IMPACT OF DIFFERENT VENTILATION STRATEGIES ON GAS EXCHANGES AND CIRCULATION DURING PROLONGED MECHANICAL CARDIO-PULMONARY RESUSCITATION IN A PORCINE MODEL

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ABSTRACT—Background: Optimal ventilation during cardio-pulmonary resuscitation (CPR) is still controversial. Ventilation is expected to provide sufficient arterial oxygen content and adequate carbon dioxide removal, while minimizing the risk of circulatory impairment. The objective of the present study was to compare three ventilation strategies in a porcine model during mechanical continuous chest compressions (CCC) according to arterial oxygenation and hemodynamic impact. Method: Ventricular fibrillation was induced and followed by five no-flow minutes and thirty low-flow minutes resuscitation with mechanical-CCC without vasopressor drugs administration. Three groups of eight Landras pig were randomized according to the ventilation strategy: 1. Standard nonsynchronized volume-control mode (SD-group); 2. synchronized bilevel pressure-controlled ventilation (CPV-group); 3. continuous insufflation with Boussignac Cardiac-Arrest Device (BC-group). We assessed 1. arterial blood gases, 2. macro hemodynamics, 3. tissular cerebral macro and micro-circulation and 4. airway pressure, minute ventilation at baseline and every 5 minutes during the protocol.

Results: Arterial PaO2 level was higher at each measurement time in SD-group (>200 mm Hg) compared to CPV-group and BC-group (P<0.01). In BC-group, arterial PaCO2 level was significantly higher (>90 mm Hg) than in SD and CPV groups (P<0.01). There was no difference between groups concerning hemodynamic parameters, cerebral perfusion and microcirculation.

Conclusion: Ventilation modalities in this porcine model of prolonged CPR influence oxygenation and decarboxylation without impairing circulation and cerebral perfusion. Synchronized bi-level pressure-controlled ventilation use avoid hyperoxia and was as efficient as asynchronized volume ventilation to maintain alveolar ventilation and systemic perfusion during prolonged CPR. KEYWORDS—Cardiac arrest, cardio-pulmonary resuscitation, ventilation methods

ABBREVIATIONS—BC-group—Boussignac Cardiac-Arrest Device; BNP—brain natriuretic peptide; CBF—Carotid Blood Flow; CCC—continuous chest compressions; CeP—Cerebral perfusion pressure; COI—continuous oxygen insufflation; CPR—cardio-pulmonary resuscitation; CPV-group—bi-level pressure mode; CVP—Central Venous Pressure; DAP—Diastolic Blood Pressure; EtCO2—End-Tidal CO2; HR—Heart Rate; IC—Intra Cranial Pressure; MCCC—mechanical continuous chest compressions; NIRS—Near Infra Red Spectroscopy; NSE—Neuron-specific Enolase; PAO2—alveolar partial pressure of oxygen; Paw—Airway Pressure; PEEP—positive end-expiratory pressure; Peso—esophageal pressure; PL—Transpulmonary pressure; rSO2—regional saturation; S100B—S100 calcium-binding protein B; SBP—Systolic Blood Pressure; SD-group—Standard volume-control mode

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Authors’ contributions: CF, TC, BL, JCMR designed the study protocol, analysed the data, and drafted the manuscript. CF was the major contributor to the experiments and in writing the manuscript. DJ, YL, JCMR, BB, MR participated in a part of the experiments. CF, BB conducted the data extraction and data management. FER, CF generated the statistics. EL did all the histology analysis. All the authors read and approved the final manuscript.

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INTRODUCTION

Neurologic prognosis of cardiac arrest is highly dependent of the quality of CPR. Both the International Liaison Committee on Resuscitation (ILCOR) and the European Resuscitation Council (ERC) Guidelines for Resuscitation emphasize the importance of minimally interrupted high-quality chest compressions during CPR and as well as the importance of early chest compressions (1,2). However, there is a lack of prospective studies or information on both optimal ventilation strategies during CPR and settings during CPR management (3–5).

