ORIGINAL RESEARCH

Alterations in Respiratory Mechanics and Neural Respiratory Drive After Restoration of Spontaneous Circulation in a Porcine Model Subjected to Different Downtimes of Cardiac Arrest

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***Background*—**The potential alterations of respiratory pathophysiology after cardiopulmonary resuscitation (CPR) are relatively undefined. While untreated arrest is known to affect post–cardiopulmonary resuscitation circulation, whether it affects respiratory pathophysiology remains unclear. We aimed to investigate the post–cardiopulmonary resuscitation changes in respiratory mechanics and neural respiratory drive with varying delays (5 or 10 minutes) in the treatment of ventricular fibrillation (VF).

***Methods and Results*—**Twenty-six male Yorkshire pigs were used. Anesthetized pigs weighing 38±5 kg were randomized into 3 groups (n=10 each in the VF5 and VF10 groups, with VF kept untreated for 5 and 10 minutes, respectively, and n=6 in the sham group without VF). Defibrillation was attempted after 6 minutes of cardiopulmonary resuscitation. Pulse-induced contour cardiac output, respiratory mechanics, diaphragmatic electromyogram, blood gas, lung imaging, and histopathology were evaluated for 12 hours. Significantly elevated mean root mean square of diaphragmatic electromyogram, transdiaphragmatic pressure, and minute ventilation were observed, but reduced minute ventilation/mean root mean square, dynamic pulmonary compliance, and Pa_{O_2} were noted in both VF groups. Despite recovery of spontaneous breathing, the abnormalities in respiratory mechanics and neural respiratory drive, Pa_{O_2}, and extravascular lung water continued to last for >12 hours. The changes in imaging (P=0.027) and histopathology (P=0.012) were more severe in the VF10 group compared with the VF5 group.

***Conclusions*—**There is an uncoupling between the respiratory center and ventilation after restoration of spontaneous circulation. Prolonged untreated arrest from cardiac arrest contributes to more serious alterations in lung pathophysiology. **(*J Am Heart Assoc*. 2019;8:e012441. DOI: 10.1161/JAHA.119.012441.)**

Key Words: cardiac arrest • cardiopulmonary resuscitation • diaphragm • lung injury • respiratory mechanics

Even though some sufferers of cardiac arrest (CA) achieve restoration of spontaneous circulation (ROSC) with successful cardiopulmonary resuscitation (CPR), subsequent multiple organ dysfunction induced by ischemia-reperfusion injury, termed post–cardiac arrest syndrome,[1] may follow and play an important role in determining the patients' morbidity and mortality. While previous studies have focused substantially on postresuscitation myocardial and cerebral dysfunctions, little research has been conducted on respiratory dysfunction in this context. Post-CPR respiratory dysfunction may result from several factors. First, the massive generation of reactive oxygen species plus an enormous amount of residual oxygen in the alveoli during post–cardiac arrest syndrome/ischemia-reperfusion injury leads to oxidative lung injury,[2] which could occur in the lungs before causing damage to other organs. Second, both lungs receive the total cardiac output, and thus an inflammation provoked in the lungs as part of post–cardiac arrest syndrome–induced systemic inflammatory response[3] may appear larger and more severe than in other organs. Third, the thoracic trauma and pulmonary congestion caused by CPR also can contribute to lung compliance deterioration. Therefore, respiratory care is an important component of post–cardiac arrest care. Since 2010, CPR guidelines have emphasized potential respiratory dysfunction after CA.[4] Unfortunately, specific evidence-based recommendations for respiratory care after resuscitation do not exist. The only

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Clinical Perspective

What Is New?

- In the present study of porcine respiratory function following resuscitation from cardiac arrest, we found an uncoupling between the respiratory center/respiratory drive and ventilation, as calculated using dynamic and simultaneous measurements of ventilation variables, respiratory pressure, and respiratory drive.

What Are the Clinical Implications?

- Respiratory care after successful cardiopulmonary resuscitation should be extended to cover a longer duration after resuscitation even if spontaneous breathing is recovered.
- Immediate resuscitation of cardiac arrest is important because even 5 minutes' delay may cause more severe alteration in respiratory function.

recommendations are relatively general, recommending that mechanical ventilation in patients following CPR should maintain a normal range of $Paco_2$ (35–45 mm Hg) and blood oxygen saturation (>94%).[5] We speculated that in-depth understanding of the changes in respiratory pathophysiology after ROSC will add to the current literature and help lead to development of effective strategies of respiratory care. In addition, the length of downtime (time from cardiac arrest to initiation of CPR) has been demonstrated to affect the recovery of circulation and the prognosis of CA,[6,7] but whether they also interfere with respiratory pathophysiology remains unclear.

In the present study, we aimed to investigate the respiratory mechanics and neural respiratory drive (NRD) in a postresuscitation spontaneous-breathing porcine model subjected to varying downtimes. With such a model, we expect to provide comprehensive and practical information about alterations in the pathophysiology of the lungs and respiratory muscles after CPR, which should have implications for clinical practice.

