Head and thorax elevation prevents the rise of intracranial pressure during extracorporeal resuscitation in swine

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Abstract

Aim: Head and thorax elevation during cardio-pulmonary resuscitation improves cerebral hemodynamics and ultimate neurological outcome after cardiac arrest. Its effect during extracorporeal cardiopulmonary resuscitation (E-CPR) is unknown. We tested whether this procedure could improve hemodynamics in swine treated by E-CPR.

Methods and Results: Pigs were anaesthetized and submitted to 15 min of untreated ventricular fibrillation followed by E-CPR. Animals randomly remained in flat position (flat group) or underwent head and thorax elevation since E-CPR institution (head-up group). Electric shocks were delivered after 30 min until return of spontaneous circulation (ROSC). They were followed during 120-min after ROSC. After 30 min of E-CPR, ROSC was achieved in all animals, with no difference regarding blood pressure, heart rate and extra-corporeal membrane of oxygenation flow among groups. The head-up group had an attenuated increase in ICP as compared to the flat group following cardiac arrest (13±1 vs 26±2 mmHg at the end of the follow-up, respectively). Cerebral perfusion pressure tended to be higher in the head-up vs flat group despite not achieving statistical difference (66±1 vs 46±1 mmHg at the end of the follow-up). Carotid blood flow and cerebral oxygen saturation were not significantly different among groups.

Conclusions: During E-CPR, head and thorax elevation prevents ICP increase. Whether it could improve the ultimate neurological outcome in this situation deserves further investigation.

Introduction

Extracorporeal cardiopulmonary resuscitation (E-CPR) is a promising strategy when conventional cardiopulmonary resuscitation (CPR) fails to provide return of spontaneous circulation (ROSC). However, despite enhancing ROSC rate, its long-term benefits are questioned regarding ultimate survival and neurological outcome (1, 2). In a recent review, only one in four patients achieved good neurologic outcome after E-CPR (3). Acute brain injury remains very common and, as well known after conventional CPR, involves an early impairment of cerebral perfusion pressure (CePP) and blood flow (4, 5), along with an intracranial pressure (ICP) increase. For instance, an ICP value above 15 mmHg had sensitivity/specificity of 68%/100 for discriminating outcome after cardiac arrest (6).

In order to improve patients outcome, head and thorax elevation, so-called head-up position, was shown to strongly reduce ICP while enhancing cerebral perfusion pressure in patients presenting severe traumatic brain injury (7, 8). Similar benefits were observed in animal models of cardiac arrest with conventional CPR (9–11). However, the effect of head and thorax elevation during E-CPR is unknown. Accordingly, we tested whether this posture could also improve hemodynamics in swine treated by E-CPR after refractory cardiac arrest.

Materials and Methods

All experiments were reviewed and approved by the ethical committee ComEth Anses-EnvA-UPEC (Committee n°16, project #23076-2019112616472793). All procedures were conducted in accordance with the European Community Standards on the Care and Use of Laboratory Animals. Animals were hosted in animal rooms maintained at 16-20°C with 12h light/dark cycles. They were fed with dry food and kept in the vivarium during at least 5-7 days after arrival before being included in the study.

Animal preparation and cardiac arrest protocol

Twelve female swine (25-33 kg) were anaesthetized with a mixture of zolazepam and tiletamine (10 mg/kg, i.m.) followed by propofol administration (1 mg/kg i.v.). After endotracheal intubation, animals were submitted to conventional mechanical ventilation (tidal volume = 8 ml/kg; FiO2 = 30%; respiratory rate = 20 breaths/min; positive end-expiratory pressure = 5 cmH2O). Ventilation parameters were modified when needed to maintain normocapnia et normoxia. Anaesthesia was maintained during the instrumentation phase by a continuous administration of propofol (10 mg/kg/h). Animals received methadone (0.3 mg/kg i.m.) and rocuronium (1mg/kg i.v.) for analgesia and muscular paralysis, respectively. Cerebral oxygen saturation was continuously monitored by near infrared spectroscopy (NIRS; INVOS™ 5100C Cerebral/Somatic Oximeter, Medtronic®).

Two catheters (9 Fr) were introduced using the Seldinger technique through the right femoral vein and artery for the continuous monitoring of right atrial and systemic arterial blood pressure, respectively. A 3 mm blood flow probe (PS-Series Probes®, Transonic, NY, USA) was placed around the internal carotid artery to monitor carotid blood flow (CBF). A pressure gauge (Millar®, SPR-524, Houston, TX, USA) was inserted into the parietal lobe of the cerebral cortex after craniotomy to monitor intracranial pressure (ICP).