Ventilation is expected to provide sufficient arterial oxygenation and adequate carbon dioxide removal, while minimizing the risk of circulatory impairment associated with the interaction between heart and intrathoracic pressure. Both the latest ERC and ILCOR guidelines called for 100% FiO2 use during CPR (1,2). Ventilation strategies may impact gas exchanges and circulation differently (6), especially when CPR with mechanical chest compression is prolonged (7). Therefore, practices in the field differ according to the teams with different underlying concepts (8). Recently, a pilot clinical study performed during cardiopulmonary resuscitation with an automated mechanical chest compression device has compared three different ventilatory modes and suggested a clinical difference in the obtained ventilatory parameters (9). For advance life support, international guidelines emphasize basic volume-mode ventilation with a respiratory rate of 10 min−1 (1,10). A specific synchronized bi-level pressure-mode ventilation approach has been recently developed through the Cardio-Pulmonary Ventilation (CPV) settings (Monnal T60, Air Liquide Medical System, Antony, France). In this bi-level pressure-mode, insufflation is synchronized with chest compressions (CC) using an upper pressure set at 20 cmH2O and a lower pressure set at 5 cmH2O, inspiratory time 1 second, expiratory time 5 seconds, FiO2 100%. This synchronized pressure-mode ventilation may limit hyperventilation or high airway pressure and keep airways open (11). Continuous oxygen insufflation (COI) has also been proposed and developed to avoid interruption of CC during CPR (12–14) because in the presence of a patent airway, chest compressions alone may result in some ventilation of the lungs (15). The Boussignac Cardiac Arrest Device (B-CARD, Vygon, Ecouen, France) (16) actively delivers oxygen at 15 L min−1. Potential benefits of this device on hemodynamics is debated (17) and COI without ventilation is not yet recommended for routine use (1,18). Since the B-CARD does not provide ventilation, we will use it as a model to study the effects of oxygenation without ventilation. Finally, the effect on intrathoracic pressure of COI differs according to experimental studies, either positive or negative (3,14).

Therefore, the objective of this study was to compare three ventilation strategies (Standard, CPV and B-CARD) on arterial oxygenation and decarboxylation and systemic and cerebral hemodynamics in a porcine model of prolonged CA under mechanical continuous chest compressions (MCCC).

METHODS

Ethics Approval
All experiments were reviewed and approved by the Nancy University Ethics Committee for Animal Experimentation (APAFIS number 10199–201706121203981v1). The procedure for the care and sacrifices of study animals was in accordance with the European Community Standards on the Care and Use of Laboratory Animals.

Animal Model
Animal preparation—Twenty-four domestic male pigs (Landrace) weighing 44 to 65 kg were acclimated to the animal facilities for 4 to 7 days and fasted overnight prior to experimentation with free access to water. All animals were premedicated with an intramuscular injection of ketamine (15 mg kg−1, Ketalar, Parke-Davis, Courbevoie, France) and midazolam (0.1 mg kg−1, Hynovel; Produits Roche, Neuilly sur Seine, France). Anaesthesia was induced as previously published (19) via the lateral auricular vein with an intravenous bolus of propofol (1 mg kg−1, Propofol-lipuro 1%, B. Braun, Melsungen AG, Germany). Animals were intubated (Teleflexixsis 7.5 I.D. mm, Teleflex Medical, Athlone, Ireland) and mechanically ventilated (Evia 1 Duna, Dräger, Luebeck, Germany) in assisted-controlled mode (30% Oxygen, tidal volume 10 mg kg−2 and respiratory rate 12). Anaesthesia was maintained with continuous infusion of sufentanil (0.2 μg kg−1 min−1, Sufentanil, Mylan, Canonsburg, Pennsylvania) and propofol (7 mg kg−1 h−1, propofol-lipuro 2%, B. Braun Melsungen AG, Germany and cisatracurium (0.9 mg kg−1 h−1, Nimbex, GlaxoSmithKline, Brentford, Middlesex, UK). Unfractionated heparin (10 UI kg−1, Heparine Sodique Choay, Sanofi-Aventis, Paris, France) was administered to avoid cannula clotting. Normothermia was maintained by administering NaCl 0.9% (10 mL kg−1, Oselia SALF, SpA Laboratorio Farmacologico, Cenate Sotto, Italie). Body temperature was controlled for a core temperature at 38°C. All experiment occurred at the same moment during circadian cycle (during morning time).

Specifically, for the procedure, after dissection of neck vessels, a venous catheter was introduced in the right external jugular vein (Swan-Ganz catheter introducer, Edwards Lifesciences, USA). A catheter was introduced in the right femoral artery (Seldicath, Plastimed Prodimed, France) to monitor systemic blood pressure. Venous and arterial catheter were connected to two pressure transducers (Emka usbACQ, usbAMP; Emka technologies SAS, Paris, France). A transit time flow probe (Transonic Systems Inc, USA) was placed around the left carotid artery.

