Original Article

Changes of end-tidal carbon dioxide during cardiopulmonary resuscitation from ventricular fibrillation versus asphyxial cardiac arrest

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BACKGROUND: Partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) has been used to monitor the effectiveness of precordial compression (PC) and regarded as a prognostic value of outcomes in cardiopulmonary resuscitation (CPR). This study was to investigate changes of $P_{ET}CO_2$ during CPR in rats with ventricular fibrillation (VF) versus asphyxial cardiac arrest.

METHODS: Sixty-two male Sprague-Dawley (SD) rats were randomly divided into an asphyxial group ($n=32$) and a VF group ($n=30$). $P_{ET}CO_2$ was measured during CPR from a 6-minute period of VF or asphyxial cardiac arrest.

RESULTS: The initial values of $P_{ET}CO_2$ immediately after PC in the VF group were significantly lower than those in the asphyxial group (12.8 ± 4.87 mmHg vs. 49.2 ± 8.13 mmHg, $P=0.000$). In the VF group, the values of $P_{ET}CO_2$ after 6 minutes of PC were significantly higher in rats with return of spontaneous circulation (ROSC), compared with those in rats without ROSC (16.5 ± 3.07 mmHg vs. 13.2 ± 2.62 mmHg, $P=0.004$). In the asphyxial group, the values of $P_{ET}CO_2$ after 2 minutes of PC in rats with ROSC were significantly higher than those in rats without ROSC (20.8 ± 3.24 mmHg vs. 13.9 ± 1.50 mmHg, $P=0.000$). Receiver operator characteristic (ROC) curves of $P_{ET}CO_2$ showed significant sensitivity and specificity for predicting ROSC in VF versus asphyxial cardiac arrest.

CONCLUSIONS: The initial values of $P_{ET}CO_2$ immediately after CPR may be helpful in differentiating the causes of cardiac arrest. Changes of $P_{ET}CO_2$ during CPR can predict outcomes of CPR.

KEY WORDS: Partial pressure of end-tidal carbon dioxide; Cardiac arrest; Cardiopulmonary resuscitation; Return of spontaneous circulation; Rats

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INTRODUCTION

Partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) is a noninvasive monitor of physiological variable which has been widely used in clinical patients, especially in critically ill patients. Under constant ventilation, $P_{ET}CO_2$ reflects the level of tissue circulation and the state of body metabolism. The 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care (ECC) recommend

quantitatively analyzing capnogram to monitor efficacy of CPR.^[1] During CPR in patients, a sudden increase in the values of $P_{ET}CO_2$ signals the return of spontaneous circulation (ROSC).^[2,3] $P_{ET}CO_2$ values also predict the outcomes of CPR in cardiac arrest patients.^[4-6]

Two clinical studies, which were conducted to assess the pattern of $P_{ET}CO_2$ changes during CPR in patients with primary cardiac arrest and those with asphyxial cardiac arrest, demonstrated the initial values of $P_{ET}CO_2$

could be useful in differentiating the causes of cardiac arrest in a prehospital setting. In asphyxial cardiac arrest, the initial values of $P_{ET}CO_2$ couldn't predict the outcomes of CPR, as they could do in ventricular fibrillation/pulseless ventricular tachycardia (VF/VT) arrest.^[6,7] In the first study, investigators found $P_{ET}CO_2$ values after 5 minutes of CPR could predict the outcomes of CPR in VF/VT and asphyxial cardiac arrest patients, as $P_{ET}CO_2$ values after 1 minute of CPR could do in the second study.

An experimental study was undertaken to compare changes in $P_{ET}CO_2$ during CPR in VF versus asphyxial cardiac arrest in piglets.^[8] The results showed that the values of $P_{ET}CO_2$ during the first five breaths of CPR were much higher after asphyxial cardiac arrest than those of VF. The high initial values of $P_{ET}CO_2$ were correlated with ROSC. After 1 minute of CPR, the values of $P_{ET}CO_2$ could predict the outcomes of CPR in patients with asphyxial cardiac arrest. However, in cardiac arrest caused by VF, the relationship between $P_{ET}CO_2$ and ROSC was not further investigated. Most of the other experimental studies evaluated the pattern of $P_{ET}CO_2$ changes during CPR either in VF arrest or in asphyxial arrest.^[9–13] Studies on the patterns of $P_{ET}CO_2$ changes during CPR in cardiac arrest rats are rare at present.

