Diagn Interv Radiol 2012; 18:127–131

Balloon occlusion of the right main bronchus in an ovine model provides sufficient time for emergent interventions in massive pulmonary embolism

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PURPOSE
Massive pulmonary embolism (PE) causes hemodynamic compromise and is associated with a high rate of mortality. We sought to create a model of massive PE and to determine whether occlusion of the right main bronchus could mitigate the physiological effects of massive PE in this model.

MATERIALS AND METHODS
We used 27 female sheep to generate a model of massive PE by either autologous blood clot injection (n=18) or detachable balloon release (n=9) into the right main pulmonary artery. Four sheep were excluded after blood clot injection, as they did not exhibit adequate declines in blood oxygen saturation (SaO_2). Nine of the sheep that received autologous blood clot and nine that received detachable balloons went on to treatment with right main bronchus occlusion. The control group (n=5) received the autologous blood clot, but no occlusion of the right main bronchus. All sheep underwent continuous monitoring of pulmonary arterial mean pressure (PAMP), SaO_2, arterial partial pressure of oxygen (PaO_2), and arterial partial pressure of carbon dioxide.

RESULTS
Twenty-three sheep (85%) subjected to PE demonstrated immediate tachycardia, tachypnea, and decline in SaO_2 of at least 25% within 30 min. After right main bronchus occlusion, 18 sheep (100%) survived for the length of the experiment and exhibited persistently higher SaO_2 and PaO_2 levels, as well as decreased PAMP compared with the controls. In the control group, two out of five sheep died within 30 min, and the three surviving subjects demonstrated significantly decreased SaO_2 and PaO_2 levels.

CONCLUSION
Occlusion of the right main bronchus in an ovine model of massive PE effectively extends life and provides favorable physiological parameters to allow emergent interventions.

Key words: • *pulmonary embolism* • *ventilation-perfusion ratio* • *balloon catheterization* • *animal experimentation*

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Received 12 April 2011; revision requested 17 April 2011; revision received 6 May 2011; accepted 31 May 2011.

Published online 24 October 2011
DOI 10.4261/1305-3825.DIR.4069-10.2

Pulmonary embolism (PE) is a major public health problem with an incidence of approximately 1 350 000 cases per year in the USA alone. Major PE, defined as PE leading to hemodynamic instability, is typically due to massive PE that leads to right heart failure, and it is associated with a thirty-day mortality of roughly 30% (1–3). In instances of acute PE, most deaths occur within one hour of presentation with mortality rates ranging from 5% to 15%; this value is increased three- to seven-fold when the condition of shock is present (4). Time-to-treatment is among the most important factors determining the success of life-saving interventions (4). First-line treatment involves anticoagulation (5). For major PE, the accepted guidelines recommend endovascular treatment if anticoagulation is contraindicated or if there is insufficient time for thrombolytic therapy to be effective (6, 7). Despite anticoagulation, thrombolytic therapy or even surgical embolectomy, rates of mortality remain high. Endovascular treatment, including mechanical thrombectomy, is a promising option, especially with current technologic advances (8–10).

The primary physiologic perturbation in PE is a ventilation-perfusion mismatch, which causes a decrease in arterial oxygen levels (PaO_2). Right-to-left shunting that occurs via intracardiac pathways, for example, is induced and contributes to hypoxemia. Massive PE also increases physiological and anatomic dead space, which causes increased arterial carbon dioxide levels ($PaCO_2$). There is compensatory pulmonary arterial vasoconstriction, causing pulmonary arterial hypertension with a doubling of the pulmonary artery mean pressure (PAMP) to approximately 40 mmHg, which, in turn, can induce right heart failure (11). Irreversible right ventricular failure is the main cause of death in patients with massive PE.

Our hypothesis was that balloon occlusion of the main bronchus ipsilateral to a massive PE will reduce the ventilation-perfusion mismatch and, consequently, delay the progressive development of this physiological cascade. To test this hypothesis, we created an ovine model of massive PE using either the injection of an autologous blood clot or deployment of a detachable balloon in the pulmonary artery. In animals with significant hypoxemia, we occluded the ipsilateral main bronchus to determine whether physiological derangements of PE were prevented or attenuated.

