Variations of Postresuscitation Lung Function after Thrombolysis Therapy in a Cardiac Arrest Porcine Model Caused by Pulmonary Thromboembolism

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Background: Study of lung function in survivor from cardiac arrest (CA) caused by pulmonary thromboembolism (PTE) was rare. The aim of this study was to investigate the variations of postresuscitation lung function after thrombolysis treatment in a CA porcine model caused by PTE.

Methods: After 2 min of untreated CA, pigs of 10–12 weeks with a weight of 30 ± 2 kg (n = 24) were treated with recombinant human tissue plasminogen activator (50 mg). Cardiopulmonary resuscitation (CPR) and ventilation were initiated after drug administration. Pulmonary function and arterial blood gas parameters were measured at baseline, return of spontaneous circulation (ROSC) immediately, and 1 h, 2 h, 4 h, and 6 h after ROSC.

Results: The dynamic lung compliance decreased significantly at ROSC immediately and 1 h after ROSC compared to baseline (21.86 ± 2.00 vs. 26.72 ± 2.20 ml/mmHg and 20.38 ± 1.31 vs. 26.72 ± 2.20 ml/mmHg, respectively; P < 0.05; 1 mmHg = 0.133 kPa). Compared with baseline, airway resistance increased significantly at ROSC immediately and 1 h after ROSC (P < 0.05). Respiratory index also increased after ROSC and showed significant differences among baseline, ROSC immediately, and 2 h after ROSC (P < 0.05). Oxygen delivery decreased at ROSC immediately compared to baseline (P < 0.05). The oxygenation index decreased significantly at any time after ROSC compared to baseline (P < 0.05). Extravascular lung water index and pulmonary vascular permeability index (PVPI) showed significant differences at ROSC immediately compared to baseline and 1 h after ROSC (P < 0.05); PVPI at ROSC immediately was also different from 6 h after ROSC (P < 0.05). Ventilation/perfusion ratios increased after ROSC (P < 0.05). Histopathology showed fibrin effusion, bleeding in alveoli, and hemagglutination in pulmonary artery.

Conclusions: Lung function remains abnormal even after CPR with thrombolysis therapy; it is essential to continue anticoagulation and symptomatic treatment after ROSC.

Key words: Heart Arrest; Pulmonary Embolism; Pulmonary Function; Resuscitation

INTRODUCTION

Cardiac arrest (CA) is a worldwide challenge. It accounts for nearly 500,000 deaths annually in the USA and Europe.[1-3] Conventionally, CA is categorized as cardiac and noncardiac origin. Unless it is caused by asphyxia, trauma, or any other noncardiogenic disease, it is presumed to be cardiac origin. The exact causes of many CA cases are unknown, and the rate of survival is still low.[4] Venous thromboembolism has a high incidence in the world.[5,6] Studies from Western Europe, North America, Australia, and Southern Latin America (Argentina) yielded consistent results with annual incidences ranging from 0.75 to 2.69 per 1000 individuals in the population.[7] Thrombosis from the deep venous system

Access this article online

Quick Response Code: 
Website: www.cmj.org
DOI: 10.4103/0366-6999.207481

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Received: 12-01-2017 Edited by: Qiang Shi
How to cite this article: Yang J, Zhao LX, Li CS, Tong N, Xiao HL, An L. Variations of Postresuscitation Lung Function after Thrombolysis Therapy in a Cardiac Arrest Porcine Model Caused by Pulmonary Thromboembolism. Chin Med J 2017;130:1475-80.
could block the pulmonary artery which leads to very serious consequences, especially high-risk pulmonary thromboembolism (PTE) which is an important reason for CA. It may contribute to 8–13% of unexplained CA cases, which may be potentially reversible processes.

