized with diaminobenzidine (Boster Biological Technology Co.). Finally, sections were counterstained with hematoxylin and mounted. Expression levels of mRNA were quantified and analyzed using PIPS-2020 pathology image analysis system (Chongqing Tianhai Company, Chongqing, China).

Immunohistochemical analysis of HIF-lα

The expression of HIF-lα protein was detected by streptavidin-peroxidase conjugate as previously described [13]. Heart and lung tissues were fixed, sliced, and inactivated. Then, sections were blocked and incubated with the primary rabbit anti-HIF-1α polyclonal antibody (1: 200, Boster Biological Technology Co.) at 4°C overnight and with the biotinylated secondary antibody (1: 100, Boster) for 1 h. After added horseradish peroxidase-tagged streptavidin working solution (S-A/HRP), the sections were developed in DAB (Boster Biological Technology Co.). The mean absorbance (A) of pulmonary arterial wall was detected and used as the relative protein expression levels of HIF-lα.

Statistical analysis

All analyses were performed with SPSS 13.0 software (SPSS Inc, Chicago, IL). Data are expressed as mean ±standard derivation (SD). Comparisons of different groups were made by one-way ANOVA with the Fisher LSD post hoc test. Correlation analysis was performed by Pearson's correlation. Significance was determined as $p<0.05$ using two-tailed testing.

Ethical approval

The research was conducted in accordance with the Declaration of Helsinki and with the Guide for Care and Use of Laboratory Animals as adopted and promulgated by the United National Institutes of Health. All experimental protocols were approved by the Review Committee for the Use of Animal Subjects of the Shanghai Fengxian District Central Hospital.

Results

Dynamic changes of mPAP, PAMT, WA/TA, and RVHI

As shown in Figure 1, mPAP level increased from initial control time to 12 weeks of PE, reaching the peak at 12 weeks,

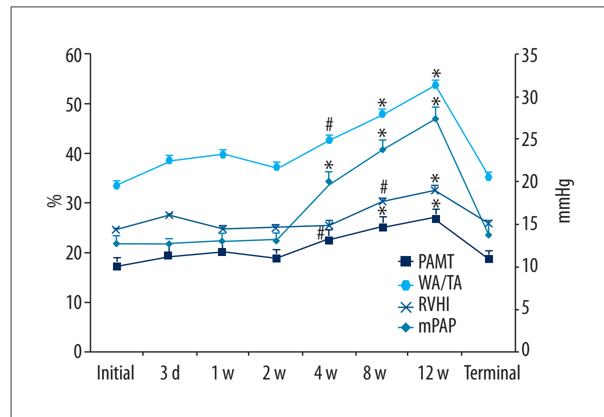

Figure 1. Dynamic changes of mean pulmonary artery pressure (mPAP), relative medial thickness of small pulmonary arteries (PAMT), vessel wall area/total area (WA/TA), and right ventricular hypertrophy index (RVHI). # $p<0.05$; * $p<0.01$. Vertical axis on the right represents mPAP levels; Vertical axis on the left represents PAMT, WA/TA, and RVHI.

and then decreased at terminal control time. mPAP level was higher in 4 weeks (19.90±1.21 mmHg), 8 weeks (23.78±1.12 mmHg), and 12 weeks (27.43±1.41 mmHg) than that in the initial group (12.70±0.93 mmHg, $p<0.01$). After 4 weeks of PE, PAMT increased compared with the initial control group (22.75±6.79% *vs.* 17.33±3.60%, $p<0.05$). PAMT further increased after 8 weeks (25.32±4.90%) and 12 weeks (27.05±7.71%) of PE compared with the initial control group ($p<0.01$). The changes of WA/TA were the same as PAMT. Compared with the initial control group (24.53±0.52%), RVHI increased in 8 weeks of PE (30.23±0.60%, $p<0.05$) and 12 weeks of PE (32.43±1.05%, $p<0.01$). No significant differences of mPAP, PAMT, WA/TA, and RVHI were found between the 2 control groups ($p>0.05$).

HIF-1α mRNA and protein expression in pulmonary artery

HIF-1α mRNA and protein expression in pulmonary artery were detected using *in situ* hybridization and immunohistochemistry, respectively. HIF-1α mRNA expression in pulmonary artery walls was increased by 4 weeks of PE (Figure 2A), and HIF-1α protein expression in pulmonary artery walls was increased by 1 week of PE (Figure 2B). As shown in Figure 2C, HIF-1α mRNA level gradually increased from 3 days of PE, reached the peak at 4 weeks, and then decreased. In addition, compared with the initial control group (0.064±0.017), HIF-1α mRNA levels increased significantly from 2 weeks (0.137±0.029) to 12 weeks (0.149±0.033) of PE ($p < 0.01$). HIF-1α protein levels increased from 3 days of PE (0.196±0.031), reached the peak at 1 week (0.228±0.032), and then decreased until 12 weeks of PE (0.095±0.020).

