Feasibility of using MgSO4 and a self-designed inspiratory impedance threshold device in cardiac arrest-cardiopulmonary resuscitation study on porcine model

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Research article

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Abstract

Cardiac arrest (CA) and cardiopulmonary resuscitation (CPR) have always been two research hotspots in emergency medicine. Problems such as optimizing animal CA models and promoting CPR efficiency are to be explored. Establishing animal CA models is the precondition of CPR study. Previous studies usually use electric shock or intravenous drug administration to induce CA in animals. Nevertheless, as electric shock is complicated to operate and the dosage for drug administration is difficult to control, many published animal CA models are not ideally stable and operable. In order to establish a stable and operable CA model for cardiac arrest- cardiopulmonary resuscitation (CA-CPR) research, this study established different pig CA models via intravenous administration of KCl, MgSO4 and ketamine respectively, and subsequently performed CPR with a self-designed inspiratory impedance threshold device (SIITD). The success rate of CPR in different CA models was evaluated according to hemodynamic and biochemical parameters of pigs. Results demonstrated that in the CA model established by intravenous administration of MgSO4, cardiac output of pigs were significantly elevated and reached the normal range at 10-min after CPR, and other vital signs and biochemical parameters in this model exhibited recovery trends throughout CPR. This study provides a more effective CA model and new ideas in methodology of future CA-CPR research.

Background

Cardiovascular disease is one of the most important causes of human morbidity and mortality, which causes about 17,000,000 deaths worldwide every year(1). A big part of patients suffering cardiovascular disease exhibiting cardiac arrest (CA), also known as sudden cardiac death (SCD), which means suddenly stop of the mechanical activity of hearts and contract of left ventricle(2). Previous studies revealed that over 80% of CA cases occurred out-of-hospital (OHCA). Every year, there are about 330,000 OHCA cases happen in the United States, about 350,000 cases happen in Europe and shockingly about 554,000 cases in China(3–5). Cardiopulmonary resuscitation (CPR) can be performed by professional clinicians and ordinary population, and it is currently the only effective way to rescue CA patients(6,7). Kouwenhoven et al. firstly reported close-chest CPR in 1960, since then, their resuscitation methods have been continuously optimized and standardized(8). At present, CPR generally includes chest compressions, artificial ventilation and external electrical defibrillation.

CA and CPR have always been research hotspots in emergency medicine. Recently, mice, rabbits, dogs and pigs have mostly been used as model animals in cardiac arrest- cardiopulmonary resuscitation (CA-CPR) studies(9). Electric shock or intravenous drug administration have been commonly used to induce CA in previously published studies(10,11). Nevertheless, both of the two methods have some disadvantages, electric shock can induce ventricular fibrillation and CA in a short time and it mostly simulated common clinical cases, however, electric shock is complicated to operate. To successfully induce ventricular fibrillation by electric shock, researchers need to transfer electrodes to the right ventricle through the right heart catheter and then induce an alternating current with certain energy to the endocardium. According to Song et al, when placing electrodes in the right ventricle of mice, ventricular fibrillation can be induced
by importing 60Hz, 1.5mA alternating current to the right ventricular endocardium, CA subsequently occurred after about 15 minutes\(^{(12)}\). Drug administration is easy to operate but drug dosage for CA induction is difficult to control. The prescription and dosage of anesthetic drugs rely on many factors including the species, age, weight and physiological features of model animals. Additionally, accumulation of drugs in the body brings problems in subsequent studies especially when investigating the efficacy of CPR drugs. Based on previous research, KCl can efficiently induce CA animals in a few seconds with only a small dosage, and hence has been commonly used to establish CA models in previous studies\(^{(13–15)}\). However, KCl can induce overwhelming pain to animals and according to our experience, KCl administration usually cause gatism to animals, which can affect the follow-up experimental operations. Alternatively, according to clinicians in our hospital, MgSO\(_4\) administration can induce CA to animals in longer time but causing less pain and no gatism to animals. Additionally, CA cases caused by excessive injection of narcotic drugs (eg. Ketamine) are clinically common\(^{(16–18)}\). For example, previous report illustrated that a 3-year-old girl suffered refractory CA after receiving intravenous local infiltration anesthesia with 0.25% bupivacaine, and the girl was not able to recover after CPR\(^{(19)}\).