Materials and methods

Subjects and general procedural technique

The study was approved by the Tianjin Medical University Institutional Animal Care and Use Committee. We used 27 adult female sheep weighing 21 to 33 kg with a mean weight of 28 kg. Anesthesia included induction with intraperitoneal injection of 5% pentobarbital sodium

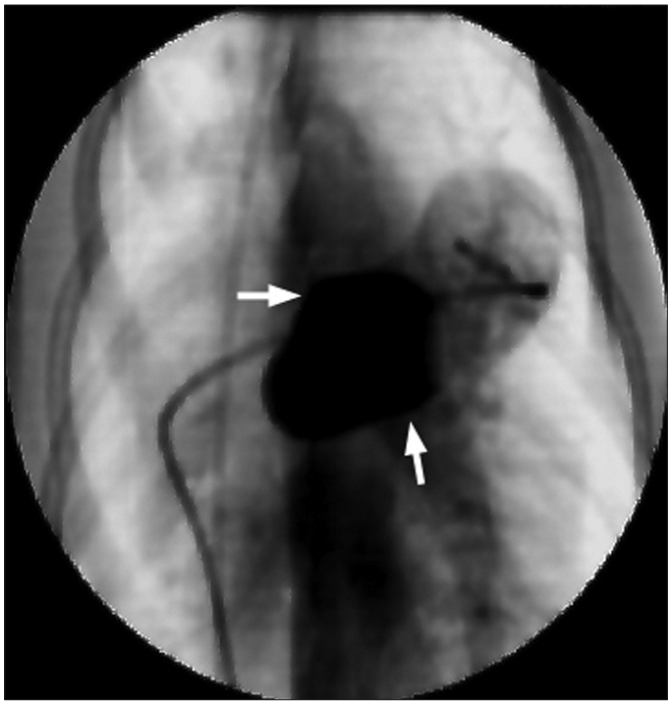

Figure 1. Plain radiograph showing the right pulmonary artery occluded by an inflated detachable latex balloon (*arrows*).

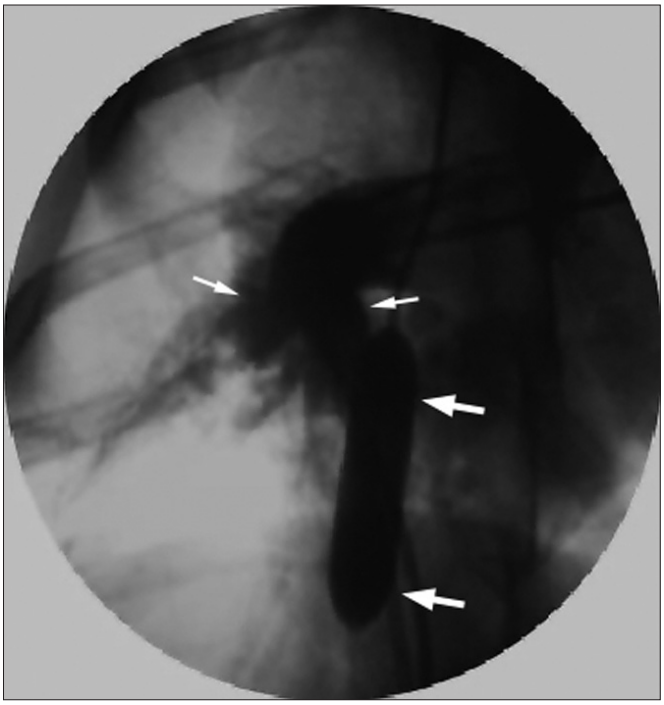

Figure 2. Plain radiograph showing the right pulmonary artery occluded via autologous blood clot (*thin arrows*), and the right main bronchus occluded by an inflated balloon (*thick arrows*).

(0.2 mL/kg), ketamine (7.5 mg/kg), and diazepam (0.25 mg/kg) followed by maintenance with a continuous intravenous drip of ketamine and diazepam. Previously described general animal care guidelines were followed (12). One or two sheep were studied per day.

The sheep were placed in the supine position, and a single lumen tracheal tube was inserted. Short vascular sheaths (Cook Medical, Bloomington, Indiana, USA) were placed, as follows: 1) on the right, a single 12 F sheath was inserted into the common femoral vein; 2) on the left, a 4 F sheath was inserted into the common femoral artery; and two 4 F sheaths were inserted into the common femoral vein. From the right-sided sheath, we withdrew 50 mL of blood and incubated the blood in a flask at 40 °C for two hours to promote clotting (13). During the incubation period, a fluoroscopically guided 4 F pigtail catheter (Cook Medical) was advanced into the abdominal aorta for continuous monitoring of the mean arterial pressure. Two additional 4 F pigtail catheters were advanced to continuously monitor central venous pressure (CVP) via the superior vena cava and PAMP via the main pulmonary artery. A 12 F guiding catheter was subsequently advanced via the right sheath to the right pulmonary artery to inject Ultravist (350 mg in 8 mL) at 6 mL/s for pulmonary angiography.