Materials and Methods

The data that support the findings of this study are available from the corresponding author upon request.

The present experimental protocol was approved by the Institutional Animal Care and Use Committee of Sun Yat-sen Memorial Hospital, Sun Yat-sen University. All animals were housed in compliance with the *Guide for the Care and Use of Laboratory Animals* prepared by the Institute of Laboratory Animal Resources and National Institutes of Health.[8]

Animal Preparation

Twenty-six male pigs (38±5 kg) were purchased from South China Agricultural University. All animals were fasted overnight but given unrestricted access to water. Anesthesia was initiated by intramuscular injection of midazolam (0.4 mg/kg), followed by intravenous injection of pentobarbital sodium (30 mg/kg). Single doses of intravenous pentobarbital sodium (8 mg/kg) were added during the procedure if necessary. A cuffed endotracheal tube was advanced into the trachea and connected with a pneumotachograph (MLT300, ADInstruments, New South Wales, Australia) and a pressure sensor (P300B, Jin-Shangjiang Sensor Technique, Peking, China) for detection of the airflow and Pao, respectively. During preparation for the experiment, the animals were temporarily ventilated on a VELA ventilator (CareFusion, San Diego, CA) with a tidal volume of 10 mL/kg body weight, peak flow below 40 L/min, and a fraction of inspired air of 0.21. End-tidal carbon dioxide pressure was measured using the capnometer module of a BeneView T5 patient monitor (Mindray, Shenzhen, China), and the respiratory frequency was adjusted to maintain end-tidal carbon dioxide pressure within the range of 35 to 40 mm Hg. Three adhesive electrodes were applied to the shaved skin of the proximal right and left upper limbs and right lower limb for ECG recording. A 6F catheter was inserted into the thoracic aorta through the right femoral artery. A 7F 4-chambered Swan-Ganz catheter (774HF75 Swan-Ganz TD Catheter, Edwards Lifesciences Corporation, Irvine, CA) was advanced from the right femoral vein into the right atrium and flushed intermittently with saline containing 5 IU/mL of bovine heparin. A 5F pacing catheter (EP Technologies Inc, Mountain View, CA) was placed through the right external jugular vein into the right ventricle to induce ventricular fibrillation (VF). To measure the extravascular lung water (EVLW) and cardiac output (CO), a 5F thermistor-tipped catheter (PV-2014L16, Pulsion Medical Systems, Munich, Germany), connected to a PICCO computer (Mindray Ltd, Shenzhen, China), was advanced into the descending aorta via the left femoral artery. A multipair esophageal electrode catheter with gastric and esophageal balloons was passed through the nose into the stomach through a guiding tube to record the esophageal pressure, gastric pressure, and diaphragmatic electromyogram (EMGdi). The position of this esophageal catheter was carefully adjusted and deemed to be satisfactory on the basis of the magnitude of recorded EMGdi signals, as follows: When the 2 largest EMGdi signals were recorded from electrode pairs 1 and 5, and the smallest signal from electrode pair 3, the electrode pair 5 was considered to be located closest to the diaphragm.[9–12] The EMGdi signals were amplified and band-pass filtered between 20 Hz and 1 kHz (RA-8, Yinghui Medical Technology Co, Ltd, Guangzhou, China). The pressure signals (esophageal and gastric pressure)

were measured using a pressure transducer and a bio-amplifier with a band-pass filter of direct current to 30 Hz. The flow channel was set with a sampling rate of 200/second and a range to 500 mV.

Experimental Procedures

After baseline measurements (see below), animals were randomized into 3 groups to receive electrically induced VF and remained untreated for 5 minutes (VF5 group, n=10), 10 minutes (VF10 group, n=10), or mock VF (sham group, n=6). Mechanical ventilation was discontinued immediately after the onset of VF or completion of sham VF. After 5 or 10 minutes of untreated VF for each animal, 2 investigators initiated 2-person CPR in a protocol based on the 2015 American Heart Association Guidelines for CPR and emergency cardiovascular care.[13] The rescuers provided high-quality CPR with 100 to 120 compressions per minute, allowing complete chest recoil and minimum interruption. The compression depth was ≈25% of the anteroposterior diameter of the thorax. The depth and rate of chest compressions were monitored by a feedback device (M-Series, Zoll Medical Corporation, Chelmsford, MA). Pure oxygen was delivered with a breathing bag linked to the endotracheal tube at a compression-oxygenation (mimicked ventilation) ratio of 30:2. At 2 minutes of CPR, a bolus of epinephrine (1 mg) was administered via the right atrium. A single 120-J biphasic shock (M-Series, Zoll Medical Corporation, Chelmsford, MA) was attempted to terminate VF at 6 minutes of CPR. ROSC was determined by an organized rhythm with a mean aortic pressure >50 mm Hg persisting for an interval of 5 minutes or more. For animals that failed ROSC, chest compression and oxygenation were immediately resumed for 2 minutes before another attempt of a single shock. The procedure was repeated for a maximum of 5 cycles. After successful resuscitation, the animals were monitored continuously for 12 hours and ventilated using a synchronized intermittent mandatory ventilation mode with a fraction of inspired air of 1.00 for the first 10 minutes, which was gradually reduced to 0.21 thereafter. The animals in the sham group followed the same intensive care program as the VF groups but without CA and CPR.

