Original Article

Risk Factor Analyses for the Return of Spontaneous Circulation in the Asphyxiation Cardiac Arrest Porcine Model

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Abstract

Background: Animal models of asphyxiation cardiac arrest (ACA) are frequently used in basic research to mirror the clinical course of cardiac arrest (CA). The rates of the return of spontaneous circulation (ROSC) in ACA animal models are lower than those from studies that have utilized ventricular fibrillation (VF) animal models. The purpose of this study was to characterize the factors associated with the ROSC in the ACA porcine model.

Methods: Forty-eight healthy miniature pigs underwent endotracheal tube clamping to induce CA. Once induced, CA was maintained untreated for a period of 8 min. Two minutes following the initiation of cardiopulmonary resuscitation (CPR), defibrillation was attempted until ROSC was achieved or the animal died. To assess the factors associated with ROSC in this CA model, logistic regression analyses were performed to analyze gender, the time of preparation, the amplitude spectrum area (AMSA) from the beginning of CPR and the pH at the beginning of CPR. A receiver-operating characteristic (ROC) curve was used to evaluate the predictive value of AMSA for ROSC.

Results: ROSC was only 52.1% successful in this ACA porcine model. The multivariate logistic regression analyses revealed that ROSC significantly depended on the time of preparation, AMSA at the beginning of CPR and pH at the beginning of CPR. The area under the ROC curve in for AMSA at the beginning of CPR was 0.878 successful in predicting ROSC (95% confidence intervals: 0.773~0.983), and the optimum cut-off value was 15.62 (specificity 95.7% and sensitivity 80.0%).

Conclusions: The time of preparation, AMSA and the pH at the beginning of CPR were associated with ROSC in this ACA porcine model. AMSA also predicted the likelihood of ROSC in this ACA animal model.

Key words: Asphyxia; Cardiac Arrest; Cardiopulmonary Resuscitation; Logistic Regression Analyses; Return of Spontaneous Circulation

Introduction

Modern cardiopulmonary resuscitation (CPR) has been performed for more than 50 years and is the most effective treatment for cardiac arrest (CA); however, CPR yields a functional survival rate of only 1.4–5.0%.[1,2] Insights into the pathophysiological processes of CA and postresuscitation syndrome have at least partially been gained from animal studies. It is generally accepted that results from animal models that more closely resemble human diseases can more reliably be extrapolated to humans.

Asphyxiation CA (ACA) is one of the most prevalent causes of sudden cardiac death, and animal models of CA are thus frequently used in basic research to more closely mirror the clinical course of CA and CPR.[3-5] However, in CPR studies that are based on the ACA animal models, the rates of the return of spontaneous circulation (ROSC) are lower than those from studies that have utilized ventricular fibrillation (VF) CA models even under experimental conditions, including the type of animal used and the time for which CA goes untreated, that are identical.[3,5-7]

The CA criterion used in asphyxiation is blood pressure, and no other indexes are used.[3,5] Once ACA is achieved, CPR is performed homogeneously according to the guidelines. Every experimental life is cherished, and any anthropogenic factor that might affect the survival of the animals should be eliminated. Building on our previous studies, the purpose of this study was to characterize some of the pre-CPR factors that are associated with ROSC in the ACA porcine model.[5]

Our previous study demonstrated that three types of arrhythmias (i.e., VF, pulseless electrical activity [PEA], and asystole) occur with 8 min of untreated CA in ACA animal models.[5] The amplitude spectrum area (AMSA) has been reported to be useful in predicting the likelihood of successful defibrillation[8] and might be an index for predicting the likelihood of ROSC in VF CA animal

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models.[6] No studies have tested the ability of AMSA to predict the likelihood of ROSC in the ACA animal model. In the present study, we chose to examine the ability of AMSA to predict ROSC in the ACA animal model.

Methods

Preparation of the animals

This prospective animal study was conducted with the approval of the Animal Care and Use Committee of Beijing Chao-Yang Hospital, affiliated with the Capital Medical University. The study was performed according to *Utstein-style guidelines*[9] on 48 healthy Wu Zhishan inbred miniature pigs of both sexes aged 6–8 months and weighing 20 ± 2 kg.