PTE has impacts on pulmonary ventilation and gas exchange. Bronchial smooth muscle contraction increases airway resistance, which increases the work of breathing; PTE increases the dead space and ventilation/perfusion (V/Q) ratio; on the other hand, alveolar collapse, atelectasis, and bronchospasm decrease the V/Q ratio. Arterial blood gas shows hyperventilation and partial pressure of oxygen (PO₂) decreasing. The patient of CA caused by PTE is difficult to rescue because of diagnostic difficulties in clinical practice. There are no diagnostic or prognostic tests currently available for detecting and tracking PTE except image. Previous studies have focused more on nonfatal PE and the diagnosis and treatment of chronic thromboembolic pulmonary hypertension, less involved in the occurrence of CA caused by PTE. The dynamic pathogenesis and pathophysiology of lung function of CA caused by PTE are still not very clear.

In view of these, we designed this experiment, a CA porcine model caused by PTE, to investigate the dynamic characteristics of pulmonary function in postresuscitation after thrombolytic treatment.

**Methods**

**Ethical approval**

This study was approved by the Capital Medical University Institutional Animal Care and Use Committee (Institutional protocol number: 2010-D-013) and the treatments for animal were in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 8023. revised 1978). We have taken all steps to minimize the animal’s pain and suffering.

**Study design**

**Animal preparation**

Twenty-four castrated Beijing Landrace male pigs aging 10–12 weeks with an average weight of 30 ± 2 kg were used in this study. Animals were fasted overnight but had free access to water. After premedication with intramuscular midazolam (0.2 mg/kg) and atropine (1 mg), anesthesia was induced by intravenous (IV) bolus of propofol (2 mg/kg) and fentanyl (5 µg/kg), and maintained with continuous IV infusion of pentobarbital (8 mg·kg⁻¹·h⁻¹) and fentanyl (5 µg·kg⁻¹·h⁻¹). Animals were intubated by a cuffed 6.5 mm endotracheal tube and ventilated by a volume-controlled ventilator (Evita 4, Drager Medical, Lubeck, Germany) with tidal volume of 8 ml/kg, and respiratory rate of 15 breaths/min with 30% oxygen. End-tidal carbon dioxide partial pressure (PetCO₂) was measured with an in-line mainstream infrared capnograph (CO₂SMO Plus Monitor, Respironics Inc., Murrysville, PA, USA). PetCO₂ was maintained between 35 and 45 mmHg (1 mmHg = 0.133 kPa) by adjusting respiratory parameters before inducing CA. Room temperature was adjusted to 27°C.

A 5-French (Fr) arterial catheter (Pulsicath PV2015L20, PULSION Medical Systems, Munich, Germany) was inserted into the left femoral artery; a 5-Fr central venous catheter (ARROWg + ard Blue Central Venous Catheters; Arrow International, Inc., USA) was placed into the left femoral vein. They were connected to a PiCCO device (PULSION Medical Systems, Munich, Germany). A Swan-Ganz catheter (Swan-Ganz CCO mbo CCO/SvO₂, 7.5 Fr; Edwards Lifesciences, Irvine, CA, USA) was advanced to the right external jugular vein and flow directed into the pulmonary artery. A large bore catheter (diameter 1 cm) was inserted into the right ventricle through the left external jugular vein for injecting blood clots.

**Embolus preparation**

For the embolus preparation, 50 ml venous blood was drawn into a 50 ml syringe, and 50 units lyophilizing thrombin solution was added into the syringe. Then, the blood was left for half an hour at room temperature to get a stable, gelatinous clot. The clot was fragmented into emboli which were 1.5 cm in diameter. 10–15 ml of thrombi was suspended in saline solution which was placed in a 50 ml syringe.

**Experimental protocol**

The animals were stabilized for 1 h before beginning the experiment. Then, the thrombi were injected into pulmonary artery through the large bore catheter within 1 min until circulation arrest occurred which presented as systolic aortic pressure <30 mmHg.[17] After 2 min of untreated CA, the pigs were treated with recombinant human tissue plasminogen activator (50 mg) (Alteplase, Boehringer Ingelheim, Shanghai, China).[18] Cardiopulmonary resuscitation (CPR) was performed and the compression-to-ventilation ratio was 30:2; ventilation was performed using a bag respirator with room air. Epinephrine (0.02 mg/kg) was given intravenously followed by CPR. If ventricular fibrillation occurred, defibrillation shock was performed at 150 J. If the defibrillation was unsuccessful, after each 2 min of CPR, a 10 s pause was interjected to prepare for the next defibrillation attempt. The electrocardiogram and the quality of chest compressions were monitored by a HeartStart MRx monitor/defibrillator (Philips Medical Systems, Best, Holland) with Q-CPR technology. Return of spontaneous circulation (ROSC) was defined as the presence of an organized rhythm with a mean aortic pressure of ≥60 mmHg maintained more than 10 consecutive min.[17]

