

Study of Cardiac Arrest Caused by Acute Pulmonary Thromboembolism and Thrombolytic Resuscitation in a Porcine Model

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Abstract

Background: The success rate of resuscitation in cardiac arrest (CA) caused by pulmonary thromboembolism (PTE) is low. Furthermore, there are no large animal models that simulate clinical CA. The aim of this study was to establish a porcine CA model caused by PTE and to investigate the pathophysiology of CA and postresuscitation.

Methods: This model was induced in castrated male pigs (30 ± 2 kg; *n* = 21) by injecting thrombi (10–15 ml) via the left external jugular vein. Computed tomographic pulmonary angiography (CTPA) was performed at baseline, CA, and return of spontaneous circulation (ROSC). After CTPA during CA, cardiopulmonary resuscitation (CPR) with thrombolysis (recombinant tissue plasminogen activator 50 mg) was initiated. Hemodynamic, respiratory, and blood gas data were monitored. Cardiac troponins T, cardiac troponin I, creatine kinase-MB, myoglobin, and brain natriuretic peptide (BNP) were measured by enzyme-linked immunosorbent assay. Data were compared between baseline and CA with paired-sample *t*-test and compared among different time points for survival animals with repeated measures analysis of variance.

Results: Seventeen animals achieved CA after emboli injection, while four achieved CA after 5–8 ml more thrombi. Nine animals survived 6 h after CPR. CTPA showed obstruction of the pulmonary arteries. Mean aortic pressure data showed occurrence of CA caused by PTE ($Z = -2.803$, $P = 0.002$). The maximal rate of mean increase of left ventricular pressure (dp/dt_{max}) was statistically decreased ($t = 6.315$, $P = 0.000$, variation coefficient = 0.25), and end-tidal carbon dioxide partial pressure ($PetCO_2$) decreased to the lowest value ($t = 27.240$, $P = 0.000$). After ROSC ($n = 9$), heart rate (HR) and mean right ventricular pressure (MRVP) remained different versus baseline until 2 h after ROSC (HR, $P = 0.036$; MRVP, $P = 0.027$). Myoglobin was statistically increased from CA to 1 h after ROSC ($P = 0.036$, 0.026, 0.009, respectively), and BNP was increased from 2 h to 6 h after ROSC ($P = 0.012$, 0.014, 0.039, respectively).

Conclusions: We established a porcine model of CA caused by PTE. The dp/dt_{max} and $PetCO_2$ may be important for the occurrence of CA, while MRVP may be more important in postresuscitation.

Key words: Heart Arrest; Hemodynamics; Pulmonary Embolism

INTRODUCTION

Sudden death caused by cardiac arrest (CA) is the greatest threat to human life in modern society. The causes of sudden death are various.^[1] Besides cardiogenic diseases, there is increasing evidence for a considerable role of pulmonary thromboembolism (PTE).^[2,3] Despite recent progress in the management of acute pulmonary embolism (PE),^[4] it remains a major contributor to global disease burden. Studies from Western Europe, North America, Australia, and Southern Latin America (Argentina) provide consistent results with annual incidences ranging from

0.75 to 2.69/1000 individuals in the general population and increases to 2–7/1000 in subjects 70 years of age.^[5] The outcomes of acute PE vary depending on patients'

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characteristics, which can be grouped into high-risk and not high-risk PE.^[6]

According to 2015 American Heart Association Guidelines update for cardiopulmonary resuscitation (CPR) and emergency cardiovascular care, percutaneous coronary intervention or thrombolytic therapy can be performed for patients who are cardiogenic after CPR.^[7] CA caused by PTE is difficult to rescue due to diagnostic difficulty. There is no diagnostic or prognostic test currently available for detecting and tracking PTE except for imaging.^[8,9] Furthermore, current therapeutic options are limited to anticoagulant therapy, thrombolysis,^[10,11] catheter-directed reperfusion,^[12,13] and surgical thromboembolectomy. In our previous report of seven cases of strongly suspected PTE for which thrombolytic therapies were performed during CPR, five patients achieved a return of spontaneous circulation (ROSC), and three were survival to hospital discharge.^[14]

There are numerous other studies that have focused on nonfatal PE and chronic thromboembolic pulmonary hypertension (CTEPH).^[15-17] However, there are limited reports on PTE leading to CA. Furthermore, although PTE patients are known to exhibit, a marked disturbance in the stoichiometric balance between hemodynamics and respiration,^[18-20] the mechanisms and pathophysiology of CA caused by PTE remain unclear.