Measurements

Hemodynamic parameters for evaluation of pulse-induced contour cardiac output were measured by CODAS/WINDAQ hardware/software (Computer Acquisition System, Cambridge, MA). Pao, esophageal pressure, gastric pressure, airflow, and EMGdi signals were recorded continuously by a PowerLab recording system (ADInstruments, Castle Hill, Australia).

Blood gas analysis

Arterial blood gases and lactic acid were measured at baseline, 0.5 hours, 2 hours, 6 hours, and 12 hours after resuscitation. Oxygenation index[14] and respiratory index[15] were calculated as previously described.

Pulse-induced contour cardiac output measurements

Pulse-induced contour cardiac output was assessed at baseline, 0.5 hours, 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, 10 hours, and 12 hours after ROSC. CO and EVLW were obtained by the transpulmonary thermodilution method.[16] The EVLW index (EVLWI) was obtained by dividing EVLW by body weight. The measurements were repeated 3 times to obtain a mean value.

Respiratory parameters

Minute ventilation (V_E), tidal volume, respiratory rate, respiratory mechanical index, and NRD were assessed at baseline, 0.5 hours, 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, 10 hours, and 12 hours after resuscitation. All measurements were scheduled to be conducted under a spontaneous breathing state, before the next injections of pentobarbital sodium, to reduce the interference of sedation. Transdiaphragmatic pressure, pressure-time product, and dynamic pulmonary compliance were calculated according to their published formulas.[17,18] Root mean square (RMS) of EMGdi was automatically computed at every 100 milliseconds. Values of 5 contiguous respiratory cycles were analyzed to determine a mean RMS (RMSmean). The ratio of V_E and RMSmean (V_E/RMSmean) was used to evaluate the ventilation-drive coupling.[11,12]

Computed tomography examination

Chest computed tomography (CT) scans were performed during spontaneous breathing in 3 randomly selected animals from each group at 12 hours after ROSC. A 128-slice spiral CT scanner (Siemens Medical Solutions, Germany) was used, with the scanning range from the apex to diaphragm. Images were acquired with the following protocol: 120-kVp, 110-mAs, collimation width of 128×0.6 mm, pitch of 0.95, field of view 255×255 mm, rack rotation time of 0.5 s/r, slice width of 0.75 mm, and no intervals, reconstructed with B70s kernel. All images were observed with settings optimized for lung evaluation (window width, 1200 HU; window level, −600 HU) and evaluated by 2 independent radiologists, according to established methods.[19]

Lung wet/dry weight

After 12 hours of observation and intensive care, the animals were euthanized. Fresh lung tissue was obtained from the lower lobes and weighed as wet weight after removing excess blood. The samples were then placed in a vacuum oven for 48

to 72 hours until the weight was stable. The wet/dry weight ratio was calculated to evaluate pulmonary edema.[20]

Lung histopathology

The caudal lobes were dissected and fixed in 10% neutral formalin for 24 hours, with subsequent paraffin embedding, sectioning, and hematoxylin-eosin staining. Stained sections were observed microscopically to evaluate the severity of lung injury. The severity of injury in histopathology was assessed by 2 independent pathologists who were blinded to the source of the histopathology.[21]

Statistical Analysis

All data were checked for normality with the Shapiro–Wilk test. Continuous variables were presented as mean±SD if normally distributed, otherwise as median and interquartile range. Variables between groups were compared using the parametric one-way ANOVA test if data are normally distributed; otherwise using the Kruskal–Wallis test. Within-group comparisons of time-based measurements were performed with repeated-measures ANOVA. A P value of <0.05 was considered significant.

Results

Baseline Characteristics and Resuscitation Outcomes

At baseline, there were no differences in characteristics (Table 1) and measurements (including hemodynamics [CO and EVLWI; see Figure 1]), blood gas (pH, Po_2, Pco_2, serum lactate, oxidation index and respiratory index; see Figure 2), and respiratory parameters (see Figure 3) among the 3 groups (all P>0.05).

All animals in the VF groups were successfully resuscitated. However, the VF10 group required significantly longer durations of CPR and more attempts at defibrillation and required larger dosages of epinephrine to achieve ROSC, compared with the VF5 group (P=0.04; Table 2).

Table 1. Baseline Physiological Information

Parameters	VF5	VF10	Sham	*P* Value
Weight, kg	38.4±2.8	38.4±1.8	38.5±0.9	1.00
Core temperature, °C	37.8±0.9	37.7±1.1	37.8±0.9	0.94
Heart rate, beats/min	136±27	128±23	129±19	0.76
Mean artery pressure, mm Hg	126±19	121±5	123±4	0.68
Central venous pressure, mm Hg	5.1±1.5	6.2±2.1	5.6±2.0	0.58
End-tidal CO_2, mm Hg	39±3	41±4	40±4	0.53

Values are presented as mean±SD. VF indicates ventricular fibrillation; VF5, 5 minutes untreated VF group; VF10, 10 minutes untreated VF group.

