Experimental paper

End-tidal CO₂-guided automated robot CPR system in the pig. Preliminary communication☆

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A R T I C L E   I N F O
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A B S T R A C T

Background: Our aim was to compare the efficacy of the end-tidal CO₂-guided automated robot CPR (robot CPR) system with manual CPR and mechanical device CPR.

Methods: We developed the algorithm of the robot CPR system which automatically finds the optimal compression position under the guidance of end-tidal CO₂ feedback in swine models of cardiac arrest. Then, 18 pigs after 11 min of cardiac arrest were randomly assigned to one of three groups, robot CPR, LUCAS CPR, and manual CPR groups (n = 6 each group). Return of spontaneous circulation (ROSC) and Neurological Deficit Score 48 h after ROSC were compared.

Results: A ROSC was achieved in 5 pigs, 4 pigs, and 3 pigs in the robot CPR, LUCAS CPR, and manual CPR groups, respectively (p = 0.47). Robot CPR showed a significant difference in Neurological Deficit Score 48 h after ROSC compared to manual CPR, whereas LUCAS CPR showed no significant difference over manual CPR. (p = 0.01; Robot versus Manual adjusted p = 0.04, Robot versus LUCAS adjusted p = 0.07, Manual versus LUCAS adjusted p = 1.00).

Conclusions: The end-tidal CO₂-guided automated robot CPR system did not significantly improve ROSC rate in a swine model of cardiac arrest. However, robot CPR showed significant improvement of Neurological Deficit Score 48 h after ROSC compared to Manual CPR while LUCAS CPR showed no significant improvement compared to Manual CPR.

1 Introduction

Despite the latest advances in resuscitation care, the survival rates among cardiac arrest victims remain low [1]. Since Kouwenhoven and colleagues introduced the concept of closed chest cardiac massage for cardiac arrest victims in 1957 [2], cardiopulmonary resuscitation (CPR) became the standard of care. Manual chest compression is a key component of CPR. Its goal is to provide oxygen-rich blood to the brain and coronary artery. Current guidelines recommend that rescuers should compress over the lower half of the sternum with a rate of at least 100 compressions/min and with a depth of at least 2 inches/5 cm [3]. High-quality manual CPR requires extreme power consumption and easily leads to physical exhaustion of rescuers. To overcome these problems in manual CPR, several mechanical CPR devices such as the Autopulse (Zoll Medical Co., MA, USA) and LUCAS (Physio-Control Inc., WA, USA) were introduced to provide an uninterrupted CPR without rescuer’s fatigue [4,5]. However, these devices are bound to the chest and compress on only one fixed position, so they must be unbound when there is a need to change the compression position. This unbinding can cause the interruption of chest compression, which decreases CPR quality. There is also insufficient evidence to support the routine use of these mechanical compression devices for cardiac arrest victims according to the current guidelines [6–8].

A robot CPR system could be a good alternative to overcome the
shortcomings of manual CPR and mechanical CPR devices. A robot has enough power to achieve high-quality CPR. It can also give a continuous CPR and change its compression position during CPR without stopping.

In 1985, Weil et al reported that end-tidal CO₂ reflected cardiac output and pulmonary blood flow during CPR in a porcine model of cardiac arrest [9]. After that, several researchers demonstrated that in both animals and human beings, the measurement of end-tidal CO₂ could be used to guide CPR. For example, Weil et al [9] showed that end-tidal CO₂ could reflect cardiac output and pulmonary blood flow during CPR in a porcine model of cardiac arrest.