Thus, the aim of the present study was to establish a porcine model of CA caused by PTE to investigate the pathophysiology of CA, which may provide a theoretical basis to improve resuscitation.

METHODS

Ethical approval

This was a laboratory study of CA caused by PTE in a porcine model. 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 all animals were in accordance with the Guide for the Care and Use of Laboratory Animals (8th edition).^[21] We have taken all steps to minimize the animal's pain and suffering. The model establishment was performed in the animal laboratory center of Capital Medical University, and enzyme-linked immunosorbent assay (ELISA) was performed in the Medical Research Center of Beijing Chao-Yang Hospital, Capital Medical University.

Animal preparation

Twenty-one castrated Beijing Landrace male pigs (10–12 weeks, 30 ± 2 kg) from Beijing Luyuan Weiye farms were used in this study. Animals were fasted overnight with free access to water. After premedication with intramuscular midazolam (0.2 mg/kg) and atropine (1 mg), the marginal ear vein was cannulated. Anesthesia was induced by an intravenous bolus of propofol (2 mg/kg) and

fentanyl (5 µg/kg), maintained with a continuous intravenous infusion of pentobarbital ($8 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) and fentanyl ($5 \text{ µg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$). Animals were intubated by a cuffed 6.5-mm endotracheal tube and ventilated by a volume-controlled ventilator (Evita 4; Draeger Medical, Lubeck, Germany) with a tidal volume of 8 ml/kg, and a respiratory rate of 15 breaths per minute with room air. Lactated ringer (10 ml/kg) was used to maintain baseline central venous pressure between 5 and 10 mmHg by continuous intravenous drip. End-tidal carbon dioxide partial pressure (PetCO₂) was measured using an inline mainstream infrared capnograph (CO₂SMO Plus Monitor; Respironics Inc., Murrysville, PA, USA). PetCO₂ was maintained between 30 and 40 mmHg by adjusting respiratory parameters before inducing CA. Room temperature was adjusted to 27°C.

The intravascular catheters were inserted by open dissections of the relevant vessels. A 5-Fr arterial catheter (Pulsioath PV2015L20; Pulsion Medical Systems, Munich, Germany) was inserted into the left femoral artery, and a 5-Fr central venous catheter (ARROWg + and Blue Central Venous Catheters; Arrow International, Inc., Reading, PA, USA) was placed into the left femoral vein. The catheters were connected to a PiCCO device (Pulsion Medical Systems). A 6-Fr introducer sheath was inserted into the right femoral artery to place a 5-Fr Straight Pigtail Catheter (Optitorque; Terumo Co., Tokyo, Japan) into the left ventricle. An 8-Fr venous sheath was inserted into the right external jugular vein, through which a pulmonary artery catheter (Swan-Ganz CCO mbo CCO/SvO₂ 7.5 F; Edwards Lifescience, Irvine, CA, USA) was placed. A large bore catheter (1 cm ID) was inserted into the right ventricle via the left external jugular vein for injecting preformed blood clots.

Embolus preparation

Venous blood (50 ml) was drawn into a 50 ml syringe, and 50 U of lyophilizing thrombin solution was added into the blood. The blood was left for 30 min at room temperature, and a stable, gelatinous blood clot was formed. The clot was then fragmented into emboli of 1.5 cm in diameter, which were washed three times with saline. Approximately, 10–15 ml of thrombi was suspended in saline solution, which was placed into a 50 ml syringe.

Experimental protocol

Animals were allowed to stabilize for 30 min after the operation, and baseline data were recorded. The thrombi were injected into the pulmonary artery through the large bore catheter over 1 min until circulatory arrest occurred, as indicated by a mean aortic pressure (MAP) <30 mmHg. The large bore catheter was then removed and the ventilator was disconnected. CA data were recorded. Computed tomographic pulmonary angiography (CTPA) was performed to estimate the PTE. A solution of 50 mg recombinant human tissue plasminogen activator (Alteplase, Boehringer Ingelheim, Shanghai, China) was injected as a bolus through a Swan-Ganz catheter.^[22,23] CPR was

initiated, and ventilation was performed using a bag respirator with room air at a compression-to-ventilation ratio of 30:2. Epinephrine (0.02 mg/kg) was injected intravenously followed by CPR. If ventricular fibrillation occurred, defibrillation shock was performed at 150 J. If this was unsuccessful, after each 2 min of CPR, 10 s pause was allowed 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. ROSC was defined as the presence of an organized rhythm with MAP \geq 60 mmHg maintained more than ten consecutive minutes.^[24] After ROSC, data were recorded at ROSC immediately, 1 h, 2 h, 4 h, and 6 h after ROSC. The animal was euthanized with intravenous potassium chloride and an overdose of propofol.

