

Peer review file

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Comment 1: It should be stated in this manuscript what the baseline values for tidal volume and respiratory rate were prearrest. What parameters were needed with native circulation to provide a ETCO₂ of 38-42 torr?

Reply 1: According to the author's suggestion, we have added a description of important ventilator parameters of animals in the baseline data collection stage (see Page 8, line 7). In this stage, a SynoVent 800 respirator (Mindray Biological Medical Electronic Co, Ltd, Shenzhen, China) was used with positive-pressure volume-controlled ventilation (VCV) with room air. A tidal volume of 10 mL/kg was applied, and the respiratory rate (RR) was adjusted to maintain PetCO₂ between 38 and 42 mmHg and pulse oxygen saturation (SPO₂) at > 95%. Through reanalysis of the data, we found that the baseline values for RR of the animals ranged from 13 breaths/min to 17 breaths/min, with an average of 15.5 breaths/min.

Changes in the text:

In the baseline data collection stage, the animals were mechanically ventilated with a SynoVent 800 respirator (Mindray Biological Medical Electronic Co, Ltd, Shenzhen, China). The respirator was started in a volume-controlled ventilation (VCV) with ventilator settings as follows: tidal volume(VT) of 10 mL/kg; positive end-expiratory pressure (PEEP) of 4 cmH₂O; inspiratory to expiratory time ratio(I:E) of 1:1.5-2. The respiratory rate (RR) was titrated to maintain PetCO₂ between 38 and 42 mmHg and pulse oxygen saturation (SPO₂) at > 95%.

Comment 2: The use of normal ventilation parameters during cardiac arrest and

CPR may be excessive when pulmonary blood flow is reduced. A “normal ventilation” scenario with 10 cc/kg x 10 bpm may over ventilate an animal with reduced pulmonary blood flow during CPR. It would be nice if the authors addressed this in the discussion section (labeled conclusions).

Reply 2: We selected “normal ventilation” parameters during CPR based on the experience of other teams’ animal experiments. In real resuscitation scenarios, the severity of pulmonary blood flow reduction varies from person to person. Accurate evaluation of pulmonary blood flow and provision of ventilation support during resuscitation will be the direction of our future research. The PV ratio is probably a potential useful parameter, but we cannot solve this problem in this experimental design. The direct measurement of pulmonary blood flow is still not feasible. There is a certain lag in obtaining information on hyperventilation from blood gas analysis. Our experiment is not perfect; we did not solve the problem of “normal ventilation parameters” in the pre-experiment stage. The setting of normal ventilation parameters can only be learned from the data of similar experiments conducted by other teams (see Page 17, line 14).

Changes in the text:

It should be noted that the definition of normal ventilation during CPR in our experiment was not accurate. The amount of gas provided by the ventilator should match the reduced pulmonary blood flow during resuscitation. The normal ventilation parameters set in the experiment may have resulted in overventilation of animals. Although we standardized the animal CA model as much as possible, the heterogeneity between individuals makes it difficult to set a unified “normal

ventilation parameter.” It is difficult to monitor pulmonary blood flow in real time. Blood gas analysis may provide some information, but it is usually delayed. Therefore, in the selection of normal ventilation parameters, our protocol is not perfect.

Comment 3: No blood gas data is provided to show how arterial and venous CO₂ levels responded to each of the ventilation scenarios. The methods don’t mention if blood gases were analyzed. It is difficult to determine if lower capnography levels during hyperventilation were associated with lower venous CO₂ levels indicating more carbon dioxide removal with a fixed cardiac output or associated with higher venous CO₂ levels indicating a negative effect of the hyperventilation on the cardiac output produced by CPR, less blood flow moving to the lungs, and CO₂ building up on the venous side.

Reply 3: During the course of the experiment, we planned to take arterial and venous blood for blood gas analysis before the end of each ventilation mode. However, in some animal experiments, some results of blood gas examination were not shown, resulting in missing data. Therefore, we did not present blood gas results in the “Results” section. Nevertheless, we thank the reviewers for their valuable suggestions. We agree that if the blood gas analysis results could be discussed, our experiment would be more complete and convincing.

Changes in the text:

There are no changes in the manuscript.

Comment 4: The authors don't report whether respirations were interposed between compressions or synchronized with compressions.

Reply 4: Chest compressions were continuously performed without interruption after the start of the experiment. Therefore, ventilation was synchronized with the mechanical chest compressions. According to the comments of the reviewers, we have added this point in the manuscript to facilitate understanding (see Page 10, line 6).

Changes in the text:

The same compression was applied throughout the experimental process, without interruption. Ventilation was synchronized with the mechanical chest compressions.

Comment 5: The authors don't report the inspiratory and expiratory times of ventilation.

Reply 5: We thank the reviewers for their suggestions. We have added the relevant content to the appropriate place in the article (see Page 10, line 9). As in the baseline data acquisition phase, we still used an inspiratory to expiratory time ratio (I:E) of 1:1.5–2 during CPR.