In the corresponding region of the left hemisphere, an intracranial pressure probe (Intracranial scisense catheter, Transonic science Inc, London, Canada) was inserted after trepanation (Codman Disposable perforator 14 mm, Johnson & Johnson Medical Ltd, Wokingham, UK). NIRS cerebral sensors were fixed on forehead (Masimo SET O3 Sensor, Masimo Corporation CA). NIRS peripheral sensor was fixed on the anterior left leg after shaving (Inspectra StO2 sensor thenar hand). Body temperature was controlled for a core temperature at 38°C. All experiment occurred at the same moment during circadian cycle (during morning time).

Flow and Airway Pressure (Paw) were measured using a Pneumotachograph (Pneumotachometer, Hans Rudolph Inc, Shawnee, OK) placed proximally to the endotracheal tube and connected to two pressure transducers (Emka usbACQ, usbAMP ; Emka technologies SAS, Paris, France). End-Tidal CO2 (EtCO2) was measured using a probe placed distally to the pneumotachograph (Irmco CO2 probe Monnal, Masimo Corporation, CA). An esophageal balloon (MBMED Prod, MBMED SA, Buenos Aires, Argentina) was inserted to measure esophageal pressure (Peso).

Measured Parameters

Haemodynamics—The following parameters were continuously monitored and recorded: Heart Rate (HR), Systolic Blood Pressure (SAP), Diastolic Blood Pressure (DBP), Cardiot Blood Flow (CBF), Intra Cranial Pressure (ICP), Central Venous Pressure (CVP), Flow and Airway Pressure (Paw), Esophageal Pressure (Peso). During CPR, SAP was assumed to be the maximum of arterial pressure generated by the chest compression, and DAB to be the minimum pressure measured during decompression. Transpulmonary pressure (PL) was calculated as Paw minus Peso, cerebral perfusion pressure (CePP) was calculated as MAP minus ICP. Data were computed using a designated analysis program (IOX2 2.9.5.73®, EMKA Technologies, France). Cerebral and peripheral NIRS data were continuously monitored and recorded and extracted with the corresponding software.

Biology—Arterial blood gas, hemoglobin and lactate levels were assessed in an acid-base and co-oximeter analyser at 38°C (VetStat™, IDEXX Laboratories, France). Lactate concentrations were determined using a Statstrip Lactate Xpress Meter (Nova Biomedical, Flintshire, UK). Plasma levels of troponin, brain natriuretic peptide (BNP), S100 calcium-binding protein B

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(S100B) and Neuron-specific Enolase (NSE) were measured using a standard chemistry analyser. The alveolar partial pressure of oxygen \((P_{A}O_{2})\) was calculated with the alveolar gas equation as (20): \[ P_{A}O_{2} = P_{I}O_{2} - PaCO_2/R = (PB - PH_2O)\times FIO2 - (PaCO_2/R) \] with \(PB\): atmospheric pressure at sea level, 760 mm Hg; \(PH_2O\): the saturated vapor pressure of water at body temperature and the prevailing atmospheric pressure, 47; \(FIO2\): The fraction of inspired gas that is oxygen, \(1\); \(PaCO_2\): The arterial partial pressure of carbon dioxide; \(R\): the respiratory exchange ratio, 0.8.

**Histology**—After sacrifice, autopsy was performed immediately with a sternotomy. From each lung, tissue sample from base, apex, anterior and posterior part were examined for injuries and atelectasis. All samples were initially immersion-fixed in 10% buffered formalin and subsequently imbedded in paraffin. Histopathological analysis was performed on 4 μm tissue cut sections. The specimens were stained with haematoyxin-eosin. Macroscopy injury of the lung was evaluated with an anatomic scale of visual contusion (percentage of the whole lung). Lung tissue samples from each part were classified for intra-alveolar haemorrhage, intra-alveolar oedema, atelectasis, alveolar distention and peri-alveolar bleeding as none (0% of the surface), light (<25% of the surface), mild (25 to 75% of the surface), severe (>75% of the surface).

**Experimental Protocol**

Cardiac arrest model—The overall protocol is shown in Figure 1. The animal position on the table was secured with legs link. LUCATM device (Jolife AB/Physio-control, Lund, Sweden) was placed on the flat surface of the pig’s thorax and securely positioned. Cardiac arrest was induced using a pacemaker wire inserted in the right ventricle through the venous catheter. Ventricular fibrillation was induced using a 9 Volt shock. The T0 time was defined as cardiac arrest. At T0, ventilation was stopped and a five minutes No-Flow period was respected. At T5 the animals were randomized according to the ventilation group and the LUCATM device was started. 100 per minute chest compressions (CC), without vasopressor administration during the protocol. Measurements occurred at Baseline Time (TB), No-flow beginning (T0), No-flow end/CPR starting (T5), and every five minutes (T10, T15, T20, T25, T30) until the end of protocol. Autopsy was then realized.