Two guidewires were also placed into the left femoral artery and vein for the further insertion of cannulas for extracorporeal membrane oxygenation (ECMO) after induction of

cardiac arrest. Unfractionated heparin (100 UI/kg i.v. bolus) was administered immediately after instrumentation. In order to compensate fluid loss, an i.v. infusion of fluid (Ringer lactate, 10 ml/kg) was performed during instrumentation.

Cardiac arrest and E-CPR protocol

After a period of stabilization, ventricular fibrillation (VF) was induced by a pacemaker catheter introduced into the right ventricle through the venous femoral sheath (A/C 10 V). VF was left untreated during 15 min (no-flow), with no mechanical ventilation. During this period, two 21 and 15 Fr cannulas were mounted around the guidewires previously inserted into the femoral vein and artery, respectively (HLS Cannulaes ®, Maquet, Rastatt, Germany). At the end of the 15 min of untreated VF, E-CPR was started with a pump flow set at 40 ml/kg/min. It was progressively reduced in case of flow limitation in the ECMO pump (Figure 1B). Mechanical ventilation restarted with tidal volume = 4 ml/kg, respiratory rate = 15 cycles/min and positive end-expiratory pressure = 5 cmH2O. The extracorporeal life support circuit included a console, a centrifugal pump (Deltastream® DP3 Pump Heads (Medos Medizintechnik AG, Stolberg,Germany), a membrane oxygenator (PLS-i Oxygenator®, Maquet, Rastatt, Germany) and a tubing set (PLS Set®, Maquet, Rastatt, Germany). The membrane oxygenator was connected to a mechanical gas blender system (Sechrist Model 20090®, Sechrist, Anaheim, Calif). The gas flow was adjusted to target a CO2 blood partial pressure between 35 and 45 mmHg. After 30 min of E-CPR, defibrillation attempts were started (150 J). Mechanical ventilation parameters were re-set to the initial parameters after ROSC (i.e., tidal volume = 8 ml/kg; FiO2 = 30%; respiratory rate = 20 breaths/min; positive end-expiratory pressure = 5 cmH2O). Fluid administration was standardized in all animals with an administration of 15 and 30 ml/kg of Ringer Lactate immediately after E-CPR initiation and over the two hours following ROSC, respectively. In order to target a mean arterial pressure (MAP) above 65 mmHg, ECMO flow was

continuously maintained at the highest possible level and epinephrine dosages were subsequently adjusted to achieve the MAP target. After cardiac arrest, we targeted a temperature of 37.0±0.5°C using thermal pads and infra-red light. All animals were followed during two hours after ROSC. Then, they were euthanized by a lethal dose of pentobarbital (60 mg/kg i.v.).

Experimental groups

As illustrated by Figure 1, animals were randomly divided in two experimental groups submitted to different head and thorax positions immediately after E-CPR initiation, *i.e.*, flat (0°; n=6) or head-up position (+22 and + 9 cm for head and thorax, respectively; n=6) (12). The latter was achieved by an automated head- and thorax-up device (EleGARD Patient Positioning System^{TM}), which allows a slow and gradual rise of 6 cm/min of the head and thorax over two minutes to a head and a thorax heights of 22 and 9 cm (12). Randomization was done using block size of 2.

Investigated parameters

Heart rate (HR), systolic and diastolic blood pressure, MAP and right atrial pressure were continuously monitored and recorded. CBF and ICP were also monitored and recorded throughout the protocol. Cerebral perfusion pressure was calculated as the difference between MAP and ICP. Arterial and venous blood pH, gases (O2 and CO2 partial pressure [pO2 and PCO2, respectively]) and lactate levels were measured at baseline, during E-CPR and after ROSC.

Statistical analysis

Data were expressed as mean ± SEM. Data normal distribution was verified by a Shapiro-Wilk normality test. At baseline, values were compared among groups using a Student t-test. After cardiac arrest, parameters with repeated measures were compared among groups using a two-way analysis of variance for repeated measures. This analysis considered the following time-points as repeated measures t= 10, 20, 40, 60, 90, 120 and 150 min after

cardiac arrest, the two first time-points being measured during ECPR and the following ones after ROSC. The p values of the corresponding time, group and time x group interaction effects are shown in Table 2. We did not perform post-hoc analysis at each time-point or between time-points in order to avoid multiple comparisons. A value of $p<0.05$ was considered statistically significant. All statistical analyses were performed using GraphPad Prism® software (GraphPad® Software, La Jolla, CA, USA).

Results

As shown in Table 1, hemodynamic and biochemical parameters were not different among groups at baseline (Table 1).