Initial sedation in each animal was achieved via intramuscular injection of ketamine (10 mg/kg) followed by ear vein injection of propofol (1.0 mg/kg). The anesthetized animals were intubated with 6.5-mm cuffed endotracheal tubes via direct laryngoscopy. Propofol (1.0 mg/kg) and fentanyl (4 μg/kg) were then intravenously administered to reach the desired depth of anesthesia and analgesia, and 9 $mg \cdot kg^{-1} \cdot h^{-1}$ propofol and 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (iv) fentanyl were subsequently used to maintain the anesthesia level. Additional doses of these drugs were administered when the heart rate exceeded 120 beats per min (BPM) and/or the systolic blood pressure exceeded 120 mmHg. The animals were mechanically ventilated with a volume-controlled ventilator (Servo 900c; Siemens, Berlin, Germany) at a tidal volume of 8 ml/kg and a respiratory frequency of 12/min with room air. End-tidal P_{CO2} was monitored with an in-line infrared capnography system (CO2SMOplus monitor; Respironics Inc., Murrysville, PA, USA). The respiratory frequency was adjusted to maintain an end-tidal P_{CO2} between 35 mmHg and 40 mmHg. Aortic pressure was measured with a fluid-filled catheter advanced from the left femoral artery into the thoracic aorta. A Swan-Ganz catheter (7F; Edwards Life Sciences, Irvine, CA, USA) was advanced from the left femoral vein and flow-directed into the pulmonary artery to collect mixed venous blood. The catheter was calibrated before use, and its tip position was confirmed by the presence of characteristic pressure traces. An electrocardiograph was continuously recorded with a multichannel physiological recorder (BL-420F Data Acquisition and Analysis System; Chengdu TME Technology Co. Ltd., Sichuan, China). All hemodynamic parameters were monitored with a multi-function monitor (M1165; Hewlett-Packard Co, Palo Alto, CA, USA).

Experimental protocols

After surgery, the animals were allowed to equilibrate for 60 min to achieve a stable resting level, and baseline data were then collected. The animals were paralyzed with 0.2 mg/kg cisatracurium to avoid gasping, and CA was then induced by clamping the endotracheal tube. The animals were asphyxiated until simulated pulselessness, defined as an aortic systolic pressure <30 mmHg, was observed.[3]

After CA had been successfully induced, mechanical ventilation and anesthetic/analgesic administration were ceased, and the endotracheal tube was opened. After 8 min of untreated CA (equivalent to the average time required for emergency medical services to arrive),[10] mechanical ventilation was resumed with 100% oxygen, and CPR was performed manually. Manual chest compressions were conducted by a designated CPR technician who compressed approximately one-third of the anteroposterior diameter of the thorax at a rate of 100 compressions per min with equal compression-relaxation durations. The quality of the chest compressions was controlled by a HeartStart MRx Monitor/Defibrillator with Q-CPR (Philips Medical Systems, Best, Holland).

After 2 min of CPR, epinephrine (0.02 mg/kg) was diluted to 10 ml by 0.9% saline solution and was bolus injected into the right atrium by Swan-Ganz catheter, and CPR was then performed manually for another 2 min. After 4 min of CPR, defibrillation (SMART Biphasic) was attempted using 4 J/kg on the first attempt. CPR was resumed for another 2 min following the attempted defibrillation. The sequence continued until ROSC or for 30 min if ROSC was not achieved. ROSC was defined as the maintenance of a systolic blood pressure ≥50 mmHg for ≥10 min.

Measurements

Based on the sample size of this study, four indexes were chosen for examination at the end time point of 8 min of untreated CA, including the gender of the animal, the preparatory phase time (defined from the time point of the first injection of ketamine to paralysis with cisatracurium), the pH of the central venous blood, and the electrocardiogram. The electrocardiographic signals were sampled and recorded at a frequency of 500 Hz and digitized with a data acquisition system (BL-420F Data Acquisition and Analysis System, China). The electrocardiographic signals were filtered between 4 Hz and 50 Hz to minimize interference. The types of electrocardiac arrhythmias included VF, PEA, and asystole. VF was defined as a disorganized rhythm with a median peak-to-peak amplitude ≥100 μV. Any rhythm with an amplitude <100 μV was defined as asystole. An episode of VF was required to persist for ≥5 s before the transition to a non-VF rhythm.[11] The subsequent recurrence of VF was considered a new episode. Successful defibrillation was defined as the termination of VF for ≥5 s independent of hemodynamic factors.[12] The AMSA was calculated according to the following formula: $\mathrm{AMSA} = \sum A_i \times F_i$, where A_i is the amplitude at the i^{th} frequency F_i. The AMSA over a 5 s interval was obtained 20 s before the initiation of CPR [Figure 1]. PEA and asystole are other types of arrhythmias that are observed in ACA and are not ignored. This study was based on the ACA animal model, and AMSAs were calculated for all rhythm types. The values were obtained directly from the acquired data (BL-420F Data Acquisition and Analysis System, China) by the software of the computer.