Creation of the massive PE model

Next, we produced a model of massive PE by one of two methods: autologous clot or balloon occlusion. The autologous clot was formed *ex vivo* (0.6 mL/kg) and was injected into the right main pulmonary arteries of 18 sheep via a 12 F guiding catheter (14, 15) (Fig. 1). We released a self-made detachable 15- to 20-mm latex balloon into the right main pulmonary artery of the other nine sheep (16) (Fig. 2). After injection of the autologous blood clot or release of the detachable balloon, immediate pulmonary angiography was performed to demonstrate occlusion of the right main pulmonary artery. Once PE was established, it was deemed to be massive only if the blood oxygen saturation (SaO_2) levels dropped by at least 25% from resting levels. We continuously monitored CVP and PAMP until levels stabilized (approximately 30 min) to ensure that massive PE had been effectively produced.

Balloon occlusion of the right main bronchus

We evaluated the physiological consequences of obstructing airflow to the right lung in subjects exhibiting a precipitous drop in SaO_2 (25% or greater). We inflated a 12×40-mm balloon (Cordis Corporation, Johnson and Johnson Medical Ltd., Bridgewater, New Jersey, USA) in the right main bronchus and recorded PAMP, SaO_2, and PaO_2 at 0, 3, 6, 10, 15, 20, 30, 45, and 60 min. Control subjects (n=5) were sheep that had received an autologous blood clot in the right main pulmonary artery but did not undergo balloon occlusion of the right main bronchus.

Statistical analysis

All quantitative data are presented as the means±standard deviations. The results were compared and analyzed with Fisher's exact test for survival rate, *t*-tests for group comparison, and the F-test for the analysis of effectiveness, as related to duration in the experimental groups. Statistical significance was defined as $P < 0.05$. The results were analyzed using a commercially available software (Statistical Package for Social Sciences, version 11, SPSS Inc., Chicago, Illinois, USA).