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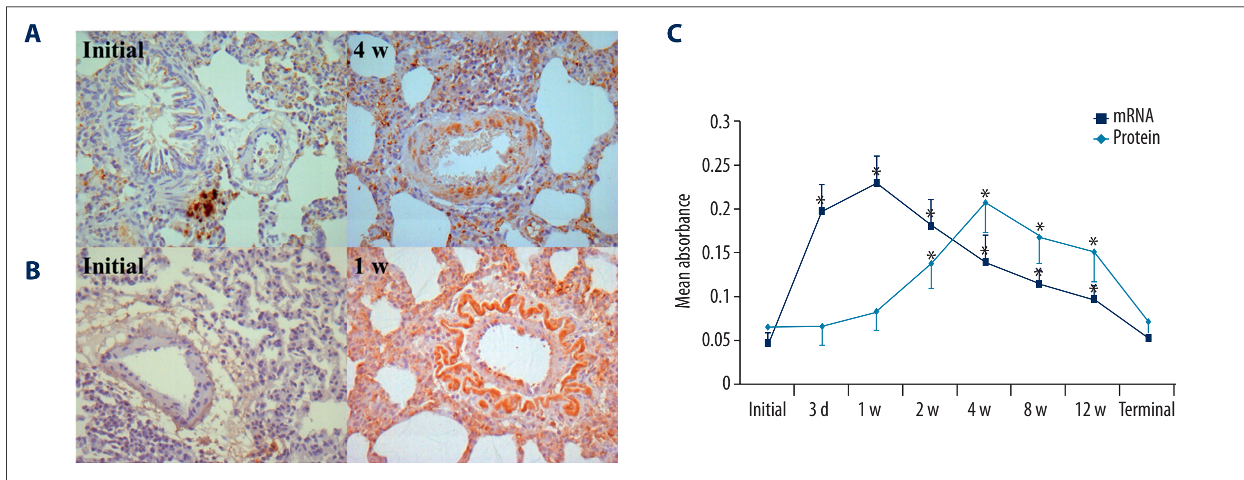

Figure 2. HIF-1α mRNA (**A**) and protein expression (**B**) using *in situ* hybridization, (400×) immunohistochemistry (400×), and the relative expression levels (**C**) in pulmonary artery. * $p<0.01$.

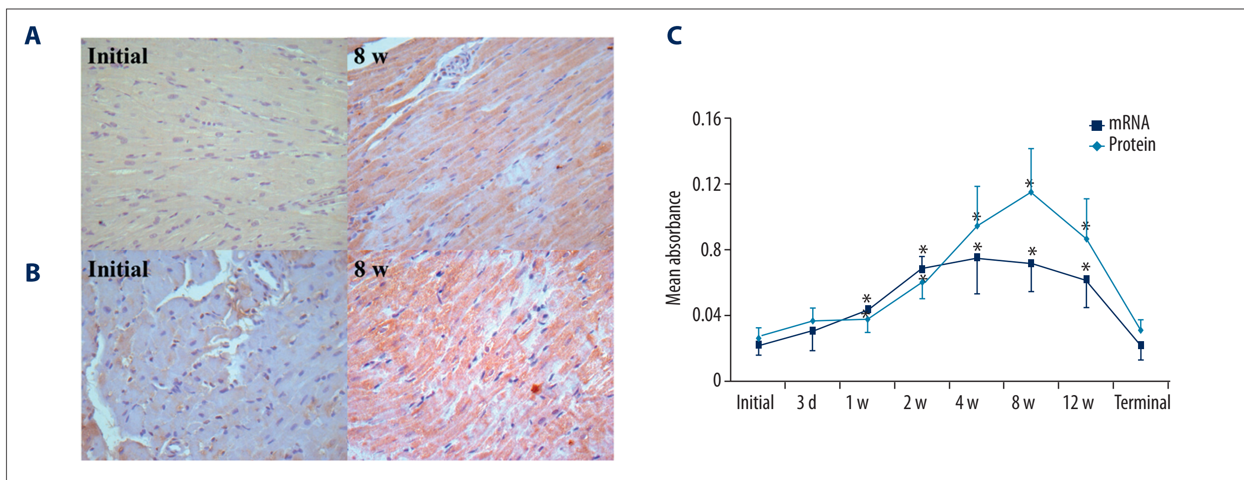

Figure 3. HIF-1α mRNA (**A**) and protein expression (**B**) using *in situ* hybridization, (400×) immunohistochemistry (400×), and the relative expression levels (**C**) in right ventricle. * $p<0.01$.

HIF-1α mRNA and protein expression in right ventricles

In the right ventricles, HIF-1α mRNA and protein staining was poorly positive in the initial control group, but strongly positive at 8 weeks of PE (Figurte 3A, 3B). As shown in Figure 3C, HIF-1α mRNA expression level began to increase from 1 week (0.037±0.007), reached the peak at 8 weeks (0.114±0.027), and was significantly higher than the initial control group (0.026±0.006, $p<0.05$). Similarly, HIF-1α protein expression level increased from 1 week until 12 weeks, and was significantly higher compared with the initial control group ($p<0.05$).