Table 1: Baseline characteristics end-tidal CO₂-guided robot CPR, LUCAS CPR and manual CPR. Data are presented as median (IQR). All comparisons were conducted using Kruskal-Wallis test. *SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial blood pressure; HR: heart rate; BT: body temperature; ETCO₂: end-tidal CO₂; CVP: central venous pressure.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Robot CPR (N = 6)</th>
<th>Manual CPR (N = 6)</th>
<th>LUCAS CPR (N = 6)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>109.0 (96.0–121.0)</td>
<td>90.5 (84.0–111.0)</td>
<td>91.0 (89.0–119.0)</td>
<td>0.190</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>77.0 (58.0–81.0)</td>
<td>57.0 (53.0–79.0)</td>
<td>63.5 (56.0–70.0)</td>
<td>0.638</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>93.5 (76.0–102.0)</td>
<td>68.0 (66.0–94.0)</td>
<td>73.5 (68.0–97.0)</td>
<td>0.203</td>
</tr>
<tr>
<td>HR (/min)</td>
<td>111.5 (96.0–121.0)</td>
<td>94.0 (90.0–118.0)</td>
<td>113.0 (91.0–132.0)</td>
<td>0.326</td>
</tr>
<tr>
<td>BT (°C)</td>
<td>36.8 (36.5–37.1)</td>
<td>37.5 (37.2–37.9)</td>
<td>38.0 (37.2–38.1)</td>
<td>0.115</td>
</tr>
<tr>
<td>ETCO₂ (mmHg)</td>
<td>42.0 (41.0–47.0)</td>
<td>38.0 (37.0–39.0)</td>
<td>40.0 (38.0–41.0)</td>
<td>0.204</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>5.0 (3.0–10.0)</td>
<td>7.5 (3.0–10.0)</td>
<td>8.0 (4.0–15.0)</td>
<td>0.673</td>
</tr>
<tr>
<td>pH</td>
<td>7.5 (7.5–7.6)</td>
<td>7.6 (7.6–7.6)</td>
<td>7.6 (7.6–7.6)</td>
<td>0.098</td>
</tr>
<tr>
<td>pCO₂ (mmHg)</td>
<td>36.0 (34.8–38.0)</td>
<td>37.9 (35.1–39.0)</td>
<td>39.7 (37.3–41.7)</td>
<td>0.441</td>
</tr>
<tr>
<td>pO₂ (mmHg)</td>
<td>156.4 (126.3–178.5)</td>
<td>185.1 (136.6–208.5)</td>
<td>136.3 (135.5–204.7)</td>
<td>0.645</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>25.0 (22.0–26.0)</td>
<td>27.5 (27.0–29.0)</td>
<td>25.0 (25.0–27.0)</td>
<td>0.085</td>
</tr>
<tr>
<td>[Na⁺] (mmol/L)</td>
<td>137.2 (135.0–140.9)</td>
<td>133.4 (122.8–138.0)</td>
<td>136.6 (136.6–137.1)</td>
<td>0.401</td>
</tr>
<tr>
<td>[K⁺] (mmol/L)</td>
<td>3.3 (2.9–3.3)</td>
<td>3.4 (3.3–3.6)</td>
<td>3.3 (3.0–3.4)</td>
<td>0.554</td>
</tr>
<tr>
<td>[Ca++] (mg/dL)</td>
<td>0.9 (0.7–1.1)</td>
<td>1.0 (0.9–1.0)</td>
<td>0.9 (0.9–1.0)</td>
<td>0.713</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>89.0 (86.0–94.0)</td>
<td>105.0 (84.0–121.0)</td>
<td>93.0 (88.0–98.0)</td>
<td>0.579</td>
</tr>
<tr>
<td>HCO₃⁻ (mmol/L)</td>
<td>31.5 (29.7–32.7)</td>
<td>36.0 (34.4–41.8)</td>
<td>38.7 (35.8–41.5)</td>
<td>0.071</td>
</tr>
</tbody>
</table>

In 1985, Weil et al reported that end-tidal CO₂ reflected cardiac output and pulmonary blood flow during CPR in a porcine model of cardiac arrest [9]. After that, several researchers demonstrated that in both animals and human beings, the measurement of end-tidal CO₂...
Table 2
Selection of the final optimal compression position to show Peak end-tidal CO₂ level according to the algorithm of end-tidal CO₂-guided robot CPR. \(^\dagger\)The highest end-tidal CO₂ level between the vertical three compression positions. \(\dagger\)The highest end-tidal CO₂ level between the horizontal three compression positions, which is the final optimal compression position. \(\dagger\) Robot CPR did not achieve ROSC.