In this study, we aimed to compare changes in $P_{ET}CO_2$ during CPR in VF versus asphyxial cardiac arrest in rats and evaluated the relation of $P_{ET}CO_2$ to ROSC and the mean aortic pressure (MAP).

METHODS

Animal preparation

Experimental studies were approved by the Institutional Animal Ethics Committee of Sun Yat-Sen University. All experiments were performed on male healthy Sprague-Dawley (SD) rats from the Experimental Animal Center of Sun Yat-Sen University, weighing 300–400 g. The rats were randomly divided into an asphyxial group ($n=32$) and a VF group ($n=30$). After an overnight fast except for free access to water, the rats were anesthetized by intraperitoneal injection of 45 mg/kg pentobarbital. Additional doses of 10 mg/kg were administered at intervals of approximately 1 hour if necessary. The trachea was orally intubated with a 14 gauge cannula (Abbocath-T, USA).

A gauge 4F polyethylene (PE) catheter (C-PMS-401J, Cook Critical Care, USA) was advanced through the right external jugular vein into the right atrium. A precurved guidewire supplied with the catheter was then advanced through this catheter into the right

ventricle until an endocardial electrogram was confirmed. The guidewire was used for inducing VF. The surgical procedure of the right external jugular vein was not conducted for the rats in the asphyxia group. Through the left femoral artery, a 23 gauge PE-50 catheter (Abbocath-T, USA) was advanced into the thoracic aorta. Another 23 gauge PE-50 catheter was also advanced through the left femoral vein into the inferior vena cava for infusion. Aortic pressure was measured with a pressure transducer (BD, Germany). Prior to insertion, the catheters were filled with physiological salt solution containing 5 IU/mL of heparin. A rectal thermometer continuously monitored rectal temperature and rectal temperature was maintained at 36.5 ± 0.5 °C with the use of an infrared thermolamp. Electrocardiogram lead II was also continuously monitored. All data were recorded in a six channel recorder (Windaq acquisition system, USA). The rats were mechanically ventilated with a rodent ventilator of our own design. Minute ventilation with a FiO_2 of 0.21 was maintained at a tidal volume of 0.65 mL/100 g body weight and a frequency of 100 breaths/min. Peak $P_{ET}CO_2$ measured with a side stream infrared CO_2 analyzer (CAPSTAR-100, CWE Inc, USA) was maintained between 30 and 40 mmHg. Baseline $P_{ET}CO_2$ (prior to cardiac arrest), $P_{ET}CO_2$ after 2 and 6 minutes of VF, and initial $P_{ET}CO_2$ immediately after PC were recorded.

Cardiac arrest model induced by VF

VF was induced with a 2–5 mA alternating current (60 Hz) delivered to the right ventricular endocardium through the guidewire. The current flow was continued for 3 minutes to prevent spontaneous reversion of VF to a supraventricular rhythm. Mechanical ventilation was discontinued after onset of VF. Six minutes after onset of VF, precordial compression (PC) was initiated with an electrically driven mechanical chest compressor developed in our laboratory. Coincident with the start of PC, mechanical ventilation was resumed. FiO_2 was increased to 1.0. Compression rate was maintained at a rate of 200/min and synchronized with a compression-ventilation ratio of 2:1 with an equal compression-relaxation duration. The depth of compression was adjusted to maintain a 1/3 decrease in the anterior-posterior chest diameter.^[14] Defibrillation was delivered with a 2J direct current at 6 minutes after compression for a maximum of three shocks. If ROSC was not observed, PC was resumed and maintained for 30 seconds before delivering a second set of up to three shocks. ROSC was defined as return of a supraventricular rhythm with MAP of about 60 mmHg lasting for at least 5 minutes.

Based on our prior study in which mean ROSC time (an interval from PC to ROSC) in the fibrillatory group was 447 seconds, so $P_{ET}CO_2$ after 1, 2, 3 and 6 minutes of PC was recorded before defibrillation. The rats regaining ROSC within 6 minutes were excluded in this study.