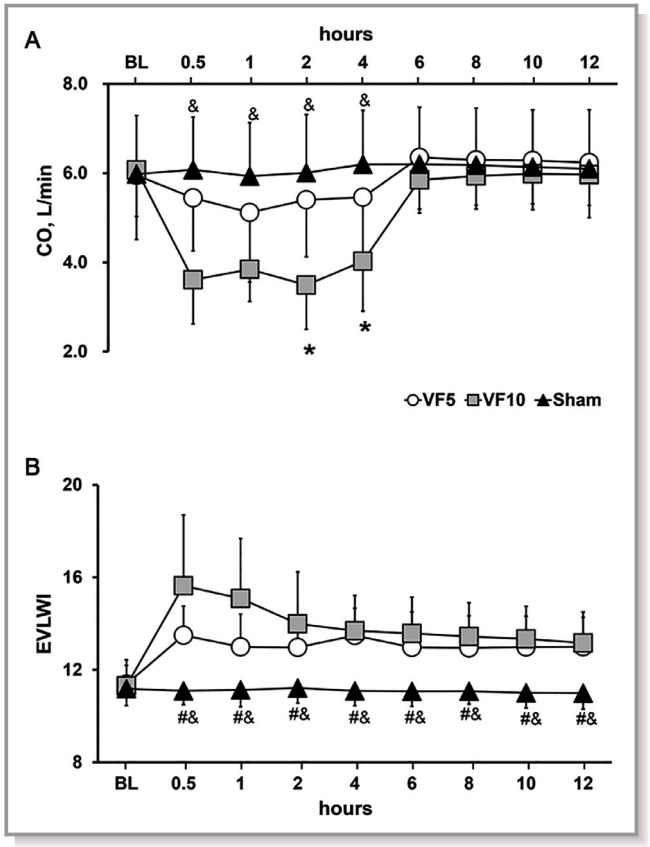

Figure 1. Changes in CO (**A**) and EVLWI (**B**). BL indicates baseline; CO, cardiac output; EVLWI, extravascular lung water index; VF, ventricular fibrillation; VF5, 5 minutes untreated VF group; VF10, 10 minutes untreated VF group. #P<0.05, VF5 vs sham (and baseline); &P<0.05, VF10 vs Sham (and baseline).

Hemodynamics

In the VF10 group, CO decreased at 0.5 to 4 hours after resuscitation but returned to baseline levels after 6 hours. Such changes were not observed in the VF5 group. A noticeable increase in EVLWI from baseline at each time point after ROSC was observed in both VF groups. Although the magnitude of the increase in EVLWI was comparable between the VF5 and VF10 groups, the increase appeared statistically significant compared with the sham group, in which EVLWI remained stable throughout the experiment (Figure 1).

Blood Gas Analysis

Reductions in pH value and serum lactate appeared at 0.5 to 2 hours after resuscitation in both VF groups but