Systemic hemodynamic and blood biochemical parameters

As illustrated in Figure 1C, MAP was maintained above 70 mmHg in both groups after the onset of E-CPR. After 20 min, it achieved 79±2 and 75±2 mmHg in Flat and Head-up groups. To achieve this goal, ECMO flow was set at 37±1 and 35±2 ml/min/kg and epinephrine doses at 3.1±0.3 and 2.1±0.4 µg/kg/min at this time-point, respectively (Figures 1B and 1D).

After 30 min of E-CPR, all animals achieved ROSC after 1.3±0.2 and 2.0±0.3 electric shocks in head-up vs flat group. 1/6 and 3/6 animals required more than one shock in each group, respectively. MAP was still maintained above 70 mmHg in both groups throughout the post-ROSC period (Figure 1C). To achieve this goal, epinephrine dosages were visually reduced in head-up vs flat group (1.7±0.4 vs 3.7±1.0 µg/kg/min at the end of the follow-up, respectively; Figure 1D), despite being not significantly different regarding the ANOVA contingency table. ECMO flows tended to be greater in Head-up vs Flat groups, due to flow limitation with ECMO in the flat group (Figure 1B). Heart rate (Figure 1E) and right atrial pressure (data not shown) were also not different among groups. When considering the total amount of epinephrine administered after cardiac arrest, it was not statistically different 357±82 vs 192±15 µg/kg between Flat and Head-up group.

Blood biochemical parameters

A profound metabolic acidosis was observed after cardiac arrest with no difference among groups, as evidenced by very high blood lactate levels and low blood pH (Figures 1F-G), as compared to baseline levels (no statistical comparison). PaO_2 and $PaCO_2$ were similar between groups throughout the protocol (data not shown).

Cerebral hemodynamic

As illustrated in Figure 2A and Table 2, the head-up group had an attenuated increase in ICP as compared to the flat group following cardiac arrest. This effect became more evident after ROSC and achieved -50% at the end of the follow-up (13±1 vs 26±2 mmHg, respectively). It was associated with a visually greater CePP at the end of the follow-up (66±1 vs 46±1 mmHg, Figure 2B), despite being not significantly different regarding the ANOVA contingency table (Table 2). This is line with the decreased ICP and similar MAP in head-up vs Flat group. Conversely, CBF was dramatically decreased in both groups without significant difference among groups (Figure 2C). Cerebral oxygen saturation assessed by NIRS was similar in both groups (Figure 2D).

Discussion

In our experimental model of E-CPR, head-up position improved cerebral hemodynamics as compared to flat position. It was evidenced by lower ICP and a trend toward greater CePP and less epinephrine need at the end of the protocol. This is of importance since epinephrine deteriorates cerebral microcirculation after cardiac arrest (13). Conversely, cerebral blood flow was neither ameliorated nor deteriorated by head-up vs flat position.

After cardiac arrest, it is well admitted that CePP impairment is closely associated with unfavorable neurological outcome (4, 5, 14). When autoregulation is impaired, as observed after resuscitation, CePP directly depends upon MAP and ICP. Accordingly, CePP should theoretically be improved by either MAP target increase or ICP decrease. However, increasing the MAP target requires the use of vasopressors that could be deleterious after cardiac arrest. For instance, we have recently demonstrated that MAP target above 80 mmHg using higher dosage of epinephrine progressively disrupt cerebral autoregulation and brain hemodynamics in swine treated by E-CPR, ultimately counterintuitively deteriorating cerebral hemodynamics (13). That is the reason why ICP decrease could be a better option to increase CePP without additional amounts of vasopressor. ICP is indeed well known to increase after cardiac arrest, due to hypoxic-ischemic encephalopathy and subsequent brain edema after ischemic brain injury. In patients, high ICP value is indeed strongly associated with unfavorable neurological outcome after cardiac arrest (6, 15).

In the present study, head and thorax elevation prevented ICP increase after ROSC and maintained ICP level below 15 mmHg throughout the protocol. This is in agreement with previous results indicating that head and thorax elevation increased CePP and decreased ICP regardless VF duration (16). The matter of angle as well as head and thorax sequence of elevation have been previously tested, demonstrating maximal benefits and improved neurological outcome with a controlled elevation over 2 min (17, 18) with a height of 22/9 cm

for head/thorax or an angle of 30° (11). Here, we used the same sequence of elevation to test its effect during E-CPR. Importantly, the ability of a head-up position to decrease ICP in other conditions than post-cardiac arrest is also well demonstrated, e.g., in patients presenting trauma brain injury (7-8). This effect is believed to be related to improved cerebral venous return and redistribution of the cerebro-spinal fluid into the subarachnoid spinal.