Although CPR acts as the primary care for critically ill patients for years, the rescue rate of patients receiving conventional CPR is not satisfactory with a survival rate of lower than 7%. To enhance the survival and rescue rates of critically ill patients after CPR, novel mechanical instruments and devices have been explored and applied\(^{(20)}\). Our group has designed a self-designed inspiratory impedance threshold device (SIITD), which is a registered patent (Patent registration No. CN 101697937 B) and has already been confirmed to be clinically effective. This SIITD can intermittently block the inhalation of gas into lungs during the elastic expansion of chest wall after each CPR compression, and hence increase intrathoracic negative pressure and returned blood volume. Therefore, the blood supply of important organs such as heart coronary arteries, brain, liver, kidney can be increased and eventually improve the success rate of CPR. In our experiments, we established different pig CA models via intravenous injection of KCl, MgSO\(_4\) and the anesthetic drug ketamine respectively, and we performed CPR on pigs with SIITD. Previous studies of pig CA models generally included over 5 pigs in each treatment groups to eliminate individual variation of pigs and ensure the difference of results in each group was statistically powerful\(^{(21–23)}\). Accordingly, considering the cost of experiment and the significance of study, we included 5 pigs in each model group. By evaluating CPR efficiency in three models, we aim to explore and establish a stable pig CA model with strong operability that can satisfy future CA-CPR studies.

**Methods**

All animal experiments were performed with the approval of Animal Ethics Committee of Kunming Medical University. Animals were managed in accordance with Chinese Association for Laboratory Animal Sciences guidelines and current legal requirements. Our animal facilities meet the standards of Laboratory Animal-Requirements of Environment and Housing Facilities (GB 14925-2010).

**2.1. Baseline data**
Fifteen healthy miniature pigs (~16 weeks old, indicating sexual maturity), both male and female, weighing (28±5) kg on average, were provided by the animal laboratory of Kunming Medical University. The pigs used in the experiment were accustomed and fed in the laboratory for more than one day until all physiological parameters tended to be stable and be prepared for the subsequent experiment. The experimental animals were subject to dietary fasting but had free access to water on the night before surgery.

2.2. Self-designed inspiratory impedance threshold device (SIITD)

The SIITD was designed based on the principle of negative pressure suction under this background. The ventilation valve of SITTD is a one-way valve, the gas can only come out through the valve. Each compression during CPR can increase the gas pressure inside SITTD and the valve will close automatically when the pressure reaches a certain level. So, this SIITD can automatically and intermittently block the inhalation of gas into lungs during the elastic expansion of chest wall after each CPR compression, and hence increase intrathoracic negative pressure and returned blood volume. Therefore, the blood supply of important organs such as heart coronary arteries, brain, liver, kidney can be increased and eventually improve the success rate of CPR. As illustrated in Figure 1, the SIITD was equipped with an oxygen supply end [10] connected with an oxygen supply pipe on the bottom [5] with a cavity [4]. It had an air supply exhalation end [9] connected with a patient’s mask or a throat catheter and an evacuation end [6] connected with the atmosphere. A single control valve [2] and the first one-way valve [3] were set on the oxygen supply end [10]. The second one-way valve [7] was designed on the evacuation end. One end of the column body [5] was fixed with the bent pipe [1]. The vertical port [10] of the bent pipe [1] was downward to form an oxygen supply end connected with the oxygen supply pipe. The other end of the column body [5] was fixed with a straight pipe [8] with a vertical upper port [6] and a vertical lower port [9], which was an air supply exhalation end to be connected with a mask or a laryngeal airway of a patient. The vertical upper port [6] of the straight pipe was an evacuation end, and the second one-way valve [7] was designed on the evacuation end to allow for exhalation, whereas prevent inhalation.

2.3. Establishment of pig models

The fifteen pigs that we chose for experiments were similar in age, weight and physical appearance. Therefore, the grouping in our study were totally random. Fifteen healthy pigs were randomly assigned into three groups and each group includes five pigs. Anesthesia was performed on all pigs during all experimental procedures, all unnecessary suffering was avoided, and research was terminated if unnecessary pain or fear resulted in our pigs.

All pigs were subject to basic anesthesia via intramuscular administration of ketamine at a dose of 15 mg/kg, atropine 0.02 mg/kg, and midazolam 0.2 mg/kg, respectively. When pigs autonomously fell down and kept motionless after anesthetic administration, the animals were transferred and fixed on the operating table. Electrocardiogram was performed to measure the blood oxygen saturation (SPO$_2$). The
auricular vein was cut open and supplemented with the balance salt solution at a dose of 20 ml/kg. Intravenous injection of propofol 3 mg/kg and fentanyl 2 μg/kg were administered. Spontaneous breathing was retained and ID6.5-7.5 endotracheal tube with bursa was inserted with a depth of 16-18 cm. After successful intubation, the breathing machine was connected to perform intermittent positive pressure mechanical ventilation (IPPV). The breathing parameters were adjusted with a breathing frequency of 15-20 times/min, a tidal volume of 8-10 ml/kg, and an inspiratory-to-expiratory ratio of 1:2. The end-expiratory carbon dioxide partial pressure (ETPCO$_{2}$) was kept at 35-40 mmHg, which was connected to the Datex. Ohmeda monitoring machine. The femoral artery puncture was performed and was connected to the transducer on the monitoring machine to measure the dynamic blood pressure. Throughout the entire experiment, the esophageal TEE probe was inserted into the esophagus by approximately 30 cm to measure the cardiac output and returned blood volume of the experimental animals.