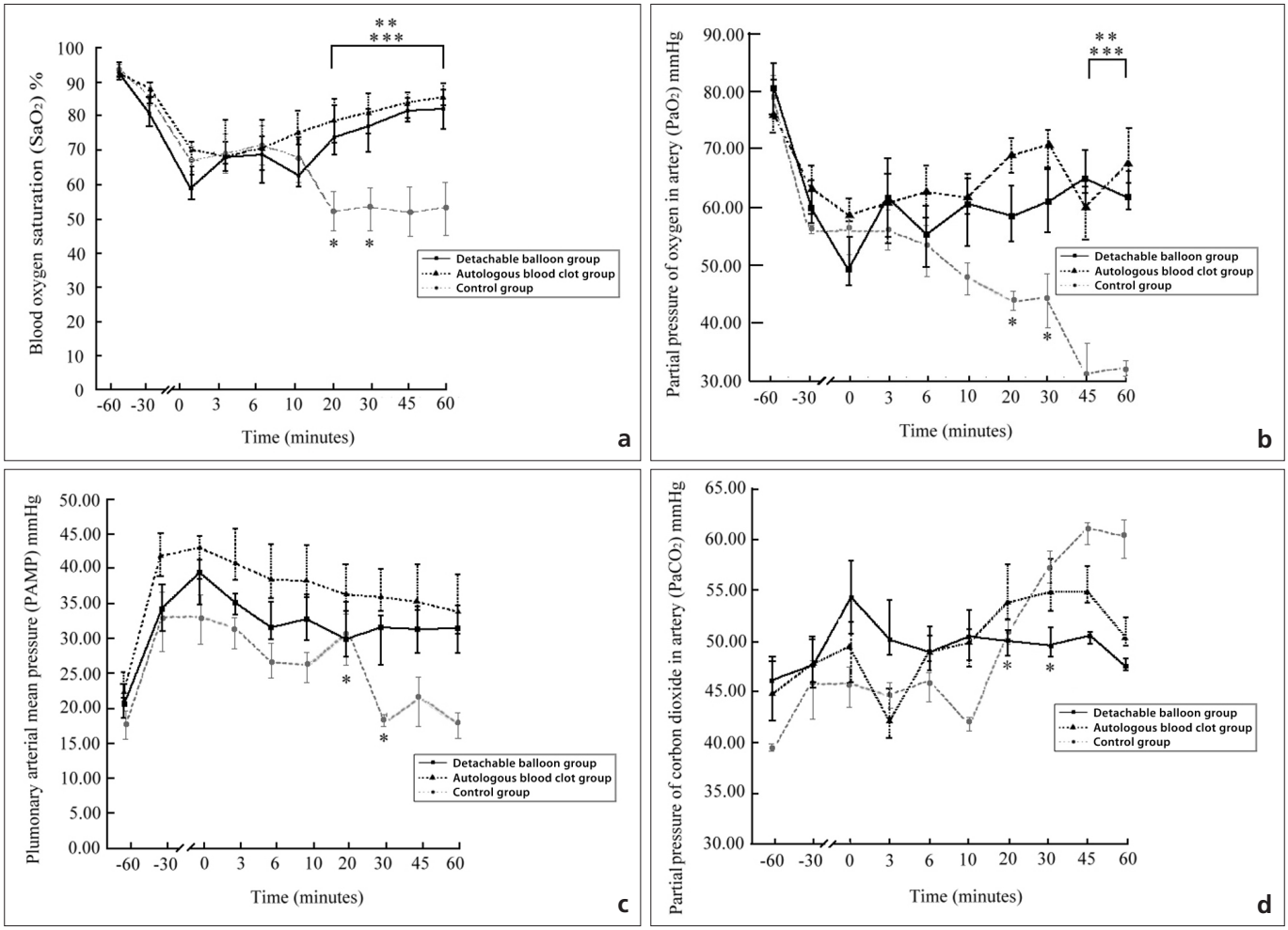

Figure 3. a–d. Massive pulmonary embolism with and without balloon occlusion of the right main bronchus. The treated groups included 18 sheep, each with massive pulmonary emboli and occluded right main bronchi. The control group included five sheep with massive pulmonary emboli only. (*) shows the occurrence of death. The time when the animal was placed on the angiography table is indicated as -60 min. The time-point at which the massive pulmonary embolus was produced is indicated as -30 min. Time 0 marks the 25% decline in SaO_2, which was the inclusion criterion for the experiment. The difference between the autologous clot group and the control group was significant (**). Statistically significant difference was noted between the balloon occlusion group and the control group (***). SaO_2 levels are plotted as a function of time in min (**a**). Partial pressure of oxygen in the peripheral artery is plotted as a function of time in min (**b**). Pulmonary artery mean pressure is plotted as a function of time (**c**). Partial pressure of carbon dioxide in the peripheral artery is plotted as a function of time (**d**).

Results

Successful creation of the massive PE model

All 27 sheep immediately developed tachycardia and tachypnea after right main pulmonary arterial delivery of the detachable balloon (n=9) or autologous blood clot (n=18). Variable rates of SaO_2 decrease were observed; within 30 min, 23 sheep (9 of 9 sheep in the detachable balloon group and 14 of 18 sheep in the autologous clot group) exhibited a drop of more than 25% in SaO_2 (for a baseline SaO_2 of 93.94±3.15%; after PE, the SaO_2 was 62.83±10.48%). Within 30 min, PaO_2 decreased from 77.28±13.03 mmHg to 52.28±15.12 mmHg, and PAMP increased from 21.78±5.54 mmHg to 41.17±15.75 mmHg. These physiological parameters are consistent with the expected findings of hemodynamically significant PE. The four sheep that did not experience a 25% drop in SaO_2 were excluded from further testing.

Right main bronchus occlusion ameliorates the physiological effects of massive PE

After 30 min of monitoring to assure adequate creation of massive PE, we deployed a right main bronchus balloon in animals of both treatment groups. The most salient finding was a significant difference in survival between the treated and control animals. In the control group, two of the five sheep died within 30 min. The remaining three sheep in the control group survived the entire length of the experiment despite low oxygen saturation levels. By comparison, all of the animals that underwent right main bronchus balloon occlusion survived for the duration of the experiment (P = 0.0395).