Statistical analyses

Statistical analyses were performed by SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). Univariate and

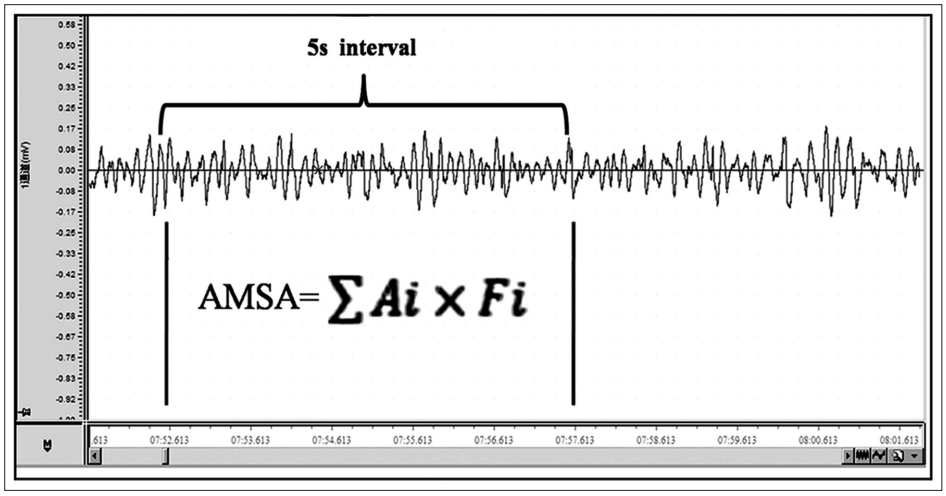

Figure 1: The AMSA was calculated according to the following formula: $AMSA=\sum A_i \times F_i$, where A_i is the amplitude at the ith frequency F_i. The AMSA over a 5-s interval was obtained 20 s before CPR was initiated. AMSA: Amplitude spectrum area; CPR: Cardiopulmonary resuscitation.

multivariable logistic regression analyses were used to identify the factors that were associated with ROSC. Receiver-operating characteristic (ROC) curve analysis was chosen to evaluate the predictive value of AMSA for ROSC. Two-sided $P < 0.05$ were considered statistically significant.

Results

Baseline characteristics and the parameters according to return of spontaneous circulation and nonreturn of spontaneous circulation

Forty-eight animals, including 24 male and 24 female animals, were subjected to CA, and only 52.1% (25/48) achieved successful ROSC. The baseline characteristics of the ROSC and non-ROSC animals are shown in Table 1. The parameters chosen in this study were significantly different between the ROSC and non-ROSC groups [Table 1].

Arrhythmia incidences and resuscitation outcomes

At 8 min after untreated CA, VF occurred in 24, PEA occurred in 10, and asystole occurred in 14 animals. The incidence of these arrhythmias varied with ROSC outcome [Table 2]. Defibrillation alone and CPR alone failed to induce ROSC. In the non-ROSC group, only four animals exhibited VF at the beginning of CPR and exhibited asystole after the first shock [Table 3].

Functional analysis at 6 h (6 h after ROSC was first observation end point) indicated that the average survival time was 2.60 ± 1.23 h [Figure 2].

Univariate and multivariate logistic regression analyses to characterize the factors associated with the return of spontaneous circulation

The univariate logistic regression analyses revealed that ROSC significantly depended on the gender of the animal, the time of preparation, and the AMSA and pH at the initiation of CPR [Table 4].

