Relationship Between Volumetric Capnography, Ventilation During Cardiopulmonary Resuscitation and Return of Spontaneous Circulation in an Experimental Model of Pediatric Asphyxial Cardiac Arrest

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Abstract

Purpose

To study the relationship between volumetric capnography (VCAP) and arterial CO$_2$ partial pressure (PCO$_2$) during cardiopulmonary resuscitation (CPR) and to analyze the ability of these parameters to predict the return of spontaneous circulation (ROSC) in a pediatric animal model of asphyxial cardiac arrest (CA).

Methods

Secondary analysis of a randomized study. Asphyxial CA was induced by muscle relaxation and extubation. CPR was started two minutes after CA occurred. Airway management was performed with early endotracheal intubation or bag-mask ventilation, according to randomization group. CPR was continued until ROSC or 24 minutes of resuscitation. End-tidal carbon dioxide (EtCO$_2$), CO$_2$ production (VCO$_2$), and EtCO$_2$/VCO$_2$/kg ratio were continuously recorded.

Results

Seventy-nine piglets were included, 26 (32.9%) of whom achieved ROSC. EtCO$_2$ was the best predictor of ROSC (AUC 0.72, p < 0.01 and optimal cutoff point of 21.6 mmHg). No statistical differences were obtained regarding VCO$_2$, VCO$_2$/kg and EtCO$_2$/VCO$_2$/kg ratios. VCO$_2$ and VCO$_2$/kg showed an inverse correlation with PCO$_2$, with higher a correlation coefficient as resuscitation progressed. EtCO$_2$ also had an inverse correlation with PCO$_2$ from minute 18 to 24 of resuscitation.

Conclusion

Our findings suggest that EtCO$_2$ is the best VCAP-derived parameter for predicting ROSC. EtCO$_2$ and VCO$_2$ showed an inverse correlation with PCO$_2$. Therefore, these parameters are not adequate to measure ventilation during CPR.

Introduction

Capnography is a useful monitoring technique in cardiopulmonary resuscitation (CPR) [1]. It has multiple applications that include verifying adequate endotracheal tube position and assessing quality of chest compressions in adult CPR [2, 3]. Moreover, some studies in adults suggest an association between capnographic values and return of spontaneous circulation (ROSC) [4].
Regarding pediatric CPR, there is insufficient evidence supporting the use of end-tidal carbon dioxide (EtCO₂) as a marker of quality or as a prognostic marker during CPR. Therefore, the European Resuscitation Council guidelines [5] advocate its use to monitor ETT position and state that it can help to rapidly detect ROSC, but do not recommend it as a marker of CPR quality, while the American Heart Association Guidelines [6] state that EtCO₂ monitoring may be considered to assess the quality of chest compressions [7].

Time-based capnography, widely accessible, provides valuable information such as end-tidal carbon dioxide (EtCO₂) values and capnography wave analysis. Other techniques as volumetric capnography (VCAP) offer a representation of CO₂ production, transport and elimination, that could be useful during CPR, although they might not be always available in a CPR setting [8]. However, there are no published studies regarding the relationship between VCAP-derived parameters and real ventilation status (based on PCO₂) or in pediatric animal models of cardiac arrest (CA).

We conducted a secondary analysis of a previously published experimental study using a pediatric animal model of asphyxial cardiac arrest [9], to analyze the relationship between VCAP-derived parameters and arterial blood CO₂ partial pressure (PCO₂) and their ability to predict ROSC.

Methods

This study is a secondary analysis of the data obtained in a randomized prospective experimental study, performed in the Experimental Medicine and Surgery Department of a third level hospital in Madrid, Spain [9]. The experimental protocol was approved by the Local Ethics Committee in Animal Research and authorized by the Autonomous Community of Madrid (reference number PROEX 096/19). The study was developed in compliance with the ARRIVE guidelines, and all methods were carried out in accordance with guidelines and regulations. The study protocol has already been thoroughly described in a previously published article [9].

Seventy-nine 3-month-old miniature pigs, weighing 9–12 kg, were included. Respiratory parameters were continuously monitored using a sensor placed at the Y piece and connected to a Respironics NM3 monitor (Philips Healthcare, Markham, ON, Canada). Chest compressions were performed guiding depth and rate with a defibrillator monitor (Zoll Z series).

After instrumentation, sedation and an initial stabilization period, an asphyxial CA was induced by extubating animals after administering an intravenous dose of atracurium. Advanced CPR was started two minutes after diagnosing CA. Early intubation or bag-mask ventilation was performed throughout CPR according to randomized resuscitation group [9]. Resuscitation was continued until ROSC or up to a maximum of 24 minutes.

Clinical and monitoring parameters were collected at baseline, 5 minutes after extubation, before the start of CPR and every 3 minutes during resuscitation. Arterial blood gases were withdrawn at baseline and
after every three minutes of CPR. Each ventilation was recorded, and respiratory parameters were registered at baseline and every 3 minutes during CPR.