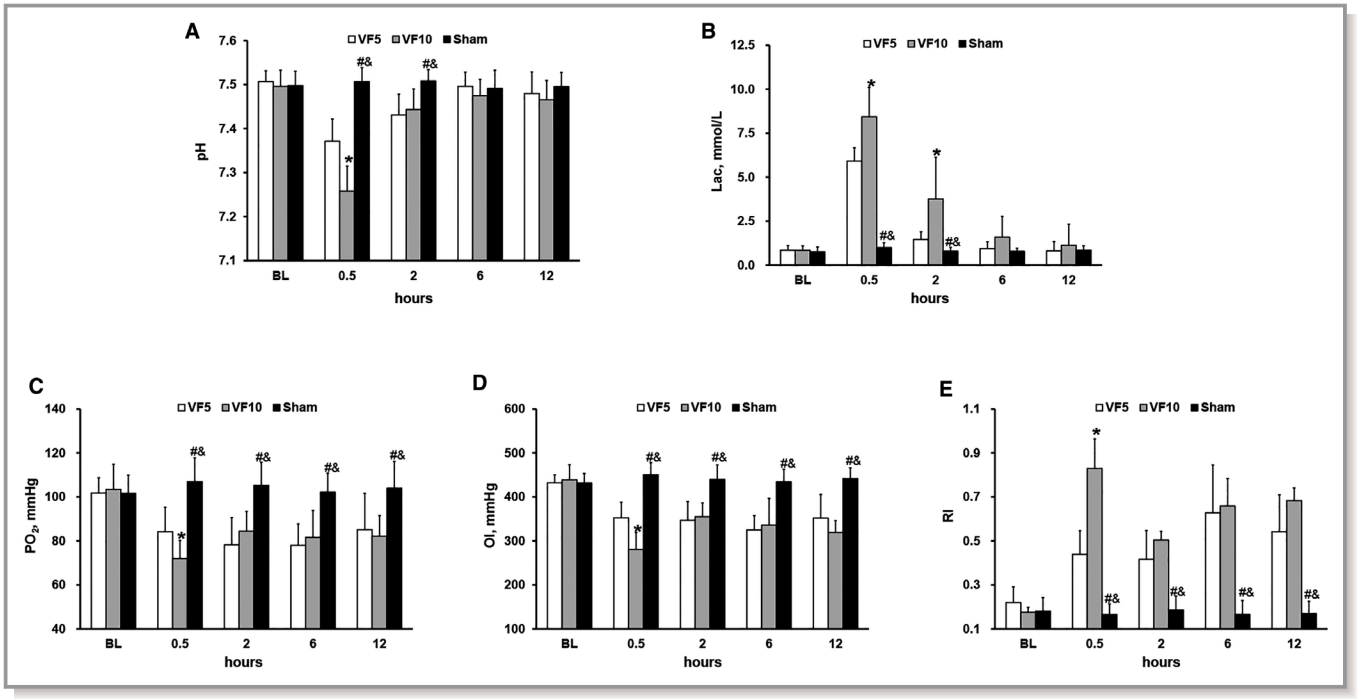

Figure 2. Blood gas analysis. Values of (**A**) pH; (**B**) Lac, concentrate of lactate; (**C**) Po_2; (**D**) OI, oxidation index; (**E**) RI, respiratory index. BL indicates baseline; VF, ventricular fibrillation; VF5, 5 minutes untreated VF group; VF10, 10 minutes untreated VF group. $^{\#}P<0.05$, VF5 vs sham (and baseline); $^{\&}P<0.05$, VF10 vs sham (and baseline); $^{*}P<0.05$, VF10 vs VF5.

returned to baseline levels after 6 hours. Significantly lower Po_2 and oxidation index levels were observed in animals subjected to VF compared with the sham group at each post-ROSC time point, but the differences in these indicators between the VF groups were only statistically significant at 0.5 hours after ROSC. When compared with baseline, there was an increase in $Paco_2$ at 0.5 hours in the VF10 group, whereas no changes were observed in the VF5 group (Figure 2).

Respiratory Parameters

All respiratory parameters in the sham group remained generally unchanged throughout the study (Figure 3). In contrast, at each post-ROSC time point in both VF groups compared with the baseline, transdiaphragmatic pressure, pressure-time product/tidal volume, and RMSmean of EMGdi increased, while dynamic pulmonary compliance and V_E/RMSmean decreased. Specifically, at 1 hour after ROSC, the VF10 group presented with higher transdiaphragmatic pressure (25.9±6.2 versus 16.4±4.0 cmH_2O, P=0.003), pressure-time product/tidal volume (27.9±4.9 versus 19.8±6.3 $cmH_2O{\cdot}s$/L, P<0.001) and RMSmean of EMGdi (24.6±3.1 versus 18.6±3.5 μV, P<0.001), but lower dynamic pulmonary compliance (0.018±0.001 versus 0.022±0.002 L/cmH_2O, P<0.001) and VE/RMSmean (0.4±0.1 versus 0.7±0.1 L/min per V, P<0.001) than those in the VF5 group.

Respiratory rate and V_E increased at 0.5 hours in both VF groups and recovered to the baseline at 2 hours, where they remained thereafter. When compared with the sham group, tidal volume of the VF5 group decreased at 0.5 to 1 hour, and no changes were observed in the VF10 group.

CT scan and histopathology

At the end of 12 hours of observation, the CT scans of lungs in both VF groups showed extensive pulmonary consolidation, especially in the dorsal region of the middle and posterior lobes bilaterally (Figure 4). The consolidation region was close to the spine, surrounded by patchy ground-glass opacities. The adjacent lung tissue appeared edematous. Histopathological sections from the areas of consolidation showed extensive alveolar collapse with thickening of interalveolar septa, serofibrinous exudates, hemorrhage, and accumulation of inflammatory cells. When compared with the sham group, CT and histopathology scores were higher in both VF groups. Moreover, the VF10 group scored higher than the VF5 group (Figure 4).

The lung wet/dry ratios were comparable among the 3 groups (P=0.35).

Discussion

Findings of this study shed light on several areas. First, the pulmonary pathophysiology after CPR may include