Measurements

Heart rate (HR), blood pressure, central venous pressure (CVP), electrocardiogram, and blood temperature were monitored (M8001A; Philips Medizin Systeme Boeblingen GmbH, Boeblingen, Germany). Left ventricular cardiac output (LVCO) was measured with transarterial thermodilution by triplicate central venous injections of 10 ml ice-cold (0°C) 0.9% saline and recorded as the average of three measurements using PICCO. The mean left ventricular pressure (MLVP) and maximal rate of increase of MLVP (dp/dt_{max}) were calculated with the straight pigtail catheter by a biological function experiment system (BL-420F; Easy Health Technology Co. Ltd., Chengdu, China). Mean right ventricular pressure (MRVP), right ventricular cardiac output (RVCO), and mean pulmonary arterial pressure (MPAP) were measured with the Swan-Ganz catheter. PetCO₂ was measured continuously using an inline mainstream infrared capnograph. Compliance of lung (C) and airway resistance (R) was monitored by a ventilator. Arterial blood samples were drawn for gas analyses (GEM Premier 3000 Blood Gas Analyzer; Instrumentation Laboratory, Lexington, MA, USA). After centrifugation of venous blood samples, serums were collected stored at -80°C until analysis for cardiac troponin T, cardiac troponin I, creatine kinase-MB, myoglobin, and brain natriuretic peptide (BNP) with ELISA kits (Porcine Elisa Kit, Elabscience, Wuhan, China).

Computed tomographic pulmonary angiography

CTPAs were performed at baseline, CA, and after ROSC. Images were acquired by a 64-slice multidetector row computed tomography (Sensation 64, Siemens Healthcare, Forchheim, Germany). Before thrombi injection, the precontrast helical scan for the whole lung was performed. Meglumine diatrizoate (1 ml/kg) was then injected (5 ml/s) immediately, and a postcontrast helical scan was performed using the same protocol as for the precontrast scan. A 500 ml solution of 0.9% saline was continuously infused intravenously to eliminate the contrast material. During CA and after ROSC, CTPAs were performed again.

Two independent, experienced radiologists evaluated the images.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences 19.0 statistics software (SPSS Inc., Chicago, IL, USA). Normally data are presented as mean \pm standard deviation (SD). Nonnormally distributed data are presented as median (Q₁, Q₃). Comparison of paired data (baseline vs. CA) was performed with the paired-sample *t*-test or Wilcoxon's matched pairs signed rank sum test. Continuous variables of surviving animals with normal distribution were compared by repeated measures analysis of variance. Bonferroni's test was used for adjustment of multiple comparisons. All *P* values were two-tailed and *P* < 0.05 was considered statistically significant.

RESULTS

Outcomes

Seventeen animals entered CA after injection of emboli (10–15 ml), while the other four entered CA after a further 5–8 ml of thrombi injection. Postmortem examination of the animals showed pulmonary infarctions and emboli in the pulmonary arteries [Figure 1]. Among these animals, seven developed ventricular fibrillation. CPR was performed after 3 min, during which time arterial blood was collected and CTPA was performed. Only 11 animals reached ROSC, of which nine survived 6 h, and two survived 1 h.

Computed tomographic pulmonary angiography

All animals had good precontrast and postcontrast helical scans before experiments [Figure 2a, 2b, 2e, and 2f]. Meglumine diatrizoate was distributed in the pulmonary arteries and capillaries [Figure 2b and 2f]. After emboli injection, the pulmonary arteries were obstructed, resulting in CA [Figure 2c and 2g]. CTPA was performed again after ROSC in surviving animals [Figure 2d and 2h].