Groups—Animals were randomly assigned into three groups at time of LUCATM initiation (T5): 1. Standard Group (SD-group), ventilation according to the international recommendations (Monnal T60, Air Liquide Medical System, Antony, France) with the following settings: Volume control (VC), Vt 6mLkg⁻¹, respiratory rate 10 min⁻¹, FiO2 100%; 2. Cardio-Pulmonary Ventilation Group (CPV-group), bi-level pressure-controlled ventilation (CPV Monnal T60, Air Liquide Medical System, Antony, France) synchronized with CC, lower pressure at 5 cmH₂O, upper pressure at 20cmH₂O, respiratory rate 10 min⁻¹, FiO2 100%; 3. B-CARD group (BC-group), continuous oxygen insufflation (COI) with Boussignac Cardiac Arrest device (B-card, Vygon, Ecouen, France), O₂ flow 15 L min⁻¹ with no additional intervention.

**Data Analysis**

For continuous data, recordel file using JOX (JOX2 2.9.5.73°, EMKA Technologies, France) were analysed with AcqKnowledge software (Acq-Knowledge 3.7.3, Biopac System, Goleta, CA). Time periods were split into intervals: baseline to T0 (TB), T0 to T5 as No-Flow period (T5), T5 to T10 (T10), T10 to T15 (T15), T15 to T20 (T20), T20 to T25 (T25), T25 to T30 (T30).

**Statistics**

Data are summarized as mean (± 1 SD) for continuous variables and count (%) for categorical variables. Comparisons between the three groups for proportions were assessed with Fisher’s exact test. Kruskal-Wallis one-way analysis of variance was used to compare continuous variables. The primary analysis compared both PaCO2 and PaO2 between the three groups. A regression model was fitted to analyze effects between groups. To account for the structure of the data, that is, longitudinal data with repeated measures and a resulting intra-subject correlation, a logistic regression model was fitted using a generalized estimating equation method. Odds ratios (OR) were provided together with their 95% confidence intervals (95%CI). Secondary outcomes were investigated in a similar approach. When appropriate, analyses were performed after multiple imputations of missing data (“mitml” package for R). The statistical power was calculated posteri ori. All statistical tests were two-sided and a p-value ≤ 0.05 considered significant. Statistical analysis was performed with R software version 3.3.3 for Windows (R Foundation for Statistical Computing, Vienna, Austria). All figures were generated with GraphPad Prism 8.0 software (GraphPad Software Inc, San Diego, CA).

**RESULTS**

A total of 24 animals were studied: eight in SD-group, eight in CVP-group and eight in the BC-group. The three groups behavior were similar during baseline period [TB-T0] for all hemodynamic, ventilatory and biology parameters as well as during the No-Flow period [T0-T5] before randomization (Table 1). All animals had an initial Ventricular Fibrillation (VF) rhythm and only gasps were observed on airways probes.

**Blood Gases and Ventilation Measurements**

From T10 to T30, the evolution of pH was significantly different \((p < 0.05)\) as detailed in Table 2. PaCO₂ was significantly higher in the BC-group (>90 mm Hg) (Fig. 2A) with a positive effect of time \((p < 0.001)\; Table ESM 1.1, http://links.lww.com/SHK/B376); PaO₂ was significantly higher in the SD group (>200 mm Hg) (Table 2, Fig. 2B) with no effect of time \((p = 0.69);\)

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**FIG. 1. Overall protocol time table and illustration of the cure obtained.** ABP indicates arterial blood pressure; BC, B-CARD Group; CA, cardiac arrest; CBF, carotid blood flow; CPV, Cardio-Pulmonary Ventilation Group; CVP central venous pressure; Daw, Airway Flow; ICP, Intra Cranial Pressure; MCC, Mechanical Chest Compression; Paw, Airway Pressure; Peso, esophageal Pressure; SD, Standard ventilation Group.
Table 1. Baseline parameters and at the end of five minutes of cardiac arrest period (just before randomization)