After successful resuscitation, the pigs underwent a 6 h intensive care period and mechanical ventilation was resumed with the same setting as before CA. At the end of the study, the pigs were euthanized with an IV bolus of propofol 60 mg and then 10 mol/L potassium chloride.
Lung ventilation/perfusion scans
High-probability ventilation-perfusion lung scans were performed at baseline and 4 h after ROSC for the surviving animal. Images were acquired with a 128 × 128 dual-head gamma camera (Helix; Elgems, Haifa, Israel). A total of 740 MBq $^{99m}$Tc aerosols were inspired through a closed delivery system by tracheal intubation and ventilation images were obtained. Then, 550 MBq $^{99m}$Tc was injected through the jugular vein, and perfusion images were obtained.

Measurements
Heart rate, blood pressure, central venous pressure, electrocardiogram, and blood temperature were monitored (M8001A, Philips Medizin Systeme Boeblingen GmbH, Germany). Arterial blood samples were drawn for blood gas analyses (GEM Premier 3000 Blood Gas Analyzer; Instrumentation Laboratory, Lexington, MA, USA). Oxygenation index (OI), respiratory index (RI), and lactate were derived from arterial blood gas analysis. Oxygen delivery (DO$_2$) was calculated from cardiac index and arterial oxygen content (CaO$_2$). Dynamic lung compliance (Cdyn) and airway resistance (Raw) were got from ventilator (Evia 4, Drager Medical, Germany). Extravascular lung water index (EVLWI) and pulmonary vascular permeability index (PVPI) were obtained from a PiCCO device (PULSION Medical Systems, Munich, Germany). PetCO$_2$ was measured using an in-line mainstream infrared capnograph (CO$_2$SMO Plus Monitor; Respironics Inc., Murrysville, PA, USA). Moreover, ventilation/perfusion (V/Q) ratio was calculated. All the above-mentioned parameters were registered at baseline, ROSC immediately, and 1 h, 2 h, 4 h, and 6 h after ROSC. After the pigs were euthanized, its lung was perfusion and mismatches were found in the pigs [Figure 1c and 1d]. The V/Q ratios increased after ROSC and showed significantly different [Figure 2].

Respiratory parameters
Data of surviving animals at different times were analyzed for 11 pigs [Table 1]. The Cdyn decreased after resuscitation and showed significant difference at ROSC immediately and 1 h after ROSC compared with baseline ($P < 0.05$). The OI decreased significantly at any time after ROSC ($P < 0.05$). EVLWI and PVPI showed significantly different at ROSC immediately compared with baseline and 1 h after ROSC ($P < 0.05$); PVPI at ROSC immediately was also different from 6 h after ROSC ($P < 0.05$). The Raw increased significantly at ROSC immediately and 1 h after ROSC ($P < 0.05$). RI also increased after ROSC and showed significantly different among baseline, ROSC immediately, and 2 h after ROSC ($P < 0.05$). DO$_2$ decreased at ROSC immediately compared to baseline ($P < 0.05$).

Histopathology
Pulmonary infarction was found in the lung specimen. Very significant histopathologic lung injuries were found after ROSC: interalveolar septum thickening, bleeding and inflammatory cell infiltration in interalveolar septum, fibrin effusion and bleeding in alveoli, and hemagglutination in pulmonary artery [Figure 3].

Discussion
CA is one of the most severe clinical heart emergencies, to which high-risk PTE plays an important role as a noncardiogenic cause. Many CA deaths were attributed to cardiac origins except those patients with deep vein thrombosis, oral contraceptives, thrombophilia or pulmonary hypertension, and increased right ventricular found with ultrasound were suspected to be caused by PTE, and those who were survival after CPR with thrombolysis therapy were diagnosed as PTE. Data of the lung function of patients with PTE have been ongoing for a long time[19-21] and also the data of heart arrest.[22,23] However, the study about CPR with thrombolysis of CA caused by PTE was reported rarely. Based on this, we performed CPR with thrombolysis in a CA porcine model caused by PTE to investigate the success rate of ROSC, short-time survival rate, and the pulmonary function variations.