Following anesthesia induction, the three groups of pigs respectively received intravenous injection of ketamine (model 1), MgSO$_4$ (model 2) and KCl (model 3). Each pig in model 1 received intravenous injection of 200 mg ketamine after anesthesia procedures for CA induction, and CA was established in about 11 minutes after ketamine administration. Each pig in model 2 received intravenous injection of 100 mg MgSO$_4$ after anesthesia procedures, and then 100 mg MgSO$_4$ were injected in every minutes until CA was established. It took overall about four minutes and 300 mg MgSO$_4$ to cause CA. Each pig in model 3 received intravenous injection of 1 g KCl after anesthesia procedures and CA was established in about 30 seconds. Establishment of CA was confirmed when the electrocardiogram hinted the signs of CA and ventricular fibrillation occurred prior to CA. By observing the ventricular fibrillation waveform of electrocardiogram, ventricular fibrillation was defined when the arterial blood pressure was lower than 40 mmHg. We found all pigs had developed ventricular fibrillation right before CA, and the ventricular fibrillation generally continued for about 30 seconds. Afterwards, no ventricular fibrillations were detected during CPR.

2.4. CPR

The ventilation during CPR was continued by the breathing machine as we used before CA. The frequency of ventilation was 10-12 times/min. The SIITD was connected and manual closed-chest CPR was initiated at the presence of CA. Chest compressions were performed by the same investigator on all pigs. To ensure the investigator has enough physical strength for each pig, the investigator was allowed to take a 30-minute break between experiment of each pig. Additionally, the investigator was blinded to all viral signs tracing devices throughout the experiment. The depth of chest compressions was traced by CPR monitoring device and was 25% (approximately 5 cm) of the anterior and posterior diameter of the chest. The compression frequency was 100 times/min to ensure the chest to fully rebound. The proportion of compression relaxation period was 1:1 to minimize the interruption as possible. To occlude the flow of gas into the lungs, SIITD was closed after each compression of CPR when the chest wall was pressed to the lowest point. The effect of increasing the blood flow to the heart was achieved by using the principle of negative pressure suction generated by increasing the elastic retraction of chest wall.
After 2-, 6- and 10-min CPR, the heart rate and hemodynamic parameters including arterial blood pressure, blood oxygen saturation, end-diastolic volume and cardiac output were quantitatively measured. The Esophageal echocardiography and blood-gas analyses were performed.

CPR was terminated after pigs were confirmed dead. No of pigs was successfully rescued after experiments. Carcass of pigs were handed over to the Animal Laboratory of Kunming Medical University for unified handling.

2.5. Data collection

After the chest compression was started, the values of the heart rate (HR), mean arterial blood pressure (MAP), pulse blood oxygen saturation (SPO$_2$), end diastolic volume (EDV), cardiac output (CO) and alternative parameters were recorded at 2 min, 4 min and 10 min, respectively.

2.6. Statistical analysis

SPSS 19.0 software was utilized for statistical analysis (SPSS Inc., Chicago, IL). Measurement data were expressed as mean ± standard deviation (x±s). Hemodynamics and blood gases during CPR were analyzed with single factor ANOVA. A $P$ value of less than 0.05 was considered as statistical significance.

Results

3.1 Comparison of hemodynamic parameters

Prior to the induction of ventricular fibrillation, heart rate (HR), systolic blood pressure (SP), diastolic blood pressure (DP) and mean arterial pressure (MAP) did not significantly differ among three models (all $P$>0.05, data not shown). At 2-, 6- and 10 min after CPR, HR was generally kept at a relatively high level among three models (Figure 2A). The SP was persistently elevated towards the reference value in the model 2 ($P$<0.05), while a downward tendency was observed in model 1 and model 3 (Figure 2B). The DP in model 3 was continuously increased ($P$<0.001), while that in model 1 and model 2 kept low and had no obvious variation tendency (Figure 2C). During the entire experiment, the MAP in the model 2 and 3 tended to elevate, whereas that in the model 1 tended to decline (Figure 2D).

3.2 Comparison of esophageal ultrasound parameters

During the whole experiment, the stroke volume (SV) in model 2 groups was significantly increased ($P$<0.01). The SV tended to decline in the model 1 and 3, whereas no statistical significance ($P$>0.05) was noted in the model 1, as illustrated in Figure 3A. At 2-, 6- and 10-min after CPR, the cardiac output (CO) was significantly increased and reached the reference value at 10-min after CPR in model 2 ($P$<0.01), whereas no statistical significance was observed in the model 1 and 3 ($P$>0.05). The CO in the model 1 and 3 groups tended to decline (Figure 3B). The ejection fraction (EF) were generally kept at a high level throughout the experiment. EF in model 1 and 2 tended to increase ($P$<0.05 in model 2), whereas the EF in model 3 tended to decline ($P$<0.05) (Figure 3C). The end diastolic volume (EDV) were increased towards
the reference value in model 2 at 2-, 6- and 10-min after CPR, while a downward tendency was detected in model 1 and the model 3 group showed a trend of decreasing first and then increasing (Figure 3D).