Correlation analysis

Linear correlation analysis was performed between different parameters. Correlation analysis (Table 1) showed that HIF-1α mRNA in pulmonary artery were positively correlated with mPAP (r=0.715, $p<0.01$), PAMT (r=0.692, $p < 0.01$), WA/TA (r=0.686, $p<0.01$) and RVHI (r=0.614, $p<0.01$). HIF-1α protein in the pulmonary artery was positively correlated with mPAP (r=0.410, $p<0.01$), PAMT (r=0.234, $p<0.05$), and WA/TA (r=0.382, $p<0.05$). In addition, HIF-1α mRNA and protein in right ventricles were positively correlated with mPAP, PAMT, WA/TA, and RVHI ($p<0.01$).

Discussion

The present study reveals 2 important concepts. First, HIF-1α mRNA and protein were progressively upregulated in the pulmonary arteries of PE rats. Second, HIF-1α in pulmonary vascular correlates with the remodeling events and pulmonary hypertension.

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Table 1. Correlation analysis of mPAP, PAMT, RVHI, WA/TA and HIF-1α.

Group	mPAP	PAMT	WA/TA	RVHI
PA HIF-1α mRNA	0.715*	0.692*	0.686*	0.614*
PA HIF-1α protein	0.410*	0.234#	0.382#	0.152
RV HIF-1α mRNA	0.837*	0.796*	0.796*	0.737*
RV HIF-1α protein	0.691*	0.740*	0.758*	0.663*

# $p<0.05$; * $p<0.01$. PA – pulmonary artery; RV – right ventricle; mPAP – mean pulmonary artery pressure; PAMT – relative medial thickness of small pulmonary arteries; RVHI – right ventricular hypertrophy index; WA – vessel wall area; TA – total area; HIF-1α – hypoxia-inducible factor-1α.

It has been found that HIF-1α can confer different kinds of target genes and plays an essential role in hypoxic-induced pulmonary hypertension [14]. In the present study, we found that HIF-1α mRNA was expressed in the experimental group and the levels gradually increased from 3 days of PE, reached a peak at 4 weeks, and then decreased. In agreement with our results, Jiang et al. [15] also found that HIF-1α mRNA and protein were expressed in pulmonary arterial walls. In addition, experiments confirmed that there was no HIF-1α protein expression in healthy human myocardial fibers, but there was time-dependant HIF-1α protein expressions in myocardial ischemia [16].

Our study found that the activation of HIF-1α in the pulmonary artery plays an essential role in vascular remodeling by promoting increased PAMT, mPAP, WA/TA, and RVHI during PE, indicating that HIF-1α might participate in pulmonary artery remodeling and right ventricular hypertrophy. Ball et al. [17] indicated that HIF-1α in smooth muscle might be correlated with pulmonary vascular remodeling and pulmonary hypertension. Studies also suggested that the activation of HIF in migratory bone marrow progenitor cells could help the remodeling response, which also implicated the HIF-independent pathways [18,19]. Right ventricular remodeling may exhibit an adaptive response to pulmonary hypertension, enhancing the ability of the heart to deal with the increase in afterload. Other reports show that pulmonary artery pressure is not the only factor regulating cardiac hypertrophy through the up-regulation of gene expression [20]. HIF-1α functions as the primary oxygen-sensing pathway, which may explain the conversion of heart metabolism to the fetal gene program [21] and the shift from fatty acids to glucose [22]. A previous study of experimental PE has shown that HIF-1α is also induced in the right ventricle [23]. Aimee et al. indicated that HIF-1α plays a significant part in the development of hypoxic pulmonary hypertension [24]. In addition, Bohuslavova et al. [25] found attenuated pulmonary hypertension and right ventricular hypertrophy during chronic hypoxia in HIF-1α heterozygous mice, again consistent with the conclusion that HIF-1α may be associated with pulmonary hypertension and right ventricular hypertrophy.

It has been confirmed that HIF-1α has about 70 target genes, such as ET-1, vascular endothelial growth factor (VEGF), and inducible nitric oxide synthase (iNOS) [26]. We speculate that HIF-1α may participate in pulmonary artery remodeling and right ventricle remodeling after PE by regulating the target genes through cell apoptosis, cell proliferation, and vessel neogenesis pathways. However, this needs to be identified and verified by bioinformatics and experiments in future.

Some limitations for this study should be noted. First, our analysis of pulmonary artery remodeling was restricted to 100–150 μm pulmonary arteries located adjacent to airways. Furthermore, smaller arteries were excluded because of the difficulty in distinguishing them from pulmonary veins. Second, mechanisms of HIF-1α functions on pulmonary artery remodeling and right ventricular hypertrophy were not studied.

Conclusions

HIF-1α mRNA and protein are expressed in the pulmonary artery and right ventricle of PE rats, and HIF-1α may be associated with pulmonary artery remodeling and right ventricular hypertrophy in rats with PE.

Conflicts of interests

All authors declare that they have no conflicts of interests to state.

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