Cardiac arrest model induced by asphyxia

The prearrest and CPR protocols were similar to the fibrillatory cardiac arrest. However, instead of inducing VF, cardiac arrest was induced by clamping the endotracheal tube. Cardiac arrest was determined by loss of aortic pulsation, defined as MAP equal or less than 20 mmHg. PC and mechanical ventilation were initiated at 6 minutes after onset of cardiac arrest. Based on our prior study in which mean ROSC time in the asphyxial group was 144 seconds, so $P_{ET}CO_2$ after 1 and 2 minutes of PC was recorded. The rats regaining ROSC within 2 minutes were excluded in this study.

Statistical analysis

SPSS 13.0 software was used for statistical analysis. Continuous variables were presented as means $\pm$ standard deviation. Data between the two groups of each measurement time were compared by analysis of variance for repeated measures. Receiver operator characteristic (ROC) analysis for $P_{ET}CO_2$ was performed to determine its ability for predicting ROSC during CPR. The analysis identified threshold values for $P_{ET}CO_2$ in terms of predicting ROSC. The threshold values of the variable for predicting ROSC were defined as the values with the maximum area of sensitivity multiply specificity. Pearson's product-moment correlation coefficient was used for analysis of correlation of $P_{ET}CO_2$ and MAP during PC. A P value less than 0.05 was considered statistically significant.

RESULTS

The initial $P_{ET}CO_2$ immediately after PC was significantly lower in the fibrillatory group than in the asphyxial group (12.8 ± 4.87 mmHg vs. 49.2 ± 8.13 mmHg; $P=0.000$). There was no significant difference between the groups at baseline $P_{ET}CO_2$ and $P_{ET}CO_2$ after 1 and 2 minutes of PC (all $P>0.05$) (Figure 1).

In the VF group, $P_{ET}CO_2$ after 6 minutes of PC for the rats with ROSC was significantly higher than that for those without ROSC (16.5 ± 3.07 mmHg vs. 13.2 ± 2.62 mmHg; $P=0.004$). There was no significant difference among those with and without ROSC at baseline $P_{ET}CO_2$, $P_{ET}CO_2$ after 2 and 6 minutes of VF, initial

$P_{ET}CO_2$ immediately after PC, and $P_{ET}CO_2$ after 1, 2 and 3 minutes of PC (all $P>0.05$). Likewise, MAP after 6 minutes of PC for the rats with ROSC was significantly higher than that for those without ROSC (37.2 ± 4.87 mmHg vs. 27.6 ± 6.67 mmHg; $P=0.000$). There was no significant difference among those with and without ROSC at baseline MAP, MAP after 2 and 6 minutes of VF, initial MAP immediately after PC and MAP after 1, 2 and 3 minutes of PC (all $P>0.05$) (Figures 2 and 3).

Figure 1. Partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) during PC in VF and asphyxial cardiac arrests.

Figure 2. Partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) before and after VF cardiac arrest. PC: precordial compression; ROSC: return of spontaneous circulation.

Figure 3. MAP before and after VF cardiac arrest. PC: precordial compression; ROSC: return of spontaneous circulation.

Figure 4. Partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) before and after asphyxial cardiac arrest. PC: precordial compression; ROSC: return of spontaneous circulation.

Figure 5. MAP before and after asphyxial cardiac arrest. PC: precordial compression; ROSC: return of spontaneous circulation.

$P_{ET}CO_2$ in VFCA	Area under curve	95% confidence interval	<i>P</i> -value
$P_{ET}CO_2 \geq 13.2$ mmHg in VFCA	0.824	0.668–0.980	0.003
	Sensitivity (%)	Specificity (%)	
	91.7	66.7

$P_{ET}CO_2$ in ACA	Area under curve	95% confidence interval	<i>P</i> -value
$P_{ET}CO_2 \geq 17.1$ mmHg in ACA	0.982	0.944–1.021	0.003
	Sensitivity (%)	Specificity (%)	
	93.8	100	

Figure 6. ROC curves for partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) in terms of predicting ROSC when measured at 6 minutes after precordial compression for VFCA rats (A) or at 2 minutes after precordial compression for ACA rats (B). The sensitivities and specificities threshold values for predicting ROSC. ROSC: return of spontaneous circulation; VFCA: ventricular fibrillation cardiac arrest; ACA: asphyxial cardiac arrest.