| Parameters          | Baseline          | T5               |
|---------------------|-------------------|------------------|
|                     | SD (n = 8) | CPV (n = 8) | BC (n = 8) | SD (n = 8) | CPV (n = 8) | BC (n = 8) |
| weight (kg)         | 50 ± 10   | 53 ± 8      | 45 ± 5     | 34 ± 9     | 34 ± 9      | 28 ± 6     |
| Hemodynamic         |          |             |            | 27 ± 2     | 29 ± 7      | 25 ± 6     |
| SAP (mm Hg)         | 135 ± 21  | 134 ± 26    | 144 ± 19   | 111 ± 19   | 112 ± 11    | 112 ± 18   |
| DAP (mm Hg)         | 88 ± 22   | 83 ± 22     | 95 ± 18    | 95 ± 18    | 95 ± 18     | 95 ± 18    |
| MAP (mm Hg)         | 104 ± 21  | 101 ± 23    | 111 ± 19   | 111 ± 19   | 111 ± 19    | 111 ± 19   |
| CBF (mL min⁻¹ kg⁻¹) | 243 ± 85  | 200 ± 99    | 191 ± 91   | 2.5 ± 2.5  | 2 ± 1.2     | 2 ± 0.6    |
| CVP (mm Hg)         | 15 ± 3    | 14 ± 3      | 13 ± 5     | 25 ± 5     | 25 ± 3      | 24 ± 5     |
| Cerebral and tissular |          |             |            | 23 ± 4     | 20 ± 5      | 21 ± 7     |
| ICP (mm Hg)         | 14 ± 4    | 11 ± 4      | 14 ± 6     | 11 ± 4     | 11 ± 4      | 11 ± 4     |
| CePP (mm Hg)        | 90 ± 24   | 91 ± 25     | 92 ± 12    | 6 ± 5      | 12 ± 8      | 6 ± 8      |
| c-rSO₂ (%)          | 55 ± 2    | 56 ± 5      | 54 ± 3     | 41 ± 3     | 45 ± 5      | 43 ± 6     |
| t-rSO₂ (%)          | 55 ± 7    | 54 ± 9      | 53 ± 9     | 24 ± 6     | 31 ± 8      | 22 ± 9     |
| Ventilatory         |          |             |            | 18 ± 11    | 17 ± 15     | 16 ± 14    |
| Paw (cmH₂O)         | 10 ± 5    | 10 ± 7      | 10 ± 5     | 0 ± 0      | 0 ± 0       | 0 ± 0      |
| Peso (cmH₂O)        | 28 ± 19   | 22 ± 23     | 24 ± 22    | 18 ± 11    | 17 ± 15     | 16 ± 14    |
| Vte (mL kg⁻¹ min⁻¹) | 9.3 ± 1.8 | 9.4 ± 0.9   | 9.9 ± 1.5  | 0 ± 0      | 0 ± 0       | 0 ± 0      |
| VI (mL kg⁻¹ min⁻¹)  | 9.8 ± 1.2 | 9.3 ± 1.5   | 9.9 ± 1.6  | 0 ± 0      | 0 ± 0       | 0 ± 0      |
| EICO₂ (mm Hg)       | 40 ± 0.6  | 36 ± 7      | 44 ± 3     | 24 ± 6     | 31 ± 8      | 22 ± 9     |
| Blood gas           |          |             |            | 7.4 ± 0.1  | 7.4 ± 0.1   | 7.4 ± 0.1  |
| pH                  | 7.4 ± 0.1  | 7.4 ± 0.1   | 7.4 ± 0.1  | 7.4 ± 0.1  | 7.4 ± 0.1   | 7.4 ± 0.1  |
| PaCO₂ (mm Hg)       | 46 ± 6    | 45 ± 5      | 45 ± 6     | 47 ± 10    | 51 ± 10     | 54 ± 17    |
| PaO₂ (mm Hg)        | 105 ± 16  | 106 ± 20    | 108 ± 9    | 74 ± 33    | 67 ± 29     | 70 ± 29    |
| PACO₂ (mm Hg)       | 90 ± 6    | 93 ± 6      | 92 ± 7     | 90 ± 14    | 85 ± 13     | 81 ± 22    |
| HCO₃⁻ (mmol L⁻¹)    | 27 ± 1    | 26 ± 1      | 27 ± 2     | 27 ± 2     | 26 ± 2      | 27 ± 3     |
| Hb (g L⁻¹)          | 9.6 ± 2   | 9.6 ± 1     | 9.1 ± 1    | 10.2 ± 1   | 10.7 ± 2    | 10.4 ± 2   |
| SpO₂ (%)            | 94 ± 3    | 94 ± 2      | 94 ± 1     | 84 ± 15    | 82 ± 14     | 82 ± 14    |
| Lactate (mmol L⁻¹)  | 1.5 ± 0.5 | 1.6 ± 0.3   | 1.5 ± 0.3  | 2 ± 0.7    | 2.5 ± 1.2   | 2.4 ± 1.3  |