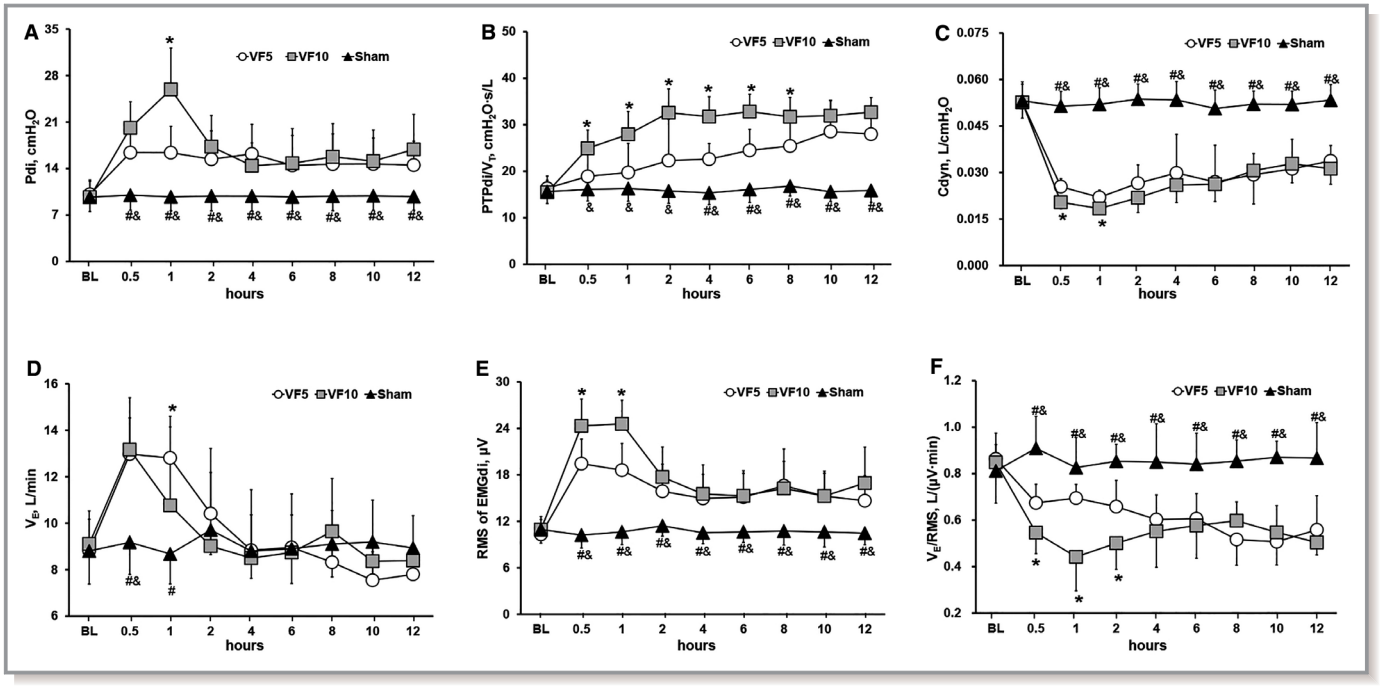

Figure 3. Changes in respiratory muscle function and neural respiratory drive. Values of (**A**) Pdi, transdiaphragmatic pressure; (**B**) PTPdi/V_T, pressure-time product of transdiaphragmatic pressure/tidal volume; (**C**) Cdyn, dynamic compliance of the lung; (**D**) V_E, ventilation; (**E**) RMS, root mean square of EMGdi; (**F**) V_E/RMS, ventilation/neural respiratory drive. BL indicates baseline; VF, ventricular fibrillation; VF5, 5 minutes untreated VF group; VF10, 10 minutes untreated VF group. $^{\#}P<0.05$, VF5 vs sham (and BL); $^{\&}P<0.05$, VF10 vs sham (and baseline); $^{*}P<0.05$, VF10 vs VF5.

deteriorated gas exchange, elevated NRD, increased inspiratory muscle activity and ventilation demand, and decreased dynamic pulmonary compliance and NRD efficiency. Second, even when spontaneous breathing was restored quickly after ROSC, abnormalities in respiratory mechanics and NRD, hypoxemia, and pulmonary edema could continue to last for >12 hours. Third, a delay in treatment of VF of even 5 minutes may cause more severe changes in gas exchange, respiratory physiology, lung imaging, and histopathology.

To our knowledge, there have been no prior studies like ours to record simultaneously the ventilation, respiratory pressure, and NRD in a porcine model after ROSC. To ensure robust measurements of these profiles, special considerations were given to the methodology after weighing the strengths and weaknesses of relevant experiments, including the selection of measurement tools, using spontaneous breathing techniques and target parameters. We therefore speculate that our work adds to the current literature by providing more comprehensive and in-depth information about respiratory pathophysiology in relation to CPR. Some studies have previously demonstrated that occlusion pressure, tidal volume, and transdiaphragmatic pressure [22] failed to assess NRD accurately in COPD patients because of the development of intrinsic positive end expiratory pressure,[23] impaired diaphragm function,[24] and uncoupling between ventilation and the respiratory center. In the present study, EMGdi signals were recorded using a 5-pair esophageal electrode catheter, which has been well demonstrated to be an ideal method to quantify NRD, as it is not easily disturbed by the activity of respiratory muscles, electrode movement, and lung volume change.[11,12] The efficiency of NRD, expressed by a ratio of minute ventilation to RMS, may reflect the unbalanced relationship between ventilation and NRD precisely. We observed an increase in NRD, inspiratory muscle activity, muscle energy consumption, and ventilation after resuscitation, but noted a reduction in NRD efficiency. This indicates that, after ROSC, generating the same level of ventilation would require a higher NRD and more inspiratory muscle effort; in other words, there is an uncoupling between the respiratory center and ventilation. The uncoupling might be explained by decreased lung compliance[25] and respiratory

Table 2. Outcomes of CPR

Parameters	VF5	VF10	Sham	*P* Value
Duration of CPR, min	6 (2)	8 (2)	-	0.04
Attempts at defibrillation, n	1 (1)	2 (1)	-	0.04
Total dosage of EPI, mg	1 (1)	2 (1)	-	0.04

Values are presented as median (interquartile range). CPR indicates cardiopulmonary resuscitation; EPI, epinephrine; VF, ventricular fibrillation; VF5, 5 minutes untreated VF group; VF10, 10 minutes untreated VF group.