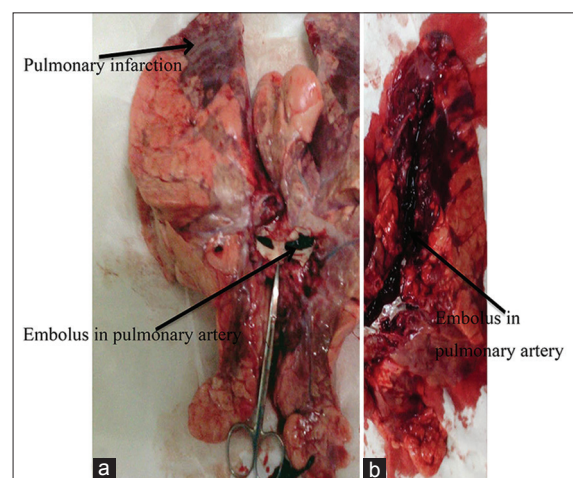


Figure 1: Specimen of pulmonary thromboembolism. (a) Embolus block the right and left pulmonary artery branches and pulmonary infarction. (b) Embolus in the small pulmonary arteries.

Three-dimensional reconstructions were performed for the statuses of baseline, CA, and after ROSC [Figure 3].

Analysis of hemodynamic parameters

Hemodynamic parameters directly reflected CA status caused by PTE. Blood temperature in all animals was $38.1 \pm 1.3^\circ\text{C}$ and was stable throughout the whole protocol ($P > 0.05$). Baseline and CA data were compared for animals that achieved CA [Table 1, $P < 0.01$ for all]. MAP, MLVP, and left dp/dt_{max} were decreased, while LVCO could not be measured during CA. By contrast, HR, MRVP, MPAP, and CVP were increased. During emboli injection, left ventricular pressure and left dp/dt_{max} varied significantly [Figure 4], and the coefficient of variation of left dp/dt_{max} (0.25) was less than MLVP, MRVP, and MPAP. Left dp/dt_{max} may have more significance in pathophysiology of CA caused by PTE. Data from survival animals were analyzed for nine pigs [Table 2]. After ROSC, there were no significant differences in MAP, MPAP, CVP, or left dp/dt_{max} compared with baseline. However, HR, MRVP, MLVP, LVCO, and RVCO were significantly different from baseline, which persisted until 2 h after ROSC for HR and MRVP (HR, $P = 0.036$; MRVP, $P = 0.027$).

Respiratory parameters and blood gas analysis

The effects of CA caused by PTE on respiratory parameters and arterial blood gas were also analyzed [Table 1, $P < 0.05$ for all]. PetCO_2 , C, PH, and standard base excess (BE_{ecf}) decreased, while R, arterial carbon dioxide tension (PaCO_2), and lactate increased. There was a small but significance decrease in the mean pH during CA ($P < 0.001$). Data analyses from survival animals are shown in Table 2. PetCO_2 and PaCO_2 were statistically different in CA and ROSC compared with baseline. However, PetCO_2 was the lowest value in CA, while PaCO_2 was the highest value in ROSC, suggesting that PetCO_2 may be more important in the diagnosis of occurrence of CA caused by PTE.

Cardiac biomarkers and brain natriuretic peptide analysis

Data analyses of survival animals are shown in Table 2. After CA, cardiac biomarkers and BNP were significantly different than at baseline, indicating myocardial ischemia injury during CA caused by PTE. Compared with baseline, myoglobin was statistically increased from CA to 1 h after ROSC ($P = 0.036$, 0.026, 0.009, respectively), and BNP was increased from 2 h to 6 h after ROSC ($P = 0.012$, 0.014, 0.039, respectively).