BC, B-CARD Group; BNP, brain natriuretic peptide; CA, cardiac arrest; CBF, carotid blood flow; CePP, Cerebral Perfusion Pressure; CPV, Cardio-Pulmonary Ventilation Group; c-rSO₂, regional saturation measured with Near Infra Red Spectroscopy; CVP, Central Venous Pressure; DAP, Diastolic Arterial Pressure; EICO₂, End-Tidal CO₂; Hb, hemoglobin; HCO₃⁻, bicarbonate; ICP, Intra Cranial Pressure; MAP, Mean Arterial Pressure; NSE, Neuron-specific Enolase; PaCO₂, arterial partial pressure of carbon dioxide; PaO₂, alveolar partial pressure of oxygen; PaO₂, arterial partial pressure of oxygen; Paw, Airway Pressure; Peso, esophageal Pressure; pH, Hydrogen Potential; S100B, S100 calcium-binding protein B; SAP Systolic Arterial Pressure; SD, Standard ventilation Group; SpO₂, peripheral oxygen saturation; t-rSO₂, tissue Near Infra Red Spectroscopy; Vte, Expiratory Tidal Volume; VI, Inspiratory Tidal Volume; Values are given as mean ±SD.

Histopathological Changes

Macroscopic estimation of the lung infarction was not different between the three groups (p = 0.09). The microscopic analysis of alveolar collapse, alveolar distension, intra-alveolar haemorrhage and peri-bronchiolar haemorrhage, are illustrated in Figure 4 with the histopathological changes.

DISCUSSION

The main results of our study are that
1. standard ventilation at FiO2 100% was associated with major hyperoxia and efficient CO₂ removal;
2. CPV was associated with normoxia and efficient CO₂ removal;
3. B-CARD was associated with normoxia and major hyper-capnia.

Despite these differences, the ventilatory strategy did not impact hemodynamic and cerebral parameters. Therefore, in this experimental model, CPV is the only ventilatory mode that
maintained arterial PO2 and alveolar ventilation in the accepted range without impacting hemodynamics and cerebral perfusion/oxygenation.

**Hyperoxia and hypercapnia issue**

Hyperoxia is still an issue leading to significant neurological damage (21,22). If the question is now well focused on the oxygenation target of patients in postcardiac arrest (avoid hyperoxia as much as possible), the target during cardiopulmonary resuscitation remains unknown (19–21) and will require further clinical investigations (23). Standard ventilation at FiO2 1 was associated with a marked hyperoxia that could be explained by a higher Vt. In order to avoid the potential toxicity of hyperoxia, a practical conclusion would be to titrate FiO2 during CPR which is impossible in the Out of hospital cardiac arrest. Therefore, ILCOR recommends giving the highest feasible inspired oxygen concentration during cardiac arrest to maximize oxygen delivery to the brain thereby minimizing hypoxic-ischemic injury. Immediately after ROSC, as soon as arterial blood oxygen saturation can be monitored reliably, titrate the inspired oxygen concentration is recommended to maintain the arterial blood oxygen saturation between 94 and 98% or arterial partial pressure of oxygen (PaO2) of 10 to 13 kPa or 75 to 100 mmHg (24).

We observe a significant difference in arterial level of CO2 depending on the ventilation strategy used. Hypercapnia (PaCO2 > 45 mm Hg) directly disables the organism’s acid-base balance and thus has a direct impact on all organ’s performances. While we were able to identify a very moderate increase in PaCO2 in the SD group, we found a significant increase in PaCO2 in the B-Card group and no major hypercapnia in the CPV group. This hypercapnia could be explained, based on the Δ Vti-Vte measurement, by trapping of the inspired volume with no exhaling during the compression phase. However, Schneider et al. were able to determine that, compared to normocapnia, hypercapnia was associated with a higher probability of survival regardless of the patient’s neurological state (25). In addition, Eastwood et al. in a multicenter prospective study highlighted that moderate hypercapnia (PaCO2 50 to 55 mm Hg) compared to normocapnia (PaCO2 35 to 45 mm Hg) induced a