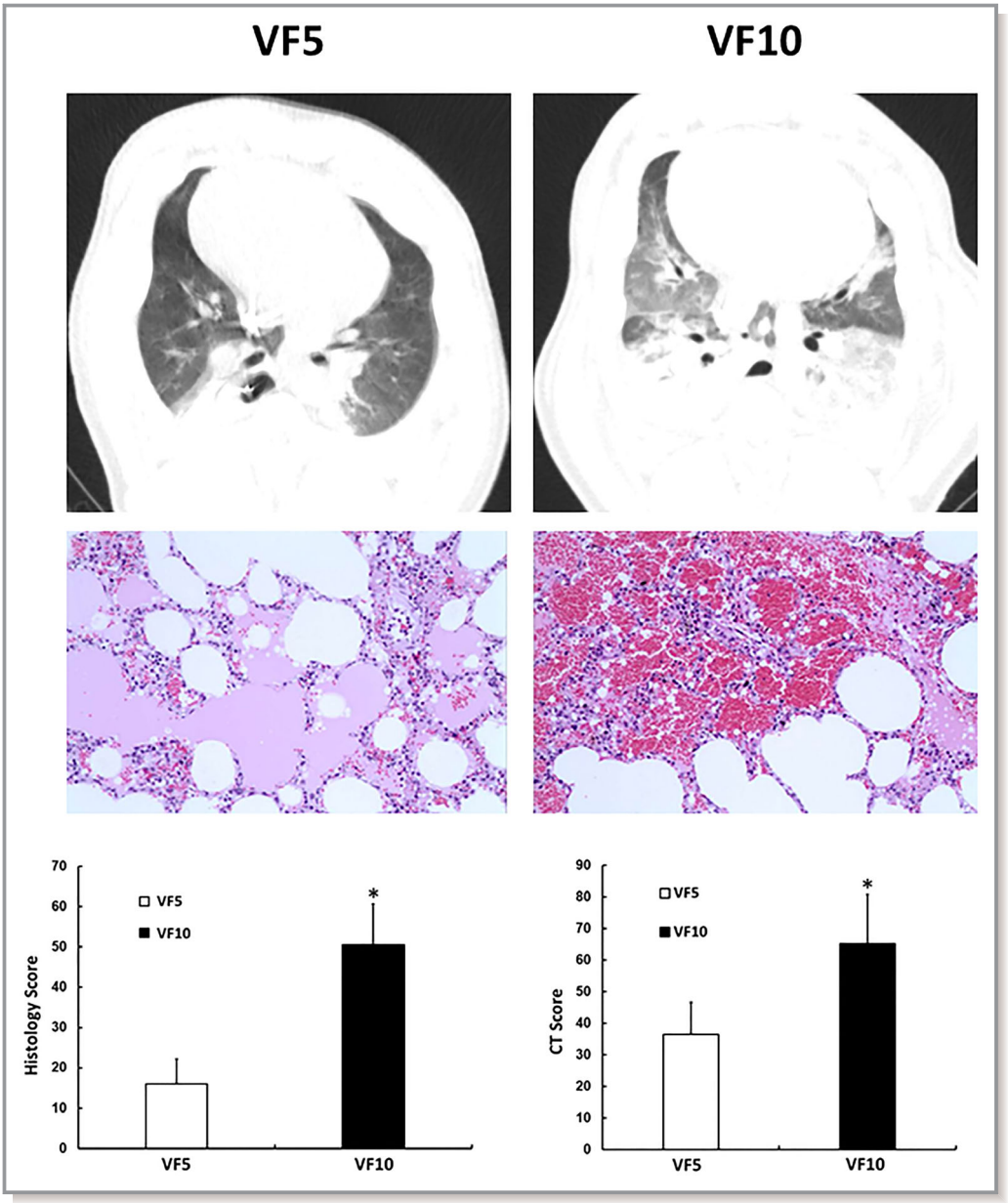

Figure 4. Evaluations of lung injury by computed tomography scan and histopathology. VF indicates ventricular fibrillation; VF5, 5 minutes untreated VF group; VF10, 10 minutes untreated VF group. *P<0.05, VF10 vs. VF5.

muscle fatigue induced by hypoxemia.[26] The respiratory rhythm and frequency are produced by the medullary respiratory center, which is regulated by various central and exogenous stimuli. The increase in NRD after resuscitation might arise from the stimulation of peripheral and central chemoreceptors, namely, stretch receptors and pulmonary J receptors, as could also be caused by hypoxemia, acidosis, and pulmonary edema. In addition, we observed an obvious increase in respiratory rate but a decrease in tidal volume early after resuscitation, suggesting that the increase of ventilation after ROSC may be achieved mainly by increasing the respiratory rate but not tidal volume.