In our study, success rate of ROSC and 6 h survival rate were 58.3% and 45.8%, respectively, which demonstrated that the CPR with thrombolysis was an effective measure to the CA caused by PTE. Lung infarction in specimen and hemagglutination in pulmonary artery in histopathology which was a sign of thrombosis were found in animals which were survivals until 6 h after ROSC; Cdyn, OI, and DO$_2$ deteriorated significantly; Raw and RI increased significantly; V/Q ratio increased significantly which demonstrated dead space ventilation and pulmonary shunt; lung ventilation/perfusion scans showed mismatches at 4 h after ROSC which demonstrated perfusion defect; EVLWI
and PVPI decreased significantly at ROSC immediately compared to baseline, and compared to ROSC immediately, they increased significantly at 1 h after ROSC; all above indicated that pulmonary dysfunction remained abnormal after ROSC that provided theoretical basis for anticoagulation after ROSC.

The dysfunctions of gas delivery and exchange are the studying focuses on treatment of postresuscitation, to which V/Q ratio, oxygen transport, and oxygen utilization are crucial factors. The Raw was a transient increase which was different from CA model caused by ventricular fibrillation. It may attribute to platelet aggregation, endothelial cell injury, release of inflammatory mediators such as serotonin, histamine, bradykinin, platelet activating factor, and endothelin which could cause bronchial smooth muscle contraction. The EVLWI and PVPI are predictors for the acute lung injury. EVLW refers to the fluid within the lung but outside the vascular compartment. Because of the obstruction of pulmonary circulation and the pulmonary vasoconstriction which was caused by hypoxia, in our study, the EVLWI showed decrease significantly at ROSC immediately. After 1 h after ROSC, the EVLWI increased abnormally which may be because of elevated hydrostatic pressure caused by pulmonary circulation recovery and pulmonary vascular permeability attributed to hypoxia and acidosis, respectively. PVPI is calculated as the ratio between EVLWI and the pulmonary blood volume. It is found to be higher in ARDS and ALI than in hydrostatic lung edema. It may help differentiate between hydrostatic and nonhydrostatic lung edema. In the histopathology, we found bleeding and inflammatory cell infiltration in interalveolar septum, fibrin effusion, and bleeding in alveoli. Hence, the PVPI variation may be because of not only permeability of the alveolocapillary barrier and lung inflammation but also the integrity of the lymph drainage and alveolar fluid clearance which may be involved in PTE.

Post-CA syndrome has association with high mortality because of not only poor neurological outcome and cardiac dysfunction but also respiratory dysfunction. After recovery of pulmonary circulation, lung injury simultaneously became an important issue. We observed the surviving animals from ROSC immediately to 6 h after ROSC. The Cydn decreased from 26.72 ± 2.20 to 20.38 ± 1.31 ml/mmHg (1 h after ROSC), Raw increased

**Figure 1:** Lung ventilation/perfusion scans in pigs. (a) Ventilation image at baseline. (b) Perfusion image at baseline. (c) Ventilation image at 4 h after ROSC. (d) Perfusion image at 4 h after ROSC. ROSC: Return of spontaneous circulation.