| Parameters | SD (n = 8) | CPV (n = 8) | BC (n = 8) | SD (n = 8) | CPV (n = 8) | BC (n = 8) | SD (n = 8) | CPV (n = 8) | BC (n = 8) |
|------------|-----------|------------|-----------|-----------|------------|-----------|-----------|------------|-----------|
| **Blood gas** |           |            |           |           |            |           |           |            |           |
| pH         | 7.32 ± 0.11 | 7.21 ± 0.07 | 7.11 ± 0.06 | 7.25 ± 0.11 | 7.15 ± 0.11 | 6.98 ± 0.06 | 7.19 ± 0.14 | 7.05 ± 0.14 | 6.89 ± 0.10 | <0.01* |
| PaCO2 (mm Hg) | 45.5 ± 10.3 | 68.9 ± 15.4 | 94.3 ± 17.2 | 45 ± 9.4 | 65.4 ± 22.7 | 120.1 ± 21.2 | 49.8 ± 22.1 | 78 ± 25.1 | 146.3 ± 45 | < 0.01* |
| PaO2 (mm Hg) | 263 ± 105 | 118 ± 50 | 96 ± 51 | 3360 ± 136 | 131 ± 84 | 96 ± 52 | 216 ± 147 | 76 ± 31 | 68 ± 44 | < 0.01* |
| HCO3 (mmol/L) | 656 ± 13 | 626 ± 19 | 595 ± 21 | 367 ± 12 | 631 ± 28 | 563 ± 26 | 651 ± 28 | 616 ± 31 | 530 ± 56 | 0.21 |
| HCO3 (mmol/L) | 20.8 ± 1.8 | 23.8 ± 2.7 | 27.2 ± 3.3 | 17.8 ± 1.6 | 19.5 ± 2.9 | 24.9 ± 2.7 | 16 ± 2.2 | 18.6 ± 2.2 | 24.1 ± 4.4 | < 0.01* |
| Hb (gdL-1) | 11.7 ± 1.5 | 12.3 ± 0.9 | 11.9 ± 1.6 | 11.4 ± 1.6 | 12.2 ± 0.9 | 12 ± 1.4 | 11.6 ± 1.9 | 12.7 ± 1.1 | 12.4 ± 2.0 | < 0.01* |
| SpO2 (%) | 99 ± 3 | 91 ± 7 | 82 ± 15 | 99 ± 1 | 90 ± 7 | 79 ± 17 | 89 ± 18 | 77 ± 14 | 70 ± 14 | < 0.01* |
| Lactate (mmol/L) | 7.5 ± 1.2 | 8.5 ± 0.9 | 8.2 ± 1.7 | 7.5 ± 1.2 | 8.5 ± 0.9 | 8.2 ± 1.7 | 0.83 |

BC, B-CARD Group; CPV, Cardio-Pulmonary Ventilation Group; Hb, hemoglobin; HCO3, bicarbonate; PaCO2, arterial partial pressure of carbon dioxide; PaO2, alveolar partial pressure of oxygen; PaO2, arterial partial pressure of oxygen; pH, Hydrogen Potential; SD, Standard ventilation Group; SpO2, peripheral oxygen saturation. Values are given as mean ± SD. Kruskal-Wallis one-way analysis of variance was used to compare continuous variables. The sign displays the Bonferroni corrected p-values from pairwise comparisons between groups performed by the Dunn’s post hoc test and Dunn’s post hoc test was used to compare groups.

*SD vs. CPV.

*SD vs. BC, § CPV vs. BC.