<table>
<thead>
<tr>
<th>Position</th>
<th>No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Left (No.)</th>
<th>Center (No.)</th>
<th>Right (No.)</th>
<th>Selected position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robot CPR</td>
<td>#1</td>
<td>28.5</td>
<td>25.6</td>
<td>31.5</td>
<td>38.2</td>
<td>32.2</td>
<td>32.1</td>
<td>8</td>
</tr>
<tr>
<td>Robot CPR</td>
<td>#2</td>
<td>25.2</td>
<td>26.0</td>
<td>28.2</td>
<td>31.5</td>
<td>28.2</td>
<td>30.8</td>
<td>8</td>
</tr>
<tr>
<td>Robot CPR</td>
<td>#3</td>
<td>21.4</td>
<td>21.3</td>
<td>20.5</td>
<td>20.8</td>
<td>21.1</td>
<td>20.9</td>
<td>1</td>
</tr>
<tr>
<td>Robot CPR</td>
<td>#4</td>
<td>25.5</td>
<td>24.1</td>
<td>24.4</td>
<td>33.0</td>
<td>35.0</td>
<td>31.5</td>
<td>1</td>
</tr>
<tr>
<td>Robot CPR</td>
<td>#5</td>
<td>28.0</td>
<td>28.9</td>
<td>27.7</td>
<td>27.7</td>
<td>29.5</td>
<td>29.4</td>
<td>2</td>
</tr>
<tr>
<td>Robot CPR</td>
<td>#6</td>
<td>28.0</td>
<td>28.9</td>
<td>27.7</td>
<td>27.7</td>
<td>29.5</td>
<td>29.4</td>
<td>2</td>
</tr>
</tbody>
</table>

2.2 Swine model of cardiac arrest

In our previous experimental study, we developed a swine model of cardiac arrest [17]. In brief, the experiments were carried out on male domestic pigs (body weight, 32–39 kg). All of the experiments conducted were approved by the Institutional Animal Care and Use Committee. After the induction of anaesthesia with intramuscular Zoletil (zolazepam and tiletamine, 5 mg/kg; Virbac AH, Fort Worth, TX), the animals were intubated with a 6.5 F endotracheal tube and mechanically ventilated using a GE Datex-Oxmeda S/5 Aspire Anaesthesia Machine (GE Healthcare, Buckinghamshire, UK). Initially, a tidal volume of 10 mL/kg and a frequency of 15/min was applied and adjusted to keep the end-tidal CO₂ level within 35–40 mm Hg. Lactated Ringer’s solution was infused at a rate of 4 mL/kg/hr through an ear vein. The right common carotid artery and internal jugular vein were exposed and sheath introducers (8.5 F; Arrow International, Cleveland, OH) were inserted into the artery and vein. A pulmonary artery catheter (7.5 F; Arrow International) was placed in the pulmonary artery through the internal jugular vein sheath introducer. After animals were stabilised for 15 min, a pacing catheter was inserted through the internal jugular vein sheath introducer and positioned in the right ventricular wall to induce ventricular fibrillation (VF). The VF was induced by delivering 9 v of direct current for 5 s. Cardiac arrest was confirmed by a VF waveform on the ECG and less than 15 mmHg of mean arterial pressure. After 11 min of no-flow time, CPR was started (5 cm of depth, 100/min) with artificial ventilation (30:2 of compression-ventilation ratio), and an IV injection of adrenaline (epinephrine, 1 mg). Five minutes after starting CPR, transthoracic defibrillation (biphasic, 150 J) was performed using a Zoll R Series Defibrillator (Zoll Medical, Chelmsford, MA), and ROSC was defined as maintenance of a systolic arterial blood pressure of at least 60 mmHg for at least 10 consecutive minutes [18].