3.3 Comparison of blood-gas parameters

The \( \text{SPO}_2 \) was significantly increased in model 2 \((P<0.05)\) throughout the experiment and restored to the normal value at 10-min after CPR (Figure 4A). In three models, the pH values were kept close to the reference value and slightly fluctuated between 6 and 8 at each time point (Figure 4B). In three models, the \( \text{PCO}_2 \) values tended to decline at each time point after CPR. At 10 min after CPR, the \( \text{PCO}_2 \) was restored to normal range in model 2, and considerably lower compared with the normal level in the model 1 and 3 group \((P<0.01\) in model 3), as demonstrated in Figure 4C. In the model 1, the \( \text{HCO}_3^- \) level was increased and subsequently decreased at each time point. In the model 2, the \( \text{HCO}_3^- \) level was persistently increased towards the reference value, whereas that was continuously declined in the model 3 \((P<0.01)\) (Figure 4D). At 10 min after CPR, the \( \text{TCO}_2 \) was almost restored to normal in model 2. The changes of \( \text{TCO}_2 \) were similar to those of \( \text{HCO}_3^- \) (Figure 4E). Beef in model 2 was significantly increased towards reference value \((P<0.01)\) (Figure 5).

In the model 1, the blood urea nitrogen (BUN) level was enhanced and then decreased at each time point. In model 2 and 3 group, the BUN level was significantly declined \((P<0.01\) in model 2). At 10 min after CPR, the BUN levels were almost restored to normal in the model 1 and 2 (Figure 6A). At each time point, the white blood cell (WBC) count was increased in the model 1 group, the WBC did not have significant change in the model 2 group \((P>0.05)\), and that tended to decline in the model 3 group. At 10 min after CPR, the WBC was considerably lower than the normal value in the model 3 group \((P<0.05)\) (Figure 6B). In the model 1 group, the red blood cell (RBC) count was increased and immediately decreased, that was slightly decreased and subsequently increased in the model 2 group and that tended to decline in the model 3 group. In the model 3 group, the RBC was significantly lower than the normal at 10 min after CPR \((P<0.05)\) (Figure 6C). Similar outcomes were obtained for the hemoglobin (HGB) levels in three model groups (Figure 6D). In the model 1 and 3 groups, the hematocrit (Hct) tended to decline, and it showed an upward trend in the model 2 group. At 10 min after CPR, the Hct the values were clearly near the normal range in the model 2 group \((P<0.05, \text{Figure } 6E)\). In the model 1 group, the value of Na was initially declined and then increased. The value of Na in model 2 group was opposite to that in group 1, while that in model 3 group tended to increase. (Figure 7A). In the model 2 group \((P<0.05)\), the value of Na was restored to normal at 10 min after CPR, that was evidently higher than the normal values in the model 1 and the model 3 group. In the model 1 group, the K level was initially increased and then decreased at each time point, and that was declined in the model 2 and 3 groups (Figure 7B). At 10 min after CPR, the value of K was restored to the reference value in the model 1 and 2 groups, while that was evidently lower than the reference value in the model 3 group \((P<0.05)\). In the model 1 group, the level of Cl was slightly decreased and then increased and that was decreased in the model 2 group, whereas persistently increased in the model 3 group. At each time point after CPR, the level of Cl in the model 2 group tended to normal, while that in model 1 and 3 groups were significantly higher than the normal levels (all \(P<0.05, \text{Figure } 7C)\).
In the model 1 and 2 groups, the Glu values tended to elevate and that was declined in the model 3 group. At 10 min after CPR, the Glu values were significantly higher than the normal levels in the model 1 and 2 groups, and that was evidently lower compared with the normal level in the model 3 group (all \( P<0.05 \), Figure 7D).

**Discussion**

Conventional manual CPR can offer the blood supply to vital organs. CPR can exert the effect upon letting the blood flow from the heart to the periphery, which can be accomplished by sufficient venous blood flow to the chest following each cycle of manual compression. During the conventional CPR, the blood flow from the peripheral veins to the heart significantly relies upon the status of natural chest wall recoil. The variations of passive chest wall recoil and subsequent intra-thoracic pressure decide the blood return to the lungs and heart in standard CPR. Although CPR acts as the primary care for critically ill patients for years, the rescue rate of patients receiving conventional CRP is not satisfactory with a survival rate of lower than 7%. Closed chest standard CPR without vasopressors cannot maintain minimal levels of vital organ blood flow required for life sustain(24–27). More studies need to be performed in the future to improve the survival rate of CPR.