In the asphyxial group, $P_{ET}CO_2$ after 2 minutes of PC for the rats with ROSC was significantly higher than that for those without ROSC (20.8 ± 3.24 mmHg vs. 13.9 ± 1.50 mmHg; $P=0.000$). There was no significant difference among those with and without ROSC at baseline $P_{ET}CO_2$, initial $P_{ET}CO_2$ immediately after PC and $P_{ET}CO_2$ after 1 minute of PC (all $P>0.05$). Likewise, MAP after 2 minutes of PC for the animals with ROSC was significantly higher than that for those without ROSC (35.2 ± 5.88 mmHg vs. 27.8 ± 3.67 mmHg; $P=0.000$). There was no significant difference among those with and without ROSC at baseline MAP, initial MAP immediately after PC and MAP after 1 minute of PC (all $P>0.05$) (Figure 4 and 5).

ROC analysis was performed and areas under the

ROC curves calculated for the $P_{ET}CO_2$ at 6 minutes after PC in VF cardiac arrest or at 2 minutes after PC in asphyxial cardiac arrest (Figure 6). Areas under the ROC curves were 0.824 for $P_{ET}CO_2$ in VF cardiac arrest and 0.982 for $P_{ET}CO_2$ in asphyxial cardiac arrest. The sensitivity and specificity for predicting ROSC at threshold value ≥ 13.2 mmHg in VF cardiac arrest was 91.7% and 66.7% of the $P_{ET}CO_2$, respectively. Also, the sensitivity and specificity for predicting ROSC at threshold value ≥ 17.1 mmHg in asphyxial cardiac arrest was 93.8 and 100% of the $P_{ET}CO_2$, respectively. During PC, $P_{ET}CO_2$ was positively correlated with MAP in spite of cardiac arrest induced by VF or asphyxia (fibrillatory arrest: $r=0.618$, $P=0.000$; asphyxial arrest: $r=0.832$, $P=0.000$).

DISCUSSION

In this study, our results are consistent with earlier evidence in clinical trial that initial $P_{ET}CO_2$ is significantly higher in asphyxial cardiac arrest than that in fibrillatory cardiac arrest.^[15] We further affirm the fact that initial $P_{ET}CO_2$ in cardiac arrest may be helpful in differentiating between the causes of cardiac arrest. During CPR in asphyxial cardiac arrest, $P_{ET}CO_2$ levels are initially high, then fast decrease to subnormal levels and promptly increase again to above-normal or near-normal levels after the onset of ROSC.^[8,9] The pattern of $P_{ET}CO_2$ changes in asphyxial arrest is different from that in fibrillatory arrest. After the onset of cardiac arrest induced by VF, $P_{ET}CO_2$ levels rapidly decrease to nearly zero and then begin to increase after providing effective CPR. Upon ROSC, $P_{ET}CO_2$ levels sharply increase again.^[15] During asphyxial arrest, pulmonary blood flow from several minutes of continued cardiac output continues for some period of time. The CO_2 produced in the tissues during the period will continue to be delivered to the lungs where it diffuses into the alveoli, thereby increasing alveolar CO_2 . At last, $P_{ET}CO_2$ levels rapidly increase once mechanical ventilation is resumed.^[8,9]