2.3 Comparison of end-tidal CO₂-guided robot CPR with LUCAS CPR and manual CPR

To compare the efficacy of end-tidal CO₂-guided robot CPR (robot CPR) with LUCAS CPR and manual CPR, 18 pigs were randomly assigned to one of three groups: robot CPR (n = 6), LUCAS CPR (n = 6), and manual CPR (n = 6). After 11 min of no-flow time, CPR was started using robot CPR, LUCAS CPR, and manual CPR, respectively. Manual CPR was guided by Zoll OneStep™ Resuscitation Electrodes (ZOLL Medical, Chelmsford, MA) (Supplementary Data 2–Table 1). When ROSC was achieved, therapeutic hypothermia was induced by a cold saline infusion (4 °C, 20 mL/kg within 30 min) and a Blanketrol II (CSZ, Cincinnati, OH), and a rectal temperature of 33 °C ± 0.5 °C was maintained for 8 h. The animals were then slowly rewarmed over a 16-h period (rewarming rate < 0.25 °C/hour). After rewarming, the animals were maintained at 37 °C ± 0.5 °C until the end of the experiment (48 h post-ROSC). When ROSC was not achieved despite 9 min of CPR, the animal was terminated. After the completion of therapeutic hypothermia, animals were weaned from ventilator support, and returned to their cages. The mean arterial blood pressure and end-tidal CO₂ levels were continuously recorded 36 times per a second and their mean values from the start of CPR to ROSC were calculated for the subsequent analysis. In robot CPR, end-tidal CO₂ levels in each position were measured for 40 s in the same way, and their mean value was expressed as end-tidal CO₂ level in each position. The ROSC rate and time to ROSC, which was defined as a time from the onset of CPR to ROSC, were also measured. A Kaplan-Meier survival analysis for ROSC was conducted. Neurological evaluation using the Neurological Deficit Score (NDS) [19] was performed 48 h after ROSC by an emergency physician who was unaware of the study design.

2.4 Statistical analysis

Categorical data were presented as the percent frequency of
occurrence and were analyzed by the Chi-square test. Continuous data were presented as the medians with interquartile ranges and were analyzed by the Kruskal-Wallis test and Mann-Whitney post hoc test with Bonferroni correction. A Kaplan-Meier analysis with the log-rank test was performed to compare the ROSC rate and survival rate 48 h after ROSC between the groups. *P* values of less than 0.05 were considered to be statistically significant. Statistical analysis was performed using STATA version 13.1 for Windows (Stata Corp, College Station, Tex).

Fig. 2. Selection of the final optimal compression position according to the algorithm of the end-tidal CO₂-guided robot CPR system.

Six samples of robot CPR data are shown (A, B, C, D, E, F). In Fig. 2A, position 3 was selected between the vertical positions 1, 2, and 3. Then the robot moves to position 8. The robot CPR system repeats the data collection and analysis through position 8, 3, and 9, horizontally and sequentially. Finally, the robot CPR system selects the position 8 as the best compression position between the 3 horizontal positions by comparing 3 end-tidal CO₂ levels. This is the optimal compression position among the 9 positions. In Fig. 2B, C, D, E, and F, the optimal compression positions were selected in the same way.

*In Fig. 2C, the position 1 was chosen as the optimal compression position. However, ROSC was not achieved because end-tidal CO₂ level (21.1 mmHg) was too low.*
CPR

3.1 Comparison of ETCO2 guided robot CPR with LUCAS CPR and manual CPR

Prior to the induction of cardiac arrest, baseline characteristics of mean arterial pressure, end-tidal CO2 level, heart rate, rectal body temperature and other laboratory data were not significantly different (Table 1). Data for the selection of the final optimal compression position according to the algorithm of the robot CPR system are shown in Table 2 and Fig. 2. Mean end-tidal CO2 level and arterial blood pressure from the start of CPR to 4 min afterwards and from 4 min after starting CPR to ROSC showed no significant difference (Table 3). A ROSC occurred in 5 of 6 pigs in robot CPR, 4 in LUCAS CPR, and 3 in manual CPR, respectively. The ROSC rate was not significantly different (robot CPR 83.3% vs LUCAS CPR 66.7% vs manual CPR 50.0%, p = 0.47). The time to ROSC also showed no significant difference between the 3 CPR groups: robot CPR 7.0 min (7.0–8.0) vs LUCAS CPR 8.0 min (6.0–9.0) vs manual CPR 8.0 min (7.5–8.5), p = 0.52. The Kaplan-Meier survival analysis for ROSC (Fig. 3A) and 48 h after ROSC showed no significant difference (log-rank test p = 0.38 and p = 0.09, respectively). During the 24 h after therapeutic hypothermia, 2 status epilepticus occurred in the LUCAS CPR and manual CPR groups, respectively. These animals were humanely killed according to the guidelines of the Institutional Animal Care and Use Committee, and their NDS were calculated as 400. Animals that underwent robot CPR showed a significant difference in NDS 48 h after ROSC compared to manual CPR, whereas animals that underwent LUCAS CPR showed no significant difference over manual CPR. (Kruskal-Wallis test p = 0.01; robot CPR vs manual CPR adjusted p = 0.04, robot CPR vs LUCAS CPR adjusted p = 0.07, manual CPR vs LUCAS CPR adjusted p = 1.00) (Fig. 3B).