Changes in the text:

VCV was selected with ventilator settings as follows: trigger was disabled, fraction of inspiratory oxygen of 100%, PEEP of 0 cmH₂O, I:E of 1:1.5–2, and the setting of either VT or RR, depending on the group allocation.

Comment 6: The authors don't report the duty cycle of compressions.

Reply 6: We thank the reviewer for this suggestion. We report the duty cycle of compressions in an appropriate place (see Page 10, line 7).

Changes in the text:

The percentage of time being compressed was 40% as a function of the entire compression cycle, and the percentage of time being held was 20%.

Comment 7: The authors indicate that they collected airway pressures but don't report them.

Reply 7: We extracted the airway pressure data from the respiratory background storage system. Chest compressions were continuously performed, without interruption. Mechanical ventilation and chest compressions were performed simultaneously. Therefore, we observed a sudden increase in airway pressure when the ventilation phase was synchronized with compression. At this time, the highest peak airway pressure could increase to 60 mmHg. During decompression, the airway pressure decreased. During the expiratory phase, due to the use of an ITD, the airway pressure was negative and decreased to a minimum before the next ventilation. The lowest airway pressure was approximately -8 mmHg. Airway pressure was greatly affected by chest compression; therefore, we did not report it in the experimental results. We made appropriate changes to the relevant sentence (see Page 11, line 5).

Changes in the text:

The RR, VT, and MV were recorded continuously using the respiratory background storage system.

Comment 8: The authors don't collect or report intrathoracic pressures during the different modes of ventilation. Are they available?

Reply 8: We did not collect intrathoracic pressure directly in our experiment.

During CPR, airway pressure was used as a surrogate for intrathoracic pressure. As mentioned above, airway pressure is significantly affected by chest compressions, and thus, we did not report airway pressure in the “Results” section.

Changes in the text: There are no changes in the manuscript.

Comment 9: The authors indicate that they ran the four groups of ventilation twice but only report the results from the first grouping. Please indicate why?

Reply 9: We ventilated each group twice. Since this manuscript is a secondary analysis of the experimental data, we did not use the data from the second stage of the experiment in this statistical reanalysis. However, to help readers understand our complete experimental design, we have reported the experimental protocol completely (see Page 9, line 15).

Changes in the text:

In this retrospective analysis, we only included data from the first session for analysis.

Comment 10: The authors don't mention if epinephrine was used during the experiment or when it was given. Epinephrine may have an effect on pulmonary blood flow and either increase or decrease it.

Reply 10: According to the reviewer's suggestion, we now state in the experimental protocol that we did not use vasoactive drugs and electric defibrillation (see Page 9, line 18). As the reviewer suggested, epinephrine may have an effect on pulmonary blood flow and either increase or decrease it.

Therefore, to avoid the effects of vasoactive drugs, epinephrine was not used in the first session of the experiment.

Changes in the text:

In the first session of the experiment, no vasoactive drugs, including epinephrine, or electric defibrillation, were used.

Comment 11: The authors mention that the capnography variables are real-time but it is not clear how/when to measure them. Figure 3 shows $V\dot{CO}_2/kg$ at 4-5 at the beginning of the ventilation cycle and down to 2 at the end. This gives values in the 3s in Table 1 and makes these values significantly different from normal ventilation which is in the 2s. But if the observer was looking at this value toward the end of the 5 min cycle it would be 2 for all of the methods and not different from “normal ventilation”. This would negate the significance of this value and of the ratio of the values shown in table 1. The authors need to address what is the appropriate value, the 4-5 at the beginning of the cycle or the 2 at the end of the 5-min cycle and how and when the reader should measure these levels. The initial, the max, the mean, the final?

Reply 11: We thank the reviewers for their questions, which greatly enhanced the readability of the article. First, we needed to provide a brief description of the calculation method and acquisition method of the two volumetric capnography-derived parameters. The capnography variables are real-time values, because they are measured breath-by-breath. For $P_{et}CO_2$, the end-tidal partial carbon dioxide pressure was the maximum during the entire exhalation. For $V\dot{CO}_2/kg$, the volume of CO_2 eliminated per min per kg of body weight is only related to the total amount of CO_2 exhaled in the previous respiratory cycle. Therefore, the acquisition time does not significantly affect the accuracy of the two

indicators, although they are real-time monitoring indicators.

As the reviewer stated, $V'\text{CO}_2/\text{kg}$ was 4–5 at the beginning of the ventilation cycle and decreased to 2 at the end. If the observer noted this value toward the end of the 5-min cycle, it would be 2 for all of the methods, and would not differ from “normal ventilation” It should be noted that the monitoring of the CPR process by V_{cap} is continuous, and that observation and analysis of $V'\text{CO}_2/\text{kg}$ are also continuous. Therefore, in the real CPR scenario, once hyperventilation occurs, there would be a sudden rise in $V'\text{CO}_2/\text{kg}$. According to our experimental results, the value of $V'\text{CO}_2/\text{kg}$ increased for 1–2 min and then decreased gradually. Such changes are also easily observed during CPR. Therefore, for this indicator, the change trend in the CPR process is more valuable than the observation value at a given point. We made an appropriate change to the Discussion section of the manuscript (see Page 16, line 4).