Table 1: The comparison of baseline characteristics and the parameters evaluated in this study between the ROSC and non-ROSC groups

Characteristics	ROSC group (n = 25)	Non-ROSC group (n = 23)	P
Weight (kg)	20.21 ± 1.79	20.33 ± 1.96	0.421
Heart rate (beats/min)	113.44 ± 11.34	118.44 ± 18.02	0.071
Hemoglobin (g/L)	125.8 ± 1.04	114.4 ± 2.11	0.068
Lactic acid (mmol/L)	1.12 ± 0.34	1.42 ± 0.41	0.057
Male/female	8/17	16/7	0.009
Time of preparation (min)	62.90 ± 8.00	80.00 ± 20.00	<0.001
AMSA at the beginning of CPR (mV×Hz)*	21.00 (17.50, 22.80)	0.00	<0.001
pH at the beginning of CPR	7.10 ± 0.07	6.90 ± 0.23	<0.001

The data are reported as the means ± SD or as numbers (n). The AMSA data were not normally distributed; thus, the medians and the quartiles are shown. *The AMSA data were not normally distributed. VF appeared in only four animals in the non-ROSC group at the beginning of CPR beginning, the interquartile range of the data was 0.00-0.00, and the median was 0.00. ROSC: Return of spontaneous circulation; AMSA: Amplitude spectrum area; CPR: Cardiopulmonary resuscitation; SD: Standard deviation; VF: Ventricular fibrillation.

Table 2: Incidences of the arrhythmias in the animals

ACA*	Animals (n)	Arrhythmias at CA			Arrhythmias at CPR		
		VF	PEA	A	VF	PEA	A
ROSC	25	20	5	0	20	4	1
Non-ROSC	23	8	7	8	4	6	13

*Mann-Whitney U-test for differences in arrhythmias between the ROSC and non-ROSC animals in the ACA group: Arrhythmias at CA, $Z = -3.780$, $P<0.001$; arrhythmias at CPR, $Z = -3.923$, $P<0.001$. A: Asystole; CA: Cardiac arrest; CPR: Cardiopulmonary resuscitation; PEA: Pulseless electrical activity; ROSC: Return of spontaneous circulation; ACA: Asphyxiation cardiac arrest; VF: Ventricular fibrillation.

The multivariate logistic regression analyses revealed that ROSC significantly depended on the time of

preparation and the AMSA and pH at the initiation of CPR [Table 5].

The predictive value of amplitude spectrum area for return of spontaneous circulation

The area under the AMSA ROC curve used to predict successful ROSC was 0.878 with 95% confidence intervals of 0.773–0.983, and the optimum cut-off value was 15.62 (specificity 95.7% and sensitivity 80.0%; Figure 3). Thus, higher AMSA values were associated with a greater likelihood of ROSC.

Discussion

Here, we presented a study of the factors associated with ROSC in ACA, and a spectrum of parameters relevant to ROSC was tested with logistic regression analyses. The major finding of the present study is that ROSC in the ACA porcine model significantly depended on the time of preparation, the AMSA and pH at the initiation of CPR.

Asphyxial causes of CA result from airway obstruction or failure of ventilation. Suboptimal exchange of oxygen and carbon dioxide is associated with progressive hypoxemia, hypercarbia, bradycardia, hypotension, and the loss of consciousness before CA. The onset of asphyxial CA is, therefore, more gradual than the onsets of pulselessness, loss of consciousness, and apnea following sudden-onset VF.[13] Therefore, the immediate restoration of ventilation with supplemental oxygen is the most important therapy for asphyxial CA;[14] if the restoration of oxygenation and chest compressions fail to restart the arrested heart, epinephrine appears to be useful.[15] We used a validated model of asphyxiation that involved clamping of the endotracheal tube in the presence of room-air ventilation with full muscle paralysis, which reliably prevents any form of gasping that would be a severe confounding variable in an asphyxia model. Moreover, this study showed that after asphyxial CA, a period of 8 min without intervention is absolutely necessary to prevent successful resuscitation with ventilation and chest compressions alone.[3,16]

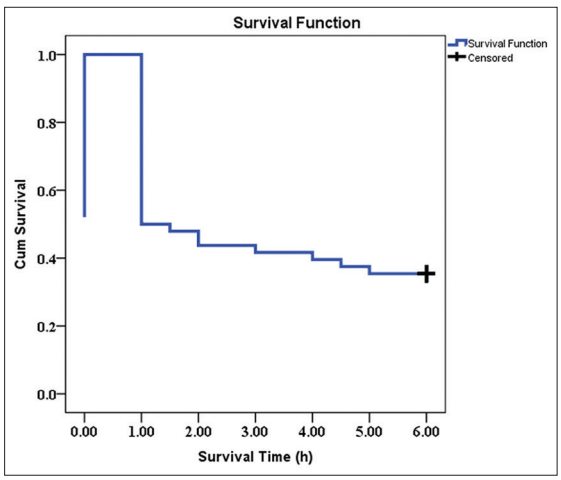

Figure 2: Functional survival analysis of the animals following ROSC (n = 48). ROSC: Return of spontaneous circulation.