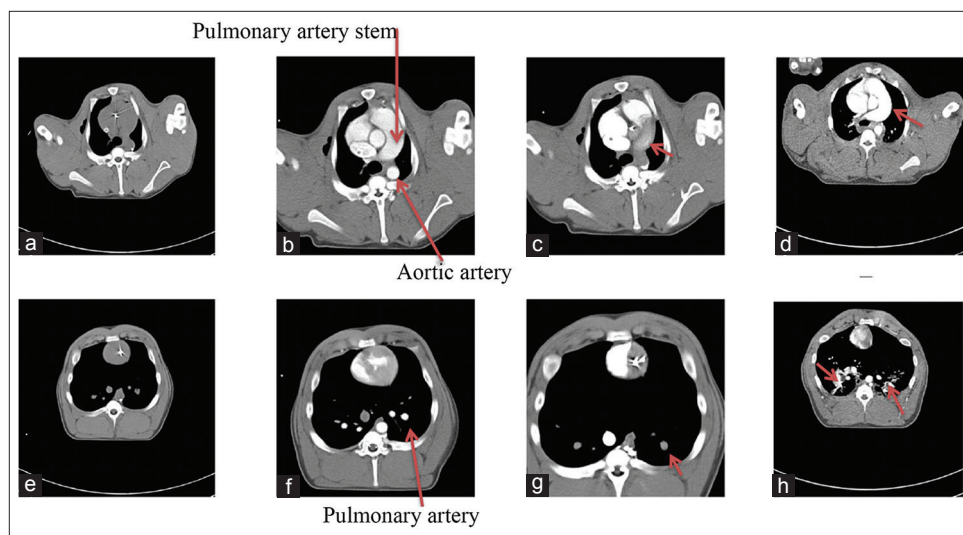


Figure 2: Computed tomographic pulmonary angiography. (a and e) Precontrast helical scans before the experiment. (b and f) Postcontrast helical scans before the experiment. (c and g) After thrombi injection, pulmonary arteries were obstructed by emboli; no flowing blood was in the left ventricle and aortic artery (arrows). (d and h) After resuscitation, a total thrombolysis in pulmonary artery stem (d), yet embolus in the little artery (h) (arrows).



Figure 3: Three-dimensional reconstruction of computed tomographic pulmonary angiography. (a) Baseline. (b) Cardiac arrest. (c) After return of spontaneous circulation and thrombolysis.

Table 1: Parameters analysis between baseline and cardiac arrest in a porcine model (n = 17)

Parameters	Baseline	CA	Statistics	P
MAP (mmHg)	99.00 (91.25, 132.00)	26.9 ± 2.92	-2.803*	0.002
HR (beats/min)	139.15 ± 28.23	179.77 ± 28.71	-6.439†	0.000
MRVP (mmHg)	18.00 ± 5.95	51.00 (30.50, 54.50)	-2.667*	0.004
MPAP (mmHg)	17.10 ± 8.11	33.00 ± 10.88	-7.940†	0.000
CVP (mmHg)	8.00 (6.00, 9.00)	15.00 (10.00, 24.00)	-2.938*	0.001
MLVP (mmHg)	49.97 ± 10.28	10.23 ± 4.25	11.153†	0.000
dp/dt _{max} (mmHg/s)	2016.44 ± 676.63	733.37 ± 190.17	6.315†	0.000
LVCO (L/min)	3.66 (2.86, 4.41)	-	-	-
PetCO ₂ (mmHg)	34.00 (32.00, 36.25)	7.00 (6.00, 11.00)	-3.006*	0.000
R (mbar·L ⁻¹ ·s ⁻¹)	9.76 ± 1.38	13.70 ± 3.66	-2.366*	0.016
C (ml/mbar)	26.99 ± 3.43	20.10 (15.30, 22.00)	-2.371*	0.016
pH	7.43 ± 0.04	7.30 ± 0.09	6.286†	0.000
PaCO ₂ (mmHg)	42.00 ± 8.72	55.40 ± 13.95	-4.314†	0.020
BEecf (mmol/L)	4.30 ± 3.41	-2.47 ± 3.47	7.531†	0.000
Lactate (mmol/L)	1.80 (1.53, 2.58)	4.20 (3.48, 6.48)	-2.521*	0.008

Data were showed as a mean ± SD or median (Q₁, Q₃). *Z values; †t values. -: Not applicable; CA: Cardiac arrest; MAP: Mean aortic pressure; HR: Heart rate; MRVP: Mean right ventricular pressure; MPAP: Mean pulmonary arterial pressure; CVP: Central venous pressure; MLVP: Mean left ventricular pressure; dp/dt_{max}: The maximal rate of increase of left ventricular pressure; LVCO: Left ventricular cardiac output; PetCO₂: End-tidal carbon dioxide partial pressure; R: Airway resistance; C: Compliance of lung; PaCO₂: Arterial carbon dioxide tension; BEecf: Standard base excess; SD: Standard deviation.