Changes in the text:

According to the change trend of $V'\text{CO}_2\text{kg}^{-1}$ provided by our animal experimental data, once hyperventilation occurs, the index will suddenly increase and then decreases to “normal” and it loses the ability to identify hyperventilation after 3 mins. Therefore, for this indicator, in the actual clinical CPR scenario, the change trend in the process of CPR is more valuable than the observation value at a given point.

Comment 12: In the abstract, the authors mention that volumetric capnography is widely used in the quality monitoring of cardiopulmonary resuscitation. This is

inaccurate in the United States where time based capnography is widely used to determine the ETCO₂ levels during CPR. Volumetric capnography is rarely used in the United States.

Reply 12: Thank you for your suggestions. We have corrected this statement in the revised manuscript (see Page 3, line 2).

Changes in the text:

Volumetric capnography is increasingly being applied in cardiopulmonary resuscitation.

Comment 13: In the methods section the authors use a 25% anteroposterior compression depth, the guidelines for resuscitation suggest a 33% ap compression depth, why the difference?

Reply 13: In the experimental design stage, we refer to the literature (1) and set two mechanical pressure depths: 25% of the anteroposterior chest diameter(ACD) and 33% of ACD. In the pre-experimental phase, we conducted the experiments at both depths. Because of the particularity of the bone structure of the pig, compression to 33% of the ACD led to bone fracture and collapse. We observed the airway pressure during CPR and found that, even if an ITD was used, it was difficult to generate negative pressure again after 1–2 min of compression at a depth of 30% ACD. Although we did not perform an X-ray examination of the chest of the animals, the possibility of chest collapse was inferred from the fact that the pig sternum could not fully rebound after compression. This phenomenon was not observed when using 25% ACD compression. Therefore, we chose 25% ACD as the experimental pressing depth.

(1) Cherry BH, Nguyen AQ, Hollrah RA, Olivencia-Yurvati AH, et al.. Modeling cardiac arrest and resuscitation in domestic pigs World J Crit Care Med 2015; 4(1): 1-12

Changes in the text: There are no changes in the manuscript.

Comment 14: The results indicate a fall in $V\dot{CO}_2/kg$ and the rise in PV ratio when a cycle of hyperventilation is switched, why is this change occurring? Why is there no change when normal ventilation is introduced? If you were hyperventilating and went to normal ventilation shouldn't you see the opposite change?

Reply 14: In the early stage of hyperventilation, the rapid emission of CO_2 causes it to increase transiently, followed by a decrease to a stable state. This rapid increase in minute CO_2 excretion after conversion to hyperventilation resulted from a significant increase in minute ventilation. However, during CPR, the amount of CO_2 produced by the body is limited, and the perfusion produced by chest compressions is significantly lower than normal. Thus, blood circulation cannot provide a continuous supply of CO_2 , maintaining $V\dot{CO}_2/kg^{-1}$ at a high level. Compared with $V\dot{CO}_2/kg^{-1}$, $PetCO_2$ changes more rapidly, which is a concentration index. When the RR or VT increases, the CO_2 concentration is diluted and immediately decreases. This leads to a change in the PV ratio. During the transition from hyperventilation to normal ventilation, the amount of CO_2 exhaled in the first 2–3 breaths decreased slightly, and then returned to a stable level. It is difficult to show obvious changes because the data collected in the experiment was obtained once every 30 s.

Changes in the text: There are no changes in the manuscript.

Comment 15: Page 11 line 287 indicates that the PV ratio is a simple calculation and shows good ability to detect hyperventilation and a rapid response in an animal

model. It is not clear what the rapid response means. A rapid response to hyperventilation? Or it allows the responders to change ventilation so that hyperventilation can be avoided? If the later, it was not studied in this manuscript, so I don't think it should be claimed.

Reply 15: The “rapid response” mentioned in the manuscript refers to the rapid and timely change in the PV ratio in the case of hyperventilation during CPR. We revised the description of the passage to avoid misleading readers (see Page 17, line 6).

Changes in the text:

The PV ratio, a new Vcap-derived parameter, can be obtained through simple calculations and shows a good ability to detect hyperventilation and changes immediately after hyperventilation in an animal model.

Comment 16: The last paragraph of the conclusions (discussion?) sounds like limitations and could be combined with the limitations section that follows it.

Reply 16: We apologize for this mistake. We thank the reviewers for their valuable suggestions. We have revised this part accordingly.

Changes in the text:

A. Page 14, line 6: “Conclusion” was changed to “Discussion”.

B. Page 18, line 16: The paragraph “a clean capnogram is difficult to obtain during CPR because of numerous issues (device malfunction, leakage/occlusion of ventilation circuit, and the ongoing CC effort) (9,25). The accuracy of our results may be due to the fact that we analyzed data from an animal model. To avoid the interference of gas oscillation in the ventilation tube caused by CC with CO₂ measurement, ITDs were also used” has been moved from the “Discussion” to the

“Limitations” section.

C. Page 19, line 3: We have added the title “Conclusion” to the right place.