Importantly, carotid blood flow and cerebral oxygenation saturation were not significantly modified with head-up position in the present study, despite a trend toward higher cerebral oxygenation saturation at 90 min after cardiac arrest. This is in agreement with previous reports indicating no difference on cerebral regional oxygen saturation in swine under head-up vs supine positions (19). Conversely, Moore et al. observed increased cerebral oxygen saturation with head-up position during high quality CPR (18). A recent pilot study also demonstrated higher cerebral regional oxygen saturation in patients undergoing head-up CPR (20). Further investigations are yet required to determine the long-term effect of head-up position on blood flow and oxygen saturation during E-CPR.

Importantly, our study presents several limitations, such as the short period of follow-up (120 min), which could has minimized the benefits due to delayed cerebral edema and ICP increase. The fact that the animals were not submitted to conventional CPR before E-CPR could also has minimized the consequences of head-up position. The pigs could also present some anatomical differences with humans that could impact the results, e.g., chest conformation. In addition, the study was also likely underpowered to evidence statistical differences regarding several parameters. That is the reason why some trends were interpreted from the visual inspection of the Figures, especially for CePP and epinephrine dosages, which is a strong limitation. In addition, the lack of difference on carotid blood flow and cerebral oxygenation saturation deserves further investigation to determine whether ICP reduction

with head-up could be sufficient to improve the ultimate neurological outcome following E-CPR. Results would also need to be confirmed in males as we only included female animals.

Conclusions

Head and thorax elevation prevents ICP increase after ROSC in swine treated by E-CPR after cardiac arrest, without deteriorating cerebral blood flow. This supports the generalization of such a position in cardiac arrest patients, as currently tested in a clinical trial with head-up position during high quality CPR (NCT03996616).

Reference

1. Belohlavek J, Smalcova J, Rob D, Franek O, Smid O, Pokorna M, Horák J, Mrazek V, Kovarnik T, Zemanek D, et al.: Effect of Intra-arrest Transport, Extracorporeal Cardiopulmonary Resuscitation, and Immediate Invasive Assessment and Treatment on Functional Neurologic Outcome in Refractory Out-of-Hospital Cardiac Arrest: A Randomized Clinical Trial. *JAMA* 327:737–747, 2022.
2. Sandroni C, D'Arrigo S, Callaway CW, Cariou A, Dragancea I, Taccone FS, Antonelli M: The rate of brain death and organ donation in patients resuscitated from cardiac arrest: a systematic review and meta-analysis. *Intensive Care Med* 42:1661–1671, 2016.
3. Migdady I, Rice C, Deshpande A, Hernandez AV, Price C, Whitman GJ, Geocadin RG, Cho SM: Brain Injury and Neurologic Outcome in Patients Undergoing Extracorporeal Cardiopulmonary Resuscitation: A Systematic Review and Meta-Analysis. *Crit Care Med* 48:e611–e619, 2020.
4. Lemiale V, Huet O, Vigué B, Mathonnet A, Spaulding C, Mira JP, Carli P, Duranteau J, Cariou A: Changes in cerebral blood flow and oxygen extraction during post-resuscitation syndrome. *Resuscitation* 76:17–24, 2008.
5. Sundgreen C, Larsen FS, Herzog TM, Knudsen GM, Boesgaard S, Aldershvile J: Autoregulation of cerebral blood flow in patients resuscitated from cardiac arrest. *Stroke* 32:128–132, 2001.
6. Balu R, Rajagopalan S, Baghshomali S, Kirschen M, Amurthur A, Kofke WA, Abella BS: Cerebrovascular pressure reactivity and intracranial pressure are associated with neurologic outcome after hypoxic-ischemic brain injury. *Resuscitation* 164:114–121, 2021.
7. Ng I, Lim J, Wong HB: Effects of head posture on cerebral hemodynamics: its influences on intracranial pressure, cerebral perfusion pressure, and cerebral oxygenation. *Neurosurgery* 2004; 54:593–597; discussion 598
8. Meixensberger J, Baunach S, Amschler J, Dings J, Roosen K: Influence of body position on tissue-pO2, cerebral perfusion pressure and intracranial pressure in patients with acute brain injury. *Neurol Res* 19:249–253, 1997.
9. Pepe PE, Scheppke KA, Antevy PM, Crowe RP, Millstone D, Coyle C, Prusansky C, Garay S, Ellis R, Fowler RL, et al.: Confirming the Clinical Safety and Feasibility of a Bundled Methodology to Improve Cardiopulmonary Resuscitation Involving a Head-Up/Torso-Up Chest Compression Technique. *Crit Care Med* 47:449–455, 2019.
10. Ryu HH, Moore JC, Yannopoulos D, Lick M, McKnite S, Shin SD, Kim TY, Metzger

A, Rees J, Tsangaris A, et al.: The Effect of Head Up Cardiopulmonary Resuscitation on Cerebral and Systemic Hemodynamics. *Resuscitation* 102:29–34, 2016.