Table 3: Resuscitation outcomes of the ROSC animals

Outcomes	ROSC group (n = 25)	Non-ROSC group (n = 23)	P
Termination of VF with first shock (n)	14	4	0.539
Number of shocks	1.76 ± 1.13	0.13 ± 1.34	<0.001
Time to ROSC (min)	8.88 ± 2.77	-	-
6 h survival (n)	17	-	-

ROSC: Return of spontaneous circulation; VF: Ventricular fibrillation.

Table 4: Univariate logistic regression analyses for ROSC in the asphyxiation CA porcine model

Items	Regression coefficient	OR	95% *CI*	P
Gender	−1.580	0.206	0.061–0.699	0.011
Time of preparation	−0.088	0.915	0.863–0.971	0.003
AMSA at the beginning of CPR	0.180	1.197	1.100–1.303	<0.001
pH at the beginning of CPR	22.685	9.851	4.501–15.202	<0.001

OR: Odds ratio; *CI*: Confidence interval; AMSA: Amplitude spectrum area; CA: Cardiac arrest; ROSC: Return of spontaneous circulation; CPR: Cardiopulmonary resuscitation.

Table 5: Multivariate logistic regression analyses for ROSC in the asphyxiation CA porcine model

Items	Regression coefficient	OR	95% *CI*	P
Gender	−1.913	0.148	0.012–1.851	0.138
Time of preparation	−0.120	0.887	0.787–0.998	0.047
AMSA at the beginning of CPR	0.129	1.138	1.009–1.283	0.035
pH at the beginning of CPR	19.408	8.429	0.434–16.424	0.039

OR: Odds ratio; *CI*: Confidence interval; AMSA: Amplitude spectrum area; CA: Cardiac arrest; ROSC: Return of spontaneous circulation; CPR: Cardiopulmonary resuscitation.

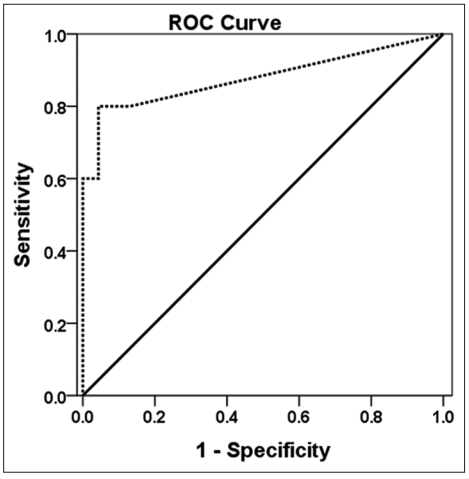

Figure 3: The ROC curve of the AMSA at the initiation of CPR beginning and the predicted probabilities of ROSC. The area under ROC curve was 0.878 with a 95% confidence interval of 0.773–0.983. Based on the maximum Youden index, the optimum cut-off value was 15.62 (specificity 95.7% and sensitivity 80.0%). ROC: Receiver-operating characteristic; AMSA: Amplitude spectrum area; CPR: Cardiopulmonary resuscitation; ROSC: Return of spontaneous circulation.

In the present study, we demonstrated some of the factors associated with ROSC in an ACA model. As an independent factor that is associated with ROSC, the time of preparation depends on the proficiency of the operators, and this is an obviously important factor for human. In this stage, the animals were subjected to anesthesia and the insertion of catheters to monitor the variables. All interventions, anesthesia doses, and analgesia drugs affect the physiological statuses of animals.[17] Reduction in operator proficiency results in longer of times of preparation. In turn, longer times of preparation result in the use of higher doses of anesthesia and analgesia drugs and increased attack severity in the animals, which reduce the likelihood of ROSC. Thus, we should improve the technical proficiencies of the operators to increase the rate of ROSC in this CA model. In the present study, we observed that the hemoglobin levels were higher in the ROSC group than in the non-ROSC group (12.58 ± 1.04 vs. 11.44 ± 2.11, $P > 0.05$). It is possible that hemorrhage during preparation was an additional risk factor, and hemorrhages should be avoided during the animal operations. The lives of experimental animals are precious, and their sacrifices for human scientific studies are honorable.