**FIG. 2.** Blood gas evolution according to the ventilatory mode randomization. A, PaCO2 arterial serum level of CO2 (carbon dioxide partial pressure) evolution; B, PaO2 arterial serum level of O2 (oxygen partial pressure) evolution. BC, B-CARD Group; CPV, Cardio-Pulmonary Ventilation Group; SD, Standard ventilation Group; Values are given as mean ± SD. The sign displays the bonferroni corrected p-values from pairwise comparisons between groups performed by the Dunn's post hoc test, *SD vs. CPV, * SD vs. BC, § CPV vs. BC.
| Parameters                  | T10    | T15    | T20    | T25    | T30    | p        |
|-----------------------------|--------|--------|--------|--------|--------|----------|
| Hemodynamic                 |        |        |        |        |        |          |
| SAP (mm Hg)                 | 107 ± 35 | 79 ± 17 | 90 ± 40 | 85 ± 39 | 73 ± 28 | 67 ± 30 |
| MAP (mm Hg)                 | 36 ± 31 | 25 ± 5  | 27 ± 12 | 22 ± 5  | 30 ± 16 | 23 ± 9  |
| MAP (mm Hg)                 | 60 ± 28 | 43 ± 7  | 48 ± 21 | 43 ± 15 | 49 ± 19 | 38 ± 15 |
| CBF (mL/min^-1)             | 80 ± 11 | 110 ± 159 | 98 ± 118 | 68 ± 38 | 67 ± 38 | 47 ± 51 |
| CVP (mm Hg)                 | 38 ± 18 | 40 ± 31 | 38 ± 17 | 33 ± 18 | 29 ± 17 | 30 ± 9  |
| Cerebral and tissular       |        |        |        |        |        |          |
| ICP (mm Hg)                 | 25 ± 6  | 22 ± 11 | 20 ± 7  | 23 ± 6  | 16 ± 5  | 17 ± 9  |
| CePP (mmHg)                 | 24 ± 18 | 26 ± 7  | 27 ± 23 | 19 ± 19 | 31 ± 16 | 22 ± 18 |
| c-rSO4 (%)                  | 40 ± 3  | 41 ± 7  | 41 ± 7  | 41 ± 4  | 43 ± 5  | 42 ± 6  |
| t-rSOa (%)                  | 23 ± 9  | 25 ± 6  | 17 ± 10 | 37 ± 4  | 37 ± 2  | 36 ± 4  |
| Ventilatory                 |        |        |        |        |        |          |
| EtCO2 (mm Hg)               | 25 ± 11 | 24 ± 12 | 28 ± 6  | 32 ± 11 | 56 ± 36 | 50 ± 33 |
| Paw (ch20)                  | 16 ± 11 | 12 ± 6  | 6 ± 4   | 15 ± 10 | 12 ± 6  | 6 ± 4   |
| Peso (ch20)                 | 37 ± 22 | 26 ± 28 | 27 ± 24 | 32 ± 21 | 23 ± 25 | 23 ± 20 |
| Vti (mL/kg^-1 min^-1)       | 11.4 ± 1.6 | 5.5 ± 1.5 | 4.5 ± 1.7 | 11.4 ± 1.4 | 5.4 ± 1.8 | 4.3 ± 1.7 |
| Vte (mL/kg^-1 min^-1)       | 7.1 ± 4.1 | 4.8 ± 1.4 | 4 ± 1.6 | 7.5 ± 3.9 | 4.8 ± 1.4 | 3.9 ± 1.5 |

BC, B-CARD Group; CBF, carotid blood flow; CePP, Cerebral Perfusion Pressure; CPV, Cardio-Pulmonary Ventilation Group; c-rSO4, regional saturation measured with Near Infra Red Spectroscopy; CVP, Central Venous Pressure; DAP, Diastolic Arterial Pressure; ICP, Intra Cranial Pressure; MAP, Mean Arterial Pressure; Paw, Airway Pressure; Peso, esophageal Pressure; PL, Transpulmonary pressure; SAP, Systolic Arterial Pressure; SD, Standard ventilation Group; t-rSOa, tissular Near Infra Red Spectroscopy; Vte, Expiratory Tidal Volume; Vti, Inspiratory Tidal Volume; Values are given as mean ± SD. Kruskal–Wallis one-way analysis of variance was used to compare continuous variables. The sign displays the Bonferroni corrected p-values from pairwise comparisons between groups performed by the Dunn's post hoc test.

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decrease in brain injury biomarker (NSE) production (26).
Other trials are in progress (NCT03114033) assessing this therapeutic target. In our model, in BC group, a major hypercapnia was observed but had no positive nor negative consequences on cerebral perfusion measurement or NIRS parameters when compared to the two other group. Classically, moderate hypercapnia increases cerebral blood flow and may also improve cerebral oxygenation. On the other hand, extreme hypercapnia, worsened lesion volume vs. mild hypocapnia and normocapnia (27). In our model, in BC group, a major hypercapnia was observed but had no positive nor negative consequences on cerebral perfusion measurement or NIRS parameters when compared to the two other group. Finally, all in one, the absence of variation of cerebral perfusion parameters in the BC group when compared to normocapnic groups is evoking of a loss of cerebrovascular reactivity to CO2 in this experimental model.

Finally, brain biomarkers trends were not correlated with PaCO2 level after 30 min of CPR.

**Hemodynamic Issue**

We did not find any impact on hemodynamic parameters (no difference on MAP, CVP) or on brain circulation regardless of the ventilatory strategy used (no difference on CePP, NIRS) despite the major variations in PaO2 and PaCO2. In parallel, hyperoxia can have a direct vasoconstrictor effect, which can lead