11. Kim T, Shin SD, Song KJ, Park YJ, Ryu HH, Debaty G, Lurie K, Hong KJ: The effect of resuscitation position on cerebral and coronary perfusion pressure during mechanical cardiopulmonary resuscitation in porcine cardiac arrest model. *Resuscitation* 113:101–107, 2017.

12. Moore JC, Duval S, Lick C, Holley J, Scheppke KA, Salverda B, Rojas-Salvador C, Jacobs M, Nystrom P, Quinn R, et al.: Faster time to automated elevation of the head and thorax during cardiopulmonary resuscitation increases the probability of return of spontaneous circulation. *Resuscitation* 170:63–69, 2022.

13. Levy Y, Hutin A, Lidouren F, Polge N, Fernandez R, Kohlhauer M, Leger PL, Debaty G, Lurie K, Lamhaut L, et al.: Targeted high mean arterial pressure aggravates cerebral hemodynamics after extracorporeal resuscitation in swine. *Crit Care* 25:369, 2021.

14. Ameloot K, Genbrugge C, Meex I, Jans F, Boer W, Vander Laenen M, Ferdinande B, Mullens W, Dupont M, Dens J, et al.: An observational near-infrared spectroscopy study on cerebral autoregulation in post-cardiac arrest patients: time to drop "one-size-fits-all" hemodynamic targets? *Resuscitation* 90:121–126, 2015.

15. Gueugniaud PY, Garcia-Darennes F, Gaussorgues P, Bancalari G, Petit P, Robert D: Prognostic significance of early intracranial and cerebral perfusion pressures in post-cardiac arrest anoxic coma. *Intensive Care Med* 17:392–398, 1991.

16. Duhem H, Moore JC, Rojas-Salvador C, Salverda B, Lick M, Pepe P, Labarere J, Debaty G, Lurie KG: Improving post-cardiac arrest cerebral perfusion pressure by elevating the head and thorax. *Resuscitation* 159:45–53, 2021.

17. Moore JC, Salverda B, Lick M, Rojas-Salvador C, Segal N, Debaty G, Lurie KG, et al.: Controlled progressive elevation rather than an optimal angle maximizes cerebral perfusion pressure during head up CPR in a swine model of cardiac arrest. *Resuscitation* 150:23–28, 2020.

18. Moore JC, Salverda B, Rojas-Salvador C, Lick M, Debaty G, Lurie K, et al.: Controlled sequential elevation of the head and thorax combined with active compression decompression cardiopulmonary resuscitation and an impedance threshold device improves neurological survival in a porcine model of cardiac arrest. *Resuscitation* 158:220–227, 2021.

19. Putzer G, Braun P, Martini J, Niederstätter I, Abram J, Lindner AK, Neururer S, Mulino M, Glodny B, Helbok R, et al.: Effects of head-up vs. supine CPR on cerebral oxygenation and cerebral metabolism - a prospective, randomized porcine study.

Resuscitation 128:51–55, 2018.
20. Kim DW, Choi JK, Won SH, Yun YJ, Jo YH, Park SM, Lee DK, Jang DH: A new variant position of head-up CPR may be associated with improvement in the measurements of cranial near-infrared spectroscopy suggestive of an increase in cerebral blood flow in non-traumatic out-of-hospital cardiac arrest patients: A prospective interventional pilot study. *Resuscitation* 175: 159-166, 2022.

Conflicts of Interest

M Kohlhauer and R Tissier are shareholders of a start-up company dedicated to total liquid ventilation (Orixha). Dr. Lurie is a coinventor of the EleGARD and he loaned the device for use in these studies.

Legends to figures

Figure 1: Experimental protocol, systemic hemodynamic parameters, blood pH and lactate levels.

E-CPR, extra-corporeal cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; P values of the contingency table of the two-way analysis are presented in Table 2; N=6 per group.

Figure 2: Cerebral hemodynamic parameters after cardiac arrest.

*E-CPR, extra-corporeal cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; *, p<0.05 for the group x time interaction effect of the two-way analysis of variance; P values of the contingency table of the two-way analysis are presented in Table 2; N=6 per group.*