Establishing stable and operable CA-CPR models is crucial in future studies. At present, published studies often use electric shock or intravenous drug administration to induce CA in animals. However, as electric shock is complicated to operate and dosage of drug administration is difficult to control, many published animal CA models are not stable enough for subsequent studies. New CA models need to be explored. In this study, we tried to explore new ideas in drug-induced CA models. We established three CA models by intravenous injection of ketamine (model 1), MgSO\(_4\) (model 2) and KCl (model 3), respectively. Among which MgSO\(_4\) is not commonly used in CA induction, we used MgSO\(_4\) as it causes less painful to animals. We used pigs in our experiments because the heart of pigs has big similarity with human's. After the establishment of three animal models, routine blood test parameters were quantitatively measured and statistically compared among three models. Our results demonstrated that in the model 2 which was established by intravenous administration of MgSO\(_4\), cardiac output of pigs were significantly elevated to the reference value throughout CPR. Other parameters including systolic blood pressure, mean arterial blood pressure, ejection fractions, SPO\(_2\), HCO\(_3\), Beecf, stroke volume, BUN, Hct and K were all elevated or reduced gradually towards the reference value. Therefore, we concluded that MgSO\(_4\)-induced CA following manual CPR was a stable CA-CPR model.

According to our results, better hemodynamic values were detected in MgSO\(_4\)-induced CA group. According to our results and previous research, we speculate that magnesium ion might have dual function during CPR. On the one hand, high blood magnesium can inhibit myocardial contraction and lead to cardiac dysfunction or cardiogenic shock. Specifically, the effect of high blood magnesium on heart is mainly manifested as inhibition of the autoregulatory cells, sinus bradycardia and conduction block. As autoregulation of high normal cells were reduced, low autoregulation cells were active, which
can produce arrhythmia and even cardiac arrest in severe cases. On the other hand, some previous studies indicated that divalent ions such as magnesium ion might be activated as calcium blockers and be positively useful in CA patients (28,29). In the future, more studies should be performed to explore the function of magnesium in resuscitation research and critical care.

Notably, our results showed that the blood pressure especially diastolic blood pressure were generally kept at a very low level in MgSO₄-induced model during CPR process, while other hemodynamic and biochemical parameters were considerably normal. We speculated that the heart blood supply in this model during CPR might come from surrounding organs and tissues in the body. We hypothesized that under normal circumstances, these internal organs and tissues can store a small amount of blood, and when emergent situation such as CA comes, this part of blood can possibly restore the blood flow to the heart. Our future studies will focus on the CA-trigged responses of multiple organs and tissues to verify our hypothesis.

Additionally, our study included fifteen pigs overall and each group had only five pigs, hence several parameters such as HCO₃, pH, WBC, BUN were highly fluctuated between individuals in each group, which leading to high standard deviation in data analysis. Our future study will take this into account and recruit more samples in experiments. Moreover, CPR in our study was all performed with a SITTD. The SITTD is a registered patent and has already been confirmed to be clinically effective to improve the success rate of CPR (Patent registration No. CN 101697937 B). The principle behind the SITTD is to mechanically change the inhalation of gas into lungs, hence we hypothesized that it would not influence the effect of chemical agent such as KCl, MgSO₄ and ketamine used in our experiments. Certainly, the hypothesis need to be proved and in our future study, and more experiments should be performed to evaluate the MgSO₄-induced CA model with the absence of SITTD.

Animal models of CA are as monitors which allow investigators to trace emergent outcomes following CA, and exploring operable CA model settles foundation in critical care and resuscitation study. Through those animal CA models, we can create critical conditions for experiments, which are unrealistic to be done in humans. Animal CA models provide opportunities to simulate human clinical scenario and promote the development of critical medicine. Our study provides a more effective CA model and new ideas in methodology of future CA-CPR research.

**Conclusions**

In this experiment, the pig models of CA were established by three techniques and the hemodynamic and biochemical parameters demonstrated that the pig model established by intravenous injection of MgSO₄ was the most stable model for CA-CPR research.

**Abbreviations**

CPR: cardiopulmonary resuscitation
Declarations

Ethics approval and consent to participate

This study involved the use of animals and was approved by the Ethics Committee of Kunming Children's Hospital.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.
Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

CL designed the SIITD and established animal models, and is the main contributor in writing the manuscript; HFG, XLH and YZ participated in the animal experiments, JQM, YTZ, LH and MZ contributed in the data collection and results analysis; LMC, JLW and WKD contributed to results analysis and figure plotting; LL provided ideas and suggestions to the study. All authors read and approved the final manuscript.