Wenzel et al[27] and Wang et al[28] reported that respiratory system compliance decreases after cardiopulmonary resuscitation. However, given that continuous chest compression has a considerable impact on thoracic compliance, respiratory system compliance cannot accurately reflect the severity of lung damage. Unlike previous studies, we calculated dynamic lung compliance during a spontaneous breathing state. Our results showed that dynamic lung compliance decreased after ROSC, suggesting decreased lung tissue elasticity and increased airway resistance.

While CO is a classic indicator of cardiac function, EVLWI is often used to reflect the severity of pulmonary edema. In

this study, although we observed an obvious and continuous increase in EVLWI after resuscitation, significant changes in CO did not occur in the VF5 group or in the first 6 hours after ROSC in the VF10 group. This indicated that postresuscitation myocardial dysfunction caused by myocardial stunning[29] might recover quickly; moreover, pulmonary edema after resuscitation might be associated not only with myocardial dysfunction but also with lung injuries. It is noteworthy to mention that increased EVLWI, hypoxemia, abnormal respiratory mechanics, and NRD, as well as changes in imaging and histopathology, lasted >12 hours even after intensive care. Such characteristics of pulmonary dysfunction highlight the importance of extending intensive care even after the recovery of spontaneous breathing, especially for those who have experienced a prolonged cardiac arrest.

It is well known that differing VF durations correlate with varied myocardial and neurological outcomes. However, little is known as to whether different VF durations interfere with lung function. In the present study, we confirmed that longer periods of untreated VF caused more pronounced changes in gas exchange, respiratory physiology, and histopathology in the early stages after ROSC. It may be proposed that prolonged VF is associated with more severe ischemia-reperfusion injury and chest compression injury.

There are several limitations in this study. First, the CPR was manually performed, and therefore it was difficult to ensure it was 100% consistent. However, the CPR in this study was completed by 2 well-trained experimenters, who were independent from the study group and alternated compressions every 2 minutes to avoid fatigue, according to the American Heart Association guidelines. Second, our model resembles a prehospital resuscitation that, unlike many in-hospital resuscitations, is more likely associated with a prolonged arrest and resultant hypoxia and ischemia.[13] As a result, we provided cycles of 30 compressions and 2 breaths. In addition, the snout of a pig doesn't allow effective ventilation (with oxygen) using a bag and mask, so an advanced airway was needed. In these aspects, the resuscitation performed differed slightly from the continuous chest compressions with asynchronous ventilation contained in the American Heart Association recommendations for CPR with an advanced airway. Third, many factors, such as mechanical ventilation, body position, and temperature, might have had effects on the lung function of the animals. For this, a sham group was designed to minimize such potential variations. Fourth, the use of sedatives may have had effects on the detection of respiratory mechanics and NRD, although all physiological tests in this study were arranged to be performed before administering subsequent rounds of sedative injections. Fifth, for the safety and care of the animals, we did not allow untreated VF for >10 minutes. Thus, it remains uncertain whether the animals would have had more serious respiratory physiological changes with a longer downtime from CA. Further studies are necessary to explore this issue. Sixth, inconsistencies between wet/dry ratio and EVLWI were shown in the present study. However, the wet/dry ratios, as nonnormal distribution data, were analyzed with the nonparametric Kruskal–Wallis test. The Kruskal–Wallis test was robust to the data distribution but less efficient, together with the small sample size, likely leading to the negative findings. Moreover, recognizing that the samples, which were obtained from the lower lobes of the lungs, might not be entirely representative of the whole organs, we used another indicator called EVLWI to evaluate the pulmonary edema. We showed that there was a significant difference in EVLWI among the 3 groups. Finally, in the present study, we did not obtain left ventricular end-diastolic pressure or pulmonary artery wedge pressure data because no catheter was advanced into the left heart ventricle or pulmonary artery. However, we performed CO measurement, which could serve as an index of myocardial function.

Nevertheless, in this study, we successfully established a large animal model to investigate the pathophysiological changes after CPR. Using this model may help facilitate basic research on proper strategies for breathing support, for example, high-flow nasal cannula oxygen therapy or other novel mechanical ventilation modes, such as neural-adjusted ventilator assist,[30] the acute respiratory distress syndrome strategy,[31] and the open lung approach.[32]

Conclusions

There is an uncoupling between the respiratory center and ventilation after ROSC. Prolonged downtime from CA contributes to more serious alterations in lung pathophysiology. Even if spontaneous breathing resumes, respiratory care after resuscitation should be extended to cover a longer duration after ROSC.

Acknowledgments

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Disclosures

None.

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