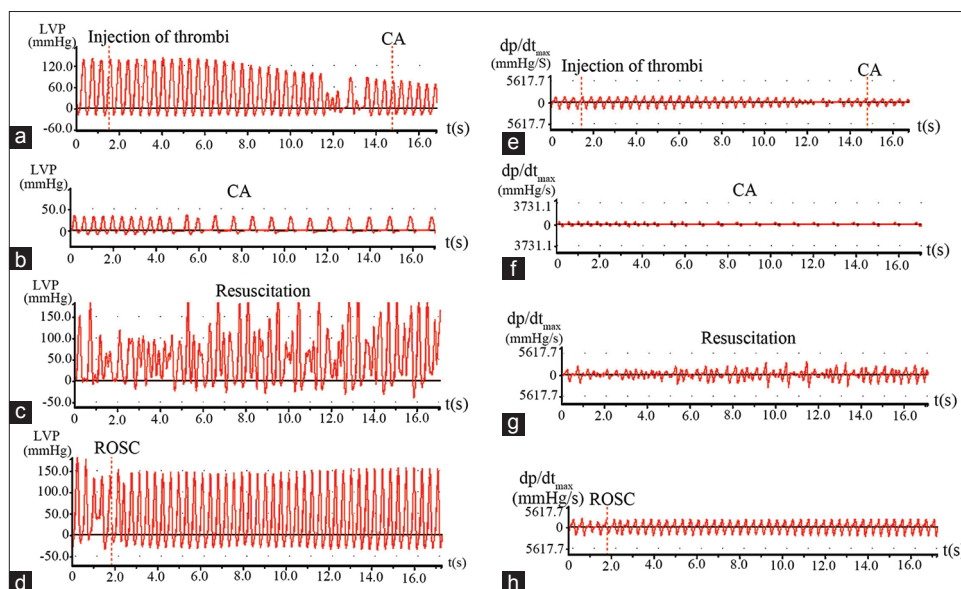


Figure 4: Variations of the left ventricular pressure and dp/dt_{max} during cardiac arrest caused by pulmonary embolism. (a-d) Variation of left ventricular pressure. (e-h) Variation of dp/dt_{max}. (a and e) Injection of thrombi. (b and f) Status of cardiac arrest. (c and g) Status during cardiopulmonary resuscitation. (d and h) Achieving return of spontaneous circulation (ROSC). LVP: Left ventricular pressure; CA: Cardiac arrest.

DISCUSSION

PTE typically develops secondary to deep vein thrombosis, likely due to venous thromboembolism. Although there are several experimental and clinical studies examining PE, they were limited to nonfatal PE. However, the lack of a large animal model of CA caused by PTE without any intervention during CA has limited our understanding of the pathophysiology of PTE, and there are limited serial mechanistic (serum/plasma testing) and interventional (device) studies at key points during CA progression. Our novel porcine model of CA caused by PTE was verified using the following

criteria: (1) appearance of ventricular fibrillation or escape beats, (2) MAP reached ≤ 30 mmHg, MPAP was more than 2.5 times that of baseline, and CVP also increased, (3) MRVP increased more than three times (the decrease in MLVP and dp/dt_{max} indicated no blood filling in the left ventricle, while CO could not be measured), (4) PetCO₂ decreased and could not be measured, while PaCO₂ increased, and (5) CTPA showed obstruction of the pulmonary artery, which is the gold standard for diagnosis of PTE.^[6] After ROSC, all hemodynamic and respiratory parameters were gradually restored to baseline, and the clots in the pulmonary artery stem were thrombolytic.

Table 2: Parameters analysis of surviving animals in a porcine model of cardiac arrest (n = 9)