Results

Seventy-nine piglets weighting $11.3 \pm 1.2$ kg were included in the study, with a ROSC rate of 32.9% (26 animals).

A Receiver Operator Characteristic (ROC) curve that included EtCO$_2$, VCO$_2$, VCO$_2$/kg and ratio EtCO$_2$/VCO$_2$/kg was performed, showing that EtCO$_2$ at three minutes of resuscitation was the only predictor of ROSC, with an AUC of 0.71 (Table 1, Fig. 1). The optimal cut-off point for predicting ROSC was an EtCO$_2$ value of 21.58 mmHg, with a sensitivity of 56% and a specificity of 89%. Sensitivity, specificity and Youden’s index for predicting ROSC of EtCO$_2$ values of 10, 15, 20 and 25 mmHg are shown in Table 2.

Animals that achieved ROSC had higher median EtCO$_2$ levels (30.1 vs 11.9 mmHg) than those who did not, regardless of airway management (intubation or bag-mask ventilation) after applying a linear multiple regression model ($p < 0.01$).
Linear correlation was performed to study the relationship between PCO$_2$ and EtCO$_2$, VCO$_2$, VCO$_2$/kg and ratio EtCO$_2$/VCO$_2$/kg (Table 3). A negative correlation was found between EtCO$_2$ and PCO$_2$ from resuscitation minutes 18 to 24. VCO$_2$ and VCO$_2$/kg had a statistically significant negative correlation with PCO$_2$ during resuscitation, with more negative correlation as resuscitation time increased. Regarding EtCO$_2$/VCO$_2$/kg ratio, it was only significantly correlated with PCO$_2$ at resuscitation minute 3.

### Table 3
Pearson’s correlation between VCAP-derived parameters and partial arterial CO$_2$ (PCO$_2$) in different time points of resuscitation.

<table>
<thead>
<tr>
<th>PCO$_2$</th>
<th>EtCO$_2$</th>
<th>VCO$_2$</th>
<th>VCO$_2$/kg</th>
<th>EtCO$_2$/ VCO$_2$/ kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCO$_2$</td>
<td>r -0.17</td>
<td>-0.37</td>
<td>-0.37</td>
<td>0.43</td>
</tr>
<tr>
<td>3’ CPR</td>
<td>p 0.15</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PCO$_2$</td>
<td>r 0.21</td>
<td>-0.29</td>
<td>-0.30</td>
<td>0.16</td>
</tr>
<tr>
<td>6’ CPR</td>
<td>p 0.15</td>
<td>0.04</td>
<td>0.03</td>
<td>0.27</td>
</tr>
<tr>
<td>PCO$_2$</td>
<td>r -0.15</td>
<td>-0.27</td>
<td>-0.29</td>
<td>0.06</td>
</tr>
<tr>
<td>9’ CPR</td>
<td>p 0.31</td>
<td>0.05</td>
<td>0.04</td>
<td>0.70</td>
</tr>
<tr>
<td>PCO$_2$</td>
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<td>-0.58</td>
<td>-0.58</td>
<td>0.15</td>
</tr>
<tr>
<td>12’ CPR</td>
<td>p 0.09</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.32</td>
</tr>
<tr>
<td>PCO$_2$</td>
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<td>-0.61</td>
<td>0.07</td>
</tr>
<tr>
<td>18’ CPR</td>
<td>p &lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.64</td>
</tr>
<tr>
<td>PCO$_2$</td>
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<td>-0.55</td>
<td>-0.55</td>
<td>0.03</td>
</tr>
<tr>
<td>21’ CPR</td>
<td>p &lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.86</td>
</tr>
<tr>
<td>PCO$_2$</td>
<td>r -0.46</td>
<td>-0.66</td>
<td>-0.65</td>
<td>0.20</td>
</tr>
<tr>
<td>24’ CPR</td>
<td>p &lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.18</td>
</tr>
</tbody>
</table>

### Discussion

This study is, as far as we know, the first experimental animal study that analyses the relationship between VCAP-derived parameters, survival, and ventilation status during pediatric cardiopulmonary resuscitation. Our results show that EtCO$_2$ is the best capnometric parameter to predict ROSC, which has already been demonstrated in previous publications [4, 10–15]. We found that animals that achieved ROSC had higher
median EtCO\(_2\) levels than non-survivors and we obtained an optimal EtCO\(_2\) cutoff point of 21.58 mmHg to predict ROSC.

A large cohort study that analyzed data of 143 pediatric cardiac arrest events [15] reported a significant difference in median EtCO\(_2\) between events that achieved ROSC and those that did not. However, when data were stratified based on patient age, this relationship was only significant in adolescents, without differences in EtCO\(_2\) levels in children and infants that achieved ROSC and those who didn't survive.

Several authors have analyzed EtCO\(_2\) cutoff points for predicting ROSC: Sorcher et al [15] used a cutoff point of 20 mmHg. Chalak et al [11] established an EtCO\(_2\) cutoff point of 14 mmHg in an experimental model of neonatal asphyxial CA, while Stine et al [12] reviewed CA episodes in patients less than 6 months hospitalized in an intensive care unit, setting an EtCO\(_2\) cutoff point of 17–18 mmHg. Both studies defined ROSC as the achievement of a heart rate higher than 60 beats per minute. Another study of intrahospitalary CA in adults set an EtCO\(_2\) cutoff point of 25.5 mmHg for predicting sustained ROSC [13].