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References

1. WHO | The world health report 2002 - Reducing Risks, Promoting Healthy Life. WHO [Internet]. 2013 [cited 2019 Sep 17]; Available from: https://www.who.int/whr/2002/en/

2. Langhelle A, Nolan J, Herlitz J, Castren M, Wenzel V, Soreide E, et al. Recommended guidelines for reviewing, reporting, and conducting research on post-resuscitation care: The Utstein style. Resuscitation [Internet]. 2005 Sep 1 [cited 2019 Sep 17];66(3):271–83. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0300957205002492

3. Nichol G, Thomas E, Callaway CW, Hedges J, Powell JL, Aufderheide TP, et al. Regional Variation in Out-of-Hospital Cardiac Arrest Incidence and Outcome. JAMA [Internet]. 2008 Sep 24 [cited 2019 Sep 17];300(12):1423. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18812533

4. Atwood C, Eisenberg MS, Herlitz J, Rea TD. Incidence of EMS-treated out-of-hospital cardiac arrest in Europe. Resuscitation [Internet]. 2005 Oct [cited 2019 Sep 17];67(1):75–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16199289
5. Hua W, Zhang L-F, Wu Y-F, Liu X-Q, Guo D-S, Zhou H-L, et al. Incidence of sudden cardiac death in China: analysis of 4 regional populations. J Am Coll Cardiol [Internet]. 2009 Sep 15 [cited 2019 Sep 17];54(12):1110–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S073510970902186X

6. Herlitz J, Bång A, Alsén B, Aune S. Characteristics and outcome among patients suffering from in hospital cardiac arrest in relation to the interval between collapse and start of CPR. Resuscitation [Internet]. 2002 Apr [cited 2019 Sep 17];53(1):21–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0300957201004853

7. Wik L, Hansen TB, Fylling F, Steen T, Vaagenes P, Åustad BH, et al. Delaying defibrillation to give basic cardiopulmonary resuscitation to patients with out-of-hospital ventricular fibrillation: a randomized trial. JAMA [Internet]. 2003 Mar 19 [cited 2019 Sep 17];289(11):1389–95. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.289.11.1389

8. Kouwenhoven WB, JUDE JR, KNICKERBOCKER GG. CLOSED-CHEST CARDIAC MASSAGE. JAMA [Internet]. 1960 Jul 9 [cited 2019 Sep 17];173(10):1064. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14411374

9. Vognsen M, Fabian-Jessing BK, Secher N, Løfgren B, Dezfulian C, Andersen LW, et al. Contemporary animal models of cardiac arrest: A systematic review. Resuscitation [Internet]. 2017 Apr [cited 2019 Sep 17];113:115–23. Available from: https://linkinghub.elsevier.com/retrieve/pii/S030095721730045X

10. Cherry BH, Nguyen AQ, Hollrah RA, Olivencia-Yurvati AH, Mallet RT. Modeling cardiac arrest and resuscitation in the domestic pig. World J Crit care Med [Internet]. 2015 Feb 4 [cited 2019 Sep 17];4(1):1–12. Available from: http://www.wjgnet.com/2220-3141/full/v4/i1/1.htm

11. Iglesias JM, López-Herce J, Urbano J, Solana MJ, Mencía S, del Castillo J. Chest compressions versus ventilation plus chest compressions in a pediatric asphyxial cardiac arrest animal model. Intensive Care Med [Internet]. 2010 Apr 11 [cited 2019 Sep 17];36(4):712–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20148320

12. Song L, Weil MH, Tang W, Sun S, Pellis T. Cardiopulmonary resuscitation in the mouse. J Appl Physiol [Internet]. 2002 Oct 1 [cited 2019 Sep 17];93(4):1222–6. Available from: https://www.physiology.org/doi/10.1152/japplphysiol.01079.2001

13. Neigh GN, Glasper ER, Bilbo SD, Traystman RJ, Courtney DeVries A. Cardiac arrest/cardiopulmonary resuscitation augments cell-mediated immune function and transiently suppresses humoral immune function. J Cereb Blood Flow Metab [Internet]. 2005 Nov 4 [cited 2019 Jul 30];25(11):1424–32. Available from: http://journals.sagepub.com/doi/10.1038/sj.jcbfm.9600137

14. Larmann J, Schmidt C, Gammelin H, Van Aken HK, Frenzel T, Lanckohr C, et al. Intercellular adhesion molecule-1 inhibition attenuates neurologic and hepatic damage after resuscitation in mice. Anesthesiology [Internet]. 2005 Dec [cited 2019 Jul 30];103(6):1149–55. Available from: https://insights.ovid.com/crossref?an=00000542-200512000-00008
15. Nakatani K, Nakagami-Yamaguchi E, Shinoda Y, Tomita S, Nakatani T. Improving the safety of high-concentration potassium chloride injection. BMJ Open Qual [Internet]. 2019 Jun 12 [cited 2019 Jul 30];8(2):e000666. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31259289

16. Crespo SG, Schoffstall JM, Fuhs LR, Spivey WH. Comparison of two doses of endotracheal epinephrine in a cardiac arrest model. Ann Emerg Med [Internet]. 1991 Mar [cited 2019 Sep 17];20(3):230–4. Available from: https://linkinghub.elsevier.com/retrieve/pii/S019606440580928X