4 Discussion

The robot CPR system, to our knowledge, is the first robot CPR device which has an algorithm to find the optimal compression position through real-time end-tidal CO2 feedback. In our study, the use of robot CPR showed a significant difference in NDS 48 h after ROSC compared to manual CPR, whereas LUCAS CPR showed no significant difference over manual CPR. In addition, robot CPR showed 83.3% of ROSC rate, which was slightly higher, but not significantly different compared to those of LUCAS CPR (66.7%) and manual CPR (50.0%). These results suggest that the optimal compression position according to the algorithm of robot CPR could lead to high-quality CPR, which resulted in slightly increased ROSC rate and significantly improved neurological outcomes compared to Manual CPR.

Robot CPR using the optimal compression position showed the highest end-tidal CO2 level. Until now, there were no data to show the correlation between the chest compression position and end-tidal CO2 level. Our study shows that there is a difference in end-tidal CO2 value, even between 2 positions that are only about 3 cm apart. Because end-tidal CO2 value is a good indicator for high-quality CPR and the detection of ROSC [14,15,20], this may indicate that a small change of the hand position on the chest which frequently occurs in an actual CPR situation can affect CPR quality and ROSC. A higher end-tidal CO2 value is also reported to be correlated with deeper chest compression [14]. Effective chest compression is a key component of high-quality CPR. Therefore, the robot CPR algorithm to find the optimal compression position with consistent depth may be an effective alternative to manual CPR.

In this study, robot CPR showed slightly decreased, but no significant differences of arterial blood pressure and end-tidal CO2 compared with those of LUCAS CPR or manual CPR. In the robot CPR system, the robot moves to 6 different positions to find the optimal position. When robot CPR was performed on the optimal compression position, the peak end-tidal CO2 level exceeded 30 mmHg while most of the other compression positions showed values around 20 mmHg, which could have contributed to the decreased mean end-tidal CO2 level. In contrast, because manual CPR or LUCAS CPR have compression at only 1 fixed position, the end-tidal CO2 level was relatively less affected. Decreased arterial blood pressure can be also explained in the same way.

Our study has several limitations. First, the number of animals to assign to each CPR group was too small to show the statistical significance of the end-tidal CO2-guided robot CPR. Second, since the robot CPR system uses 6 degrees of freedom, it can freely change...
compression rate and depth as well as compression position. In this study, however, we evaluated the performance of robot CPR according to the compression position only. The development of an algorithm including compression depth, rate and position is very complex and challenging. In the near future, the algorithm to combine depth, rate, and position as well as data for patient's body type using artificial intelligence will improve the performance of robot CPR. Lastly, this was a porcine study and the human thorax is widely different from the pig's. Because there are anatomical and physiological differences between the pig and human, much more data and assessment of the safety and efficacy of robot CPR are needed prior to clinical application.

5 Conclusion

We first developed the end-tidal CO₂-guided automated robot CPR system which has an algorithm to find the optimal compression position through real-time end-tidal CO₂ feedback. Robot CPR did not significantly improve the ROSC rate in a swine model of cardiac arrest. However, robot CPR showed significant improvement of Neurological Deficit Score 48 h after ROSC compared to Manual CPR while LUCAS CPR showed no significant improvement compared to Manual CPR. The robot CPR system could be a promising alternative to manual CPR. Further study be needed to show the efficacy of the robot CPR system.

Conflict of interest

None.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.resuscitation.2018.04.011.

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