In addition to reduced mortality, treatment groups also demonstrated decreased hypoxemia. SaO_2 levels began to increase in both groups by 3 min after balloon inflation. For the autologous clot group, statistical significance was observed at t=30 min, reaching levels of 73.11±13.17% (P = 0.0234) compared with SaO_2 levels of 58.22±12.02% at t=0. SaO_2 levels continued to rise with time and remained significantly greater compared with the baseline, reaching 79.56±8.26% at

45 min ($P = 0.0005$) and 80.11±15.46% at one hour ($P = 0.0040$). In the balloon occlusion group, baseline t=0 SaO_2 levels were 67.44±6.42% and reached statistical significance at t=20 min (75.44±9.3%, $P = 0.0496$). SaO_2 levels continued to increase over time, remaining significantly elevated at t=30 min (78.75±7.92%, $P = 0.0043$), at t=45 min (82.63±6.32%, $P = 0.0001$) and at t=1 hour (84.89±5.90%, $P < 0.0001$).

In comparison, SaO_2 levels in the five control sheep that did not undergo right main bronchus balloon occlusion remained persistently low. After 30 min, autologous clot injection (equivalent to t=0 in the treatment subjects), the surviving three sheep of the control group displayed SaO_2 levels of 53.50±14.85%. After 30 min, SaO_2 levels were 53.00±18.52% ($P > 0.5$).

In addition to decreasing hypoxemia, balloon occlusion of the right main bronchus was also associated with a trend toward increasing PaO_2. At baseline, PaO_2 levels were 56.64±15.16 mmHg for controls, 49.70±14.73 mmHg for the autologous clot group and 58.85±15.35 mmHg for the balloon occlusion group. After 30 min, the three surviving control sheep had significantly reduced PaO_2 compared with the baseline (32.30±8.86 mmHg, $P = 0.0473$), whereas the treated sheep experienced a non-significant trend toward an increase in PaO_2 (autologous clot group, 60.74±12.75 mmHg; balloon occlusion group, 70.66±29.28 mmHg; $P > 0.5$).

Following balloon occlusion of the right main bronchus in the treated group, PAMP levels ranged from approximately 33 to 37 mmHg and demonstrated no statistical significance throughout the one-hour experimental period. However, in the five sheep that made up the control group, PAMP levels initially rose from normal levels of 21.78±5.54 mmHg to 41.17±15.75 mmHg. Following this initial increase, PAMP levels decreased significantly to levels of 18.50±4.95 mmHg, while two sheep died from massive PE. Fig. 3 depicts the changes in the values described above.

Discussion

Massive PE is a worldwide public health problem with a high mortality rate. Death often occurs within the first hour of presentation from a predictable cascade of physiologic derangements due to ventilation-perfusion mismatch, including redistribution of pulmonary blood flow, elevated capillary permeability, decreased levels of pulmonary surfactant, and increased atelectasis. PE leads to pulmonary arterial hypertension with eventual right heart failure (17, 18).

The most significant finding of our study, which utilized an ovine massive PE model, was that occlusion of the right main bronchus attenuated many of these often fatal hemodynamic changes. After inflation of an occlusive balloon in the right main bronchus, all 18 animals undergoing massive PE survived until the end of the experiment compared with the control sheep, of which three out of five died (19). Right main bronchus occlusion decreased PE-induced hypoxemia, inducing a significant increase in SaO_2 and a trend toward increased PaO_2.

We developed two ovine models of massive PE, both of which were validated by measuring hemodynamic parameters. Both models demonstrated physiological derangements characteristic of PE, including decreased SaO_2 and PaO_2 and increased PAMP. The experiments using autologous blood clot involved injection via a 12 F guiding catheter, providing a maximal diameter of only 4 mm, thereby limiting the size of the blood clot that could be delivered. Therefore, pulmonary arterial occlusion may have been localized more distally in smaller pulmonary vessels. To assure that a model of massive PE had been achieved, only sheep with a 25% drop in oxygen saturation and with a visibly extensive clot burden in the main pulmonary artery (as determined by angiography) were included in the study. We included the additional PE model with balloon occlusion of the right pulmonary artery to provide data related to more central arterial occlusion. The results obtained via both modalities were similar, suggesting that both models similarly depict PE. Arguably, a large central clot burden from peripheral pulmonary arterial emboli may reflect the PE observed clinically in human patients more accurately.

Hypothetically, by reducing the ventilation-perfusion mismatch, bronchial occlusion attenuates many of the physiological effects of PE. Maintaining improved blood oxygen saturation theoretically allows more time to perform potentially life-saving thrombolysis and/or thrombectomy. In conclusion, balloon occlusion of the right main bronchus in an ovine massive pulmonary embolus model produces a setting in which SaO_2 and PaO_2 are increased and PAMP is decreased. This intervention successfully widens the time-to-treatment window to allow more time for surgical or endovascular treatments.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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