**Figure 2:** The variation of ventilation/perfusion ratio of pigs at baseline and postresuscitation. *P < 0.05 versus baseline, † P < 0.05 versus ROSC. V/Q: Ventilation/perfusion ratio; ROSC: Return of spontaneous circulation.
form 12.72 ± 2.12 to 17.16 ± 2.24 cmH\(_2\)O·L\(^{-1}\)·s\(^{-1}\) 1 h after ROSC (1 cmH\(_2\)O = 0.098 kPa), and OI decreased from 473.97 ± 23.84 to 245.15 ± 34.64 mmHg 6 h after ROSC. Pulmonary dysfunction remained for a period after ROSC which may contribute to chronic thromboembolic pulmonary hypertension.\[31\] Lung is the target organ of PTE, according to whose pathophysiology it is essential to make the appropriate therapeutic measures. Inappropriate mechanical ventilator settings could do harm to the lung. Protective mechanical ventilation with low tidal volumes is standard of care for patients with acute respiratory distress syndrome (ARDS)\[32\] and also is associated with a lower risk of development of pulmonary complications in patients without ARDS.\[33\] In our study, EVLWI at 1 h after ROSC increased significantly. Positive-pressure ventilation (PPV) has a beneficial effect on pulmonary edema. PPV could reduce hypoxemic-induced pulmonary vasoconstriction and decrease metabolic demand. Former studies have shown that the application of positive end-expiratory pressure could increase the alveolar fluid clearance rate and decrease the EVLWI.\[34,35\] There were still limitations in our study. First, the injected thrombosis size was large; thrombi quantities were different among pigs. Second, the CPR was manually performed, its quality could not be 100% consistent, even by an independent, well-trained experimenter and monitored by Q-CPR technology. Third, the success rate of ROSC was relatively low. Fourth, the lung anatomy of pig is different from human.

In conclusion, the variations of lung function in CA caused by PTE are different from those by cardiogenic diseases. Moreover, lung dysfunction remains abnormal significantly even after CPR with thrombolysis therapy; it is essential to continue anticoagulation and symptomatic treatment after ROSC.

**Table 1: Lung function analysis of surviving pigs**

| Variables | Baseline | Immediately | 1 h | 2 h | 4 h | 6 h |
|-----------|----------|-------------|-----|-----|-----|-----|
| Raw (cmH\(_2\)O·L\(^{-1}\)·s\(^{-1}\)) | 12.72 ± 2.12 | 17.58 ± 2.20* | 17.16 ± 2.24* | 14.59 ± 1.03 | 16.11 ± 1.45 | 16.24 ± 1.44 |
| OI (mmHg) | 473.97 ± 23.84 | 223.88 ± 19.86* | 251.76 ± 34.6* | 282.09 ± 24.20* | 239.09 ± 30.99* | 245.15 ± 34.64* |
| RI       | 0.26 ± 0.05  | 2.15 ± 0.36* | 2.69 ± 1.11 | 1.18 ± 0.18* | 1.54 ± 0.50 | 1.32 ± 0.43 |
| DO\(_2\) (ml·min\(^{-1}\)·m\(^{-2}\)) | 665.65 ± 52.7 | 393.46 ± 61.47* | 456.76 ± 37.61 | 479.98 ± 75.25 | 440.25 ± 76.8 | 498.02 ± 83.58 |
| Cdyn (ml/mmHg) | 26.72 ± 2.20 | 21.86 ± 2.00* | 20.38 ± 1.31* | 23.49 ± 1.94 | 22.39 ± 2.09 | 22.15 ± 1.92 |
| EVLWI (ml/kg) | 9.15 ± 0.48 | 7.21 ± 0.35* | 11.76 ± 0.58† | 10.21 ± 1.02 | 9.91 ± 0.81 | 10.66 ± 0.85 |
| PVPI     | 2.12 ± 0.08  | 1.75 ± 0.08* | 2.76 ± 0.15† | 2.67 ± 0.22 | 2.79 ± 0.33 | 2.78 ± 0.23† |

*P<0.05 versus baseline; †P<0.05 versus ROSC immediately. Raw: Airway resistance; OI: Oxygenation index; RI: Respiratory index; DO\(_2\): Oxygen delivery; Cdyn: Dynamic lung compliance; EVLWI: Extravascular lung water index; PVPI: Pulmonary vascular permeability index; ROSC: Return of spontaneous circulation.

**Figure 3:** Specimen and histopathology of the lung of pigs (HE staining, ×400). (a) Pulmonary specimen, lung infarction. (b) Pig without CA caused by PTE. (c) Postresuscitation of CA pig caused by PTE. ① Fibrin effusion and bleeding in alveoli. ② Bleeding and inflammatory cell infiltration in interalveolar septum. CA: Cardiac arrest; PTE: Pulmonary thromboembolism.
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