17. Liu D, Hu J, Zhang M, Shao Y, Xue H, Wu Q. Low-dose ketamine combined with pentobarbital in a miniature porcine model for a cardiopulmonary bypass procedure: a randomized controlled study. Eur J Anaesthesiol [Internet]. 2009 May [cited 2019 Sep 17];26(5):389–95. Available from: https://insights.ovid.com/crossref?an=00003643-200905000-00006

18. Dewhirst E, Frazier WJ, Leder M, Fraser DD, Tobias JD. Cardiac Arrest Following Ketamine Administration for Rapid Sequence Intubation. J Intensive Care Med [Internet]. 2013 Nov 29 [cited 2019 Jul 30];28(6):375–9. Available from: http://journals.sagepub.com/doi/10.1177/0885066612448732

19. Vijay BS, Mitra S, Jamil SN. Refractory cardiac arrest due to inadvertent intravenous injection of 0.25% bupivacaine used for local infiltration anesthesia. Anesth essays Res [Internet]. 2013 [cited 2019 Sep 17];7(1):130–2. Available from: http://www.aeronline.org/text.asp?2013/7/1/130/114020

20. Aufderheide TP, Frascone RJ, Wayne MA, Mahoney BD, Swor RA, Domeier RM, et al. Standard cardiopulmonary resuscitation versus active compression-decompression cardiopulmonary resuscitation with augmentation of negative intrathoracic pressure for out-of-hospital cardiac arrest: a randomised trial. Lancet (London, England) [Internet]. 2011 Jan 22 [cited 2019 Apr 11];377(9762):301–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21251705

21. Yang M, Che L, Hua T, Zou Y, Yang Z. Beneficial Effects of Ivabradine on Post-Resuscitation Myocardial Dysfunction In A Porcine Model of Cardiac Arrest. Shock [Internet]. 2019 Jul 3 [cited 2019 Sep 17];1. Available from: http://insights.ovid.com/crossref?an=00024382-900000000-97616

22. Mayr VD, Wenzel V, Voelckel WG, Krismer AC, Mueller T, Lurie KG, et al. Developing a vasopressor combination in a pig model of adult asphyxial cardiac arrest. Circulation [Internet]. 2001 Oct 2 [cited 2019 Sep 17];104(14):1651–6. Available from: https://www.ahajournals.org/doi/10.1161/hc3901.095896

23. Jung YH, Ryu DH, Jeung KW, Na J-Y, Lee DH, Lee BK, et al. Effect of pralidoxime on coronary perfusion pressure during cardiopulmonary resuscitation in a pig model. Clin Exp Emerg Med [Internet]. 2019 May 7 [cited 2019 Sep 17]; Available from: http://www.ceemjournal.org/journal/view.php?doi=10.15441/ceem.18.036

24. Berg RA, Hilwig RW, Berg MD, Berg DD, Samson RA, Indik JH, et al. Immediate post-shock chest compressions improve outcome from prolonged ventricular fibrillation. Resuscitation [Internet]. 2008 Jul [cited 2019 Apr 11];78(1):71–6. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0300957208001238
25. Plaisance P, Lurie KG, Vicaut E, Martin D, Gueugniaud P-Y, Petit J-L, et al. Evaluation of an impedance threshold device in patients receiving active compression-decompression cardiopulmonary resuscitation for out of hospital cardiac arrest. Resuscitation [Internet]. 2004 Jun [cited 2019 Apr 11];61(3):265–71. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0300957204000450

26. Staffey KS, Dendi R, Brooks LA, Pretorius AM, Ackermann LW, Zamba KD, et al. Liquid ventilation with perfluorocarbons facilitates resumption of spontaneous circulation in a swine cardiac arrest model. Resuscitation [Internet]. 2008 Jul [cited 2019 Apr 11];78(1):77–84. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0300957208001172

27. Yannopoulos D, Matsuura T, McKnite S, Goodman N, Idris A, Tang W, et al. No assisted ventilation cardiopulmonary resuscitation and 24-hour neurological outcomes in a porcine model of cardiac arrest. Crit Care Med [Internet]. 2010 Jan [cited 2019 Apr 11];38(1):254–60. Available from: https://insights.ovid.com/crossref?an=00003246-201001000-00036

28. Maekawa T. Divalent ions in cardiopulmonary-cerebral resuscitation. Magnesium [Internet]. 1989 [cited 2019 Sep 17];8(3–4):154–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2682041

29. Allegra J, Lavery R, Cody R, Birnbaum G, Brennan J, Hartman A, et al. Magnesium sulfate in the treatment of refractory ventricular fibrillation in the prehospital setting. Resuscitation [Internet]. 2001 Jun [cited 2019 Sep 17];49(3):245–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11719117

**Figures**

Figure 1
Structure of the self-designed inspiratory impedance threshold device. [1]. Bent pipe; [2]. Control valve; [3]. First one-way valve; [4]. Cavity; [5]. Oxygen supply pipe; [6]. Evacuation end; [7]. Second one-way valve; [8]. Straight pipe; [9]. Vertical lower port; [10]. Vertical port.