Parameters	Baseline	CA	ROSC immediately	ROSC 1 h	ROSC 2 h	ROSC 4 h	ROSC 6 h
MAP (mmHg)	114.78 ± 12.91	28.56 ± 1.59*	123.00 ± 27.87	102.67 ± 23.17	104.22 ± 21.06	103.00 ± 24.08	107.67 ± 17.60
HR (beats/min)	126.00 ± 22.40	161.56 ± 30.82	189.11 ± 29.89 [†]	179.67 ± 22.58 [†]	176.67 ± 28.12 [†]	164.89 ± 29.56	168.67 ± 19.58
MRVP (mmHg)	20.56 ± 4.95	44.33 ± 7.47*	35.78 ± 6.89*	29.78 ± 7.97 [†]	27.00 ± 4.95 [†]	26.11 ± 4.43	22.89 ± 3.76
MPAP (mmHg)	21.56 ± 9.10	46.89 ± 16.86 [‡]	37.44 ± 17.53	31.11 ± 15.94	29.78 ± 17.88	27.00 ± 14.31	30.56 ± 21.61
CVP (mmHg)	8.78 ± 2.49	16.22 ± 4.27 [‡]	10.78 ± 3.56	9.78 ± 4.15	10.44 ± 3.36	9.33 ± 3.46	9.33 ± 2.87
MLVP (mmHg)	59.77 ± 7.04	26.04 ± 3.53*	48.60 ± 7.97 [†]	54.70 ± 9.26	61.49 ± 11.53	56.10 ± 10.98	53.69 ± 8.73
Left dp/dt _{max} (mmHg/s)	1908.36 ± 924.61	761.60 ± 279.19 [†]	1579.67 ± 695.27	1735.17 ± 760.23	2291.02 ± 639.15	2096.20 ± 574.85	1862.54 ± 555.56
LVCO (L/min)	3.19 ± 0.73	—	2.23 ± 0.73 [†]	2.58 ± 0.58	2.46 ± 0.69	2.46 ± 0.82	2.60 ± 0.90
RVCO (L/min)	3.40 ± 0.64	—	1.99 ± 0.93 [‡]	2.97 ± 0.99	2.86 ± 1.22	2.76 ± 1.17	2.51 ± 1.16
PetCO ₂ (mmHg)	37.56 ± 8.25	14.22 ± 8.20*	25.33 ± 6.91*	32.78 ± 8.20	32.22 ± 8.56	29.33 ± 6.54	29.00 ± 8.29
R (mbar·L ⁻¹ ·s ⁻¹)	12.34 ± 6.76	16.20 ± 6.55	17.64 ± 6.96 [†]	16.31 ± 7.40	14.91 ± 2.71	15.68 ± 4.89	16.31 ± 4.58
C (ml/mbar)	25.40 ± 6.66	15.68 ± 4.45 [‡]	19.57 ± 3.92	18.93 ± 2.76	20.61 ± 4.77	20.73 ± 5.88	20.68 ± 4.65
pH	7.46 ± 0.57	7.40 ± 0.12	7.30 ± 0.10 [†]	7.28 ± 0.09 [‡]	7.29 ± 0.06 [†]	7.33 ± 0.08	7.30 ± 0.05 [†]
PaCO ₂ (mmHg)	34.44 ± 2.60	45.89 ± 7.18 [†]	58.22 ± 15.14 [†]	56.33 ± 17.51	56.44 ± 14.60 [†]	53.11 ± 13.90	47.00 ± 12.70
BEecf (mmol/L)	3.09 ± 2.75	-0.6 ± 3.47 [‡]	-1.47 ± 4.56 [†]	-1.93 ± 5.55*	0.86 ± 4.69	1.76 ± 4.49	0.94 ± 5.32
Lactate (mmol/L)	2.58 ± 1.03	3.50 ± 1.43 [†]	4.82 ± 2.06 [‡]	4.17 ± 2.76	2.94 ± 2.29	2.00 ± 1.30	2.34 ± 0.76
BNP (ng/L)	35.32 ± 4.82	49.21 ± 5.06	46.70 ± 3.98	50.79 ± 4.34	50.84 ± 3.27 [†]	54.62 ± 2.62 [†]	50.68 ± 2.61 [†]
Mb (ng/L)	2815.48 ± 111.27	3710.89 ± 132.84 [†]	3794.95 ± 145.81 [†]	4074.55 ± 206.34 [‡]	3922.25 ± 309.04	4098.56 ± 355.28	4351.95 ± 353.87
CTnI (ng/L)	260.07 ± 8.43	315.08 ± 12.04 [†]	312.18 ± 11.87	315.72 ± 16.84	326.16 ± 13.75	327.70 ± 19.58	370.06 ± 6.96*
CTnT (ng/L)	404.70 ± 21.67	518.44 ± 11.48 [†]	540.74 ± 12.86 [†]	519.59 ± 45.60	534.85 ± 50.51	546.54 ± 41.35	564.60 ± 21.40 [†]
CK-MB (pg/ml)	44.91 ± 1.19	65.63 ± 7.01	66.89 ± 3.77 [†]	62.04 ± 4.28	61.37 ± 5.69	61.09 ± 4.04	68.32 ± 3.82 [†]

Data were showed as a mean ± SD. * $P < 0.001$ versus baseline, $0.01 < P < 0.05$ versus baseline, $0.001 < P < 0.01$ versus baseline. —: Not applicable; CA: Cardiac arrest; ROSC: return of spontaneous circulation; MAP: Mean aortic pressure; HR: Heart rate; MRVP: Mean right ventricular pressure; MPAP: Mean pulmonary arterial pressure; CVP: Central venous pressure; MLVP: Mean left ventricular pressure; dp/dt_{max}: The maximal rate of increase of left ventricular pressure; LVCO: Left ventricular cardiac output; RVCO: Right ventricular cardiac output; PetCO₂: End-tidal carbon dioxide partial pressure; R: Airway resistance; C: Compliance of lung; PaCO₂: Arterial carbon dioxide tension; BEecf: Standard base excess; BNP: Brain natriuretic peptide; Mb: Myoglobin; CTnI: Cardiac troponin I; CTnT: Cardiac troponin T; CK-MB: Creatine kinase-MB; SD: Standard deviation.