Given these differences between studies and the number of influencing factors (hyperventilation, drug administration...) [1], it is specially challenging to establish an absolute EtCO\(_2\) cutoff point for predicting ROSC. Therefore, a case-control study of adult out-of-hospital CA suggested that CO\(_2\) trends were more useful to predict ROSC, as survivors had more positive trends than non-survivors [16].

Some authors suggested that VCO\(_2\) and VCO\(_2\)/kg were also good predictors of ROSC [14, 17, 18], although these parameters did not demonstrate utility for this purpose in our study. Most of these studies induced a ventricular-fibrillation cardiac arrest. Nevertheless, cardiac arrest of sudden cardiac origin (such as ventricular fibrillation) is not associated with high CO\(_2\) levels at the beginning of CPR, as in CA of respiratory origin [19–21]. This fact could explain the different performance of VCO\(_2\) and VCO\(_2\)/kg in our study. However, another experimental study of asphyxial cardiac arrest in neonatal piglets found that both EtCO\(_2\) and VCO\(_2\) during CPR were higher in survivors [22].

Regarding the relationship between EtCO\(_2\) and PCO\(_2\), we found an inverse correlation from minute 18 to minute 24 of CPR. It would be expected that changes in PCO\(_2\) would be associated with parallel changes in EtCO\(_2\). Nevertheless, EtCO\(_2\) is greatly affected by pulmonary blood flow (as with decreased cardiac output), which can explain the negative correlation.

These findings were consistent with a previous study showing a progressive increase of PCO\(_2\) and decrease of EtCO\(_2\) throughout CPR [23]. Another study in out of hospital CA in adult patients, however, showed moderate correlation between EtCO\(_2\) and PCO\(_2\) during reanimation. Nevertheless, blood samples in that study were obtained at any point of CPR when an arterial line was obtained, regardless of the duration of CA or resuscitation [24].
Zhang et al found that EtCO\(_2\) was a useful parameter to predict ROSC, and that VCO\(_2\)/kg ratio had similar capacity to predict ROSC in an experimental porcine cardiac arrest model [17]. This group also analyzed the relationship between EtCO\(_2\)/VCO\(_2\)/kg and ventilation during CPR in an experimental study with adult pigs, finding that this ratio showed good performance in discriminating hyperventilation from non-hyperventilation [10].

Regarding VCO\(_2\) and VCO\(_2\)/kg, our results show an inverse correlation of both parameters with PCO\(_2\), which became more significant as resuscitation progressed in time. VCO\(_2\) values are determined by tidal volume and EtCO\(_2\). Therefore, if tidal volume remains stable, VCO\(_2\) will be affected by the same factors that affect EtCO\(_2\): the decrease of cardiac output and pulmonary perfusion during CPR modifies ventilation/perfusion ratio, reducing expired CO\(_2\) fraction, and consequently, VCO\(_2\).

As for EtCO\(_2\)/VCO\(_2\)/kg ratio, we only found correlation with PCO\(_2\) at minute 3 of resuscitation. Zhang et al [17] reported that this parameter was a good predictor of hyperventilation, although PCO\(_2\) was not measured during resuscitation.

VCO\(_2\) measurement requires the use of a specific volumetric capnograph. Such capnographs are not widely available and, according to our results, this parameter doesn’t accurately reflect ventilation during CPR. In the light of these findings, VCAP parameters don’t seem to offer any additional benefits than regular capnography during CPR. However, these findings should be validated with specific pediatric clinical studies.

Our study has several limitations. Although we used a validated pediatric animal model for this purpose, the results from animal experiments cannot be directly extrapolated to children. Besides, the variability of VCAP measurement when using an endotracheal tube or a face mask could interfere with the results.

**Conclusions**

In an experimental model of pediatric asphyxial cardiac arrest, EtCO\(_2\) was the only VCAP-derived parameter for predicting ROSC. VCO\(_2\) and VCO\(_2\)/kg and EtCO\(_2\) had an inverse correlation with PCO\(_2\) during CPR. Therefore, they are not suitable for assessing PCO\(_2\) during resuscitation. These findings highlight the importance of measuring arterial CO\(_2\) partial pressure during CPR.

**Declarations**

**AUTHOR CONTRIBUTIONS**

and all authors contributed substantially to its revision. S.M.N, G.M. and J.L.H. take responsibility for the paper as a whole.

**DATA AVAILABILITY STATEMENT**

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

**ADDITIONAL INFORMATION**

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**Competing interests:** The authors declare no competing interests.

**References**


Figures

Figure 1

ROC curve showing performance of VCAP-derived parameters in predicting ROSC. EtCO₂: end-tidal carbon dioxide, VCO₂: CO₂ production.