Figure 2

Comparison of hemodynamic parameters. A. At 2-, 6- and 10 min after CPR, HR was generally kept at a relatively high level among three models. B. The SP was persistently elevated towards the reference value in the model 2 (P<0.05), while a downward tendency was observed in model 1 and model 3. C. The DP in model 3 was continuously increased (P<0.001), while that in model 1 and model 2 kept low and had no obvious variation tendency. D. During the entire experiment, the MAP in the model 2 and 3 tended to elevate, whereas that in the model 1 tended to decline.
Comparison of esophageal ultrasound parameters. A. During the whole experiment, SV in model 2 groups was significantly increased (P<0.01). The SV tended to decline in the model 1 and 3, whereas no statistical significance (P>0.05) was noted in the model 1. B. At 2-, 6- and 10-min after CPR, the CO was significantly increased and reached the reference value at 10-min after CPR in model 2 (P<0.01), whereas no statistical significance was observed in the model 1 and 3 (P>0.05). The CO in the model 1 and 3 groups tended to decline. C. The EF were generally kept at a high level throughout the experiment. EF in model 1 and 2 tended to increase (P<0.05 in model 2), whereas the EF in model 3 tended to decline (P<0.05). D. The EDV were increased towards the reference value in model 2 at 2-, 6- and 10-min after CPR, while a downward tendency was detected in model 1 and the model 3 group showed a trend of decreasing first and then increasing.
Figure 4

Comparison of SPO2, pH, PCO2, HCO3 and TCO2 among different groups. A. The SPO2 was significantly increased in model 2 (P<0.05) throughout the experiment and restored to the normal value at 10-min after CPR. B. In three models, the pH values were kept close to the reference value and slightly fluctuated between 6 and 8 at each time point. C. In three models, the PCO2 values tended to decline at each time point after CPR. At 10 min after CPR, the PCO2 was restored to normal range in model 2, and considerably lower compared with the normal level in the model 1 and 3 group (P<0.01 in model 3). D. In the model 1, the HCO3 level was increased and subsequently decreased at each time point. In the model 2, the HCO3 level was persistently increased towards the reference value, whereas that was continuously declined in the model 3 (P<0.01). E. At 10 min after CPR, the TCO2 was almost restored to normal in model 2. The changes of TCO2 were similar to those of HCO3.
Figure 5

Comparison of Beeef values among different groups. Beeef in model 2 was significantly increased towards reference value (P<0.01).

Figure 6

A Blood Urea Nitrogen

B White Blood Cell

C Red Blood Cell

D Hemoglobin

E Hematocrit
Comparison of BUN, WBC, RBC, HGB and Hct among different groups. A. In the model 1, the BUN level was enhanced and then decreased at each time point. In model 2 and 3 group, the BUN level was significantly declined (P<0.01 in model 2). At 10 min after CPR, the BUN levels were almost restored to normal in the model 1 and 2. B. At each time point, the WBC count was increased in the model 1 group, the WBC did not have significant change in the model 2 group (P>0.05), and that tended to decline in the model 3 group. At 10 min after CPR, the WBC was considerably lower than the normal value in the model 3 group (P<0.05). C. In the model 1 group, the RBC count was increased and immediately decreased, that was slightly decreased and subsequently increased in the model 2 group and that tended to decline in the model 3 group. In the model 3 group, the RBC was significantly lower than the normal at 10 min after CPR (P<0.05). D. HGB exhibited similar outcomes with RBC in three model groups. E. In the model 1 and 3 groups, the hematocrit (Hct) tended to decline, and it showed an upward trend in the model 2 group. At 10 min after CPR, the Hct the values were clearly near the normal range in the model 2 group (P<0.05).

**Figure 7**

Comparison of Na, K, Cl and Glu among different groups. A. In the model 1 group, the value of Na was initially declined and then increased. The value of Na in model 2 group was opposite to that in group 1, while that in model 3 group tended to increase. In the model 2 group (P<0.05), the value of Na was restored to normal at 10 min after CPR, that was evidently higher than the normal values in the model 1 and the model 3 group. B. In the model 1 group, the K level was initially increased and then decreased at each time point, and that was declined in the model 2 and 3 groups. At 10 min after CPR, the value of K
was restored to the reference value in the model 1 and 2 groups, while that was evidently lower than the reference value in the model 3 group (P<0.05). C. In the model 1 group, the level of Cl was slightly decreased and then increased and that was decreased in the model 2 group, whereas persistently increased in the model 3 group. At each time point after CPR, the level of Cl in the model 2 group tended to normal, while that in model 1 and 3 groups were significantly higher than the normal levels (all P<0.05). D. In the model 1 and 2 groups, the Glu values tended to elevate and that was declined in the model 3 group. At 10 min after CPR, the Glu values were significantly higher than the normal levels in the model 1 and 2 groups, and that was evidently lower compared with the normal level in the model 3 group (all P<0.05).

Supplementary Files

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