It is widely accepted that the pathophysiology of PTE involves hemodynamics and gas exchange. In the present study, the main cause of CA by PTE was the increase in right ventricular pressure, and the left ventricle was then compressed by the enlarged right ventricle. The left dp/dt_{max} and preload of the left ventricle decreased, and CO was reduced, resulting in decreased MAP and occurrence of CA. CTEPH is a common complication in PTE survivors.^[25] In our model, the MPAP increased during CA, and CTEPH occurred regularly during the follow-up of acute PTE.^[26] The increased afterload of the right ventricle caused by pulmonary hypertension, combined with tachycardia, contributed to the high oxygen consumption in the right ventricle. The right ventricular pressure increased more than three times during CA, and the right ventricular pressure was associated with mortality after acute PE (hazard ratio, 1.03; 95% confidence interval, 1.01–1.05).^[27] In addition, the right ventricular volume increased during CA [Figure 2b and 2c]. Right ventricular enlargement measured by CTPA in acute PE could be used to assess the right ventricle dysfunction.^[28] The right ventricular volume and pressure caused displacement of the interventricular septum from right to left, and worsening of left ventricular function [Figure 2b and 2c]. In this model, the MLVP and left dp/dt_{max} both decreased. By CTPA and autopsy, we found no blood flow into the left ventricle, and the preload was reduced, which may have caused decreased cardiac

output. The gas exchange should always be concerned in PTE. A dead space was created after the pulmonary artery was obstructed, which immediately affected PaCO₂ and PetCO₂. Our model showed an increase in PaCO₂ during CA ($P < 0.05$). The PaCO₂ values varied with differing degrees of PE. In nonfatal PE, when minute ventilator gas volume (V_E) did not change, such as with the use of mechanical ventilator support, PaCO₂ increased, while it decreased in the majority of people with higher V_E . In extensive PE, PaCO₂ increased. A number of experimental model studies have demonstrated that PaCO₂ does not vary in near-fatal PE.^[29] In the present study, PetCO₂ had a high negative predictive value in excluding PE.^[30] In the diagnosis of high-risk PE, a decrease in PetCO₂ was suggested to be an earlier detection of intraoperative pulmonary emboli.^[31] In our model, MRVP and PaCO₂ remained different from baseline for both CA and ROSC at immediately, 1 h, and 2 h after ROSC, demonstrating a high pulmonary vascular resistance and presence of a dead space. The increase in cardiac biomarkers indicative of myocardial injury may be attributed to (1) restriction of the endocardium by the enlarged right ventricle, (2) decreased coronary blood supply caused by CA, and (3) occurrence of coronary spasm due to neurohormonal factors. BNP was also increased because of increased tension of the right ventricle. Thus, it is essential to perform dynamic monitoring of cardiac biomarkers and BNP for detection of PTE.

There are several advantages of our model. First, this model of CA caused by PTE in the porcine, and no intervention was required during CA. Second, we monitored several parameters to confirm the occurrence of CA caused by PTE. Third, we performed CPR and studied changes in these parameters after ROSC to assess the pathophysiology. Finally, the size of embolus was moderate. In preexperiment, we found that injecting enough thrombosis or a very large embolus could cause CA, and these clots usually blocked the right atrium or ventricle. Kjaergaard *et al.* found no increase in pulmonary artery pressure during CA, and suggested that the tip of the pulmonary artery catheter may have been located distal to the embolus.^[32] Finally, our model may provide the basis for understanding the pathophysiology and thrombolysis in clinical practice and help in the detection of patients with suspected CA caused by PTE.

There are some limitations of our study. First, the thrombi were formed *in vitro*, which may not have the same properties as those *in vivo*. Second, the thrombus size and quantity should be matched with the animal size for success of the CA model. Third, the quantity of the clots may have been large. Finally, the rate of long-term survival was low, and further studies are required to fully assess the pathophysiology and potential interventions in our model.

In summary, we developed a new model of CA caused by PTE. The left dp/dt_{max} and $PetCO_2$ for the occurrence of CA, and MRVP for assessment of postresuscitation may be the most useful parameters. We suggest the model may be useful in diagnosis, therapy, and prognosis for this fatal disease.

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Conflicts of interest

There are no conflicts of interest.

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