The acidemia and consequent cellular acidosis that result from asphyxiation have been attributed to critical reductions in oxygen transport and the consequent anaerobic metabolism and metabolism lactic acidosis that result from increased blood lactic acid concentrations. In this porcine CA preparation, we observed that pH had obviously decreased at the initiation of CPR beginning. pH is a specific and important index for ACA. Asphyxiation can be caused by airway obstruction or abnormal ventilation. When asphyxiation occurs, the entire body suffers hypoxemia, hypercarbia, and acidemia, which lead to metabolic disorders, cells dysfunction, and morphological damage.[7,18] In this study, a logistic regression analysis revealed that pH at the beginning of CPR independently predicted successful ROSC. Based pathophysiological analyses of asphyxiation, pH reflected the overall severity of the animal's suffering due to severe oxygen metabolic disorders and irreversible injuries to the mitochondrial respiratory chain during the endotracheal tube clamping and the 8 untreated min following the induction of CA achieved. Lower pHs are associated with more severe mitochondrial damage and worse energy preservation within the electron transport chain, and these factors are more favorable in the few animals that are successfully resuscitated.[7,19]

In recent years, there has been a constant decrease in the occurrence of VF and a rapid rise in the occurrence of PEA as the presenting rhythm in CA settings.[20] The mechanisms responsible for the decline in VF as the presenting rhythm remain unknown. One explanation is that the implementation of recommended primary and secondary coronary artery disease prevention strategies is responsible.[21] The second explanation is that the distribution of the etiologies of CA has changed, and the incidence of non-cardiogenic CA (e.g., pulmonary embolism and asphyxiation) has increased in recent decades.

Studies have demonstrated that the outcomes of CPR are significantly better when the presenting rhythm of CA is VF. The discharge rate is approximately 3% when VF is not the presenting rhythm compared with 50% in patients with VF.[22] Patients or animals who present with PEA or asystole typically have higher mortality rates and reduced chances of achieving ROSC.[23-26] During the untreated 8 min after CA, the electrocardiographs exhibited several changes, including VF, PEA, and asystole. Approximately, 50% of the animals in this study exhibited VF prior to CPR.

Electrocardiogram wavelets reflect both the electrical and metabolic conditions of the myocardium.[27,28] The AMSA reflects the levels of metabolic substrates and high-energy phosphate stores in the myocardium.[8] The AMSA has been shown be associated with a positive predictive value for successful defibrillation that is superior to those of the mean amplitude and median frequency of VF.[6] AMSA is well-correlated with coronary perfusion pressure which is highly correlated with coronary blood flow during cardiac resuscitation.[8] However, the measurement of coronary perfusion pressure requires invasive interventions that are not usually feasible, especially in patients of out-of-hospital CA. No previous studies have tested the value of the AMSA in the prediction of the likelihood of ROSC in an ACA animal model. The results from this revealed that the AMSA at the beginning of CPR was independently associated with ROSC and was useful in the prediction of ROSC. Higher AMSA values at the initiation of CPR were associated with a greater probability of successful ROSC. We, therefore, anticipate that CPR will ultimately be guided by objective analyses like AMSA.

Estrogen has been considered to be a protective factor for the cardiovascular system, and female animals typically exhibit good prognoses for a variety of attacks.[29-31] In this study, the male gender was associated with ROSC in the ACA porcine model in the univariate logistic regression analysis, but this association was not present in the multivariate logistic regression analysis. These results might have been due to the small sample size of this study.

Some limitations of this study should be noted, including the limited sample size and the fact that we were unable to include a greater number of indexes that might also have been associated with ROSC. We used young, healthy pigs; in contrast, in clinical practice, the majority of individuals exhibiting CA have underlying pathological alterations. Furthermore, this study addressed VF but not PEA or asystole. Whether PEA or asystole could have affected our results remains to be evaluated.

In conclusion, the time of preparation, AMSA at the initiation of CPR beginning and pH at the initiation of CPR was associated with ROSC in this ACA porcine model. Furthermore, AMSA at the initiation of CPR might be a useful index for predicting successful ROSC in this CA porcine model and should be investigated in the future

research. AMSA might also the likelihood of ROSC in ACA animal models.

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