The clinical trials of Lah and Grmec in which initial $P_{ET}CO_2$ values in primary VF/VT cardiac arrest had a prognostic value for outcomes of ROSC contrasted with the present study.^[6,7] Our data demonstrated that initial $P_{ET}CO_2$ values in fibrillatory cardiac arrest could not predict the outcomes of ROSC; however, the prognostic value for ROSC was achieved after 6 minutes of CPR in fibrillatory arrest. This may be a result of high-quality CPR delivered to patients with ROSC in primary cardiac arrest, which caused higher initial $P_{ET}CO_2$ values. The extrapolation has been supported by the evidence that the measurement of $P_{ET}CO_2$ during CPR serves as a non-invasive monitor of the effective CPR.^[16-18] In asphyxial cardiac arrest, initial values of $P_{ET}CO_2$ do not have a prognostic value for outcomes of ROSC since initial values of $P_{ET}CO_2$ in asphyxial cardiac arrest generally reflect alveolar CO_2 prior to CPR. The pattern of MAP changes in fibrillatory cardiac arrest was consistent with that of $P_{ET}CO_2$ changes, indicating that there was no difference in the effectiveness of PC before 6 minutes of CPR. So there was no difference in initial $P_{ET}CO_2$ values for rats with and without ROSC in the fibrillatory group. The significant difference in $P_{ET}CO_2$ values for rats with and without ROSC was achieved at 6 minutes after CPR in the fibrillatory group. In asphyxial cardiac arrest, the significant difference in $P_{ET}CO_2$ and MAP values for rats with and without ROSC was achieved at 2 minutes after

CPR. Thereby, $P_{ET}CO_2$ values after 2 minutes of CPR had a prognostic value for ROSC outcomes in the asphyxial group.

ROC curves of $P_{ET}CO_2$ showed that threshold values for predicting ROSC in VF and asphyxial cardiac arrest were 13.2 and 17.1 mmHg, respectively. For rats in the group with fibrillatory cardiac arrest, a $P_{ET}CO_2$ exceeding 13.2 mmHg after 6 minutes of CPR meant a great success of ROSC. However, if it was less than 13.2 mmHg, the outcome was likely poor. So, a $P_{ET}CO_2$ less than 13.2 mmHg after 6 minutes of CPR indicated that more aggressive strategies such as high-quality chest compressions would be carried out. The information may be instructive in light of the evidence that high-quality chest compressions improve outcomes of resuscitation.^[19] For rats in the group with asphyxial cardiac arrest, if a $P_{ET}CO_2$ was more than 17.1 mmHg after 2 minutes of CPR, a good outcome would be predicted. Likewise, if it was less than 17.1 mmHg, the outcome would be also poor.

Under constant ventilation, $P_{ET}CO_2$ reflects cardiac output and pulmonary blood flow during CPR.^[20-22] A previous study^[23] showed that MAP was a determinant of perfusion during CPR. Positive correlations between $P_{ET}CO_2$, MAP, coronary perfusion pressure and cardiac output have been shown in several studies.^[11,21,24] In the two cardiac arrest models, $P_{ET}CO_2$ was also positively correlated with MAP during PC. It should be noted that baseline and post-ROSC values of $P_{ET}CO_2$ and MAP were not included when the relationship between $P_{ET}CO_2$ and MAP was analyzed in our experimental study.

Limitation of the present study includes the fact that coronary perfusion pressure is not analyzed. Coronary perfusion pressure is an important determinant of cardiac perfusion during CPR and $P_{ET}CO_2$ is significantly correlated with coronary perfusion pressure. Consequently, coronary perfusion pressure should be included in further studies. Another potential limitation is that healthy animals were used in our study. In fact, VF in cardiac arrest patients is mostly caused by ischemic heart disease, and asphyxial cardiac arrest is usually accompanied with intoxication and trauma. Therefore, the findings of this study should be interpreted with caution when applied into clinical practice.

In conclusion, initial $P_{ET}CO_2$ was significantly higher in asphyxial cardiac arrest than that in fibrillatory cardiac arrest in our study. In fibrillatory cardiac arrest, $P_{ET}CO_2$ values after 6 minutes of CPR could predict ROSC outcomes. In asphyxial cardiac arrest, $P_{ET}CO_2$ values after 2 minutes of CPR could predict ROSC outcomes. Initial $P_{ET}CO_2$ might be helpful in differentiating the causes of cardiac arrest.

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Ethical approval: The study was approved by the Animal Care and Use Committee of Sun Yat-sen University, Guangzhou, China.

Conflicts of interest: The authors declare that there is no conflict of interest.

Contributors: Lin QM proposed the study, analyzed the data and wrote the first draft. All authors contributed to the design and interpretation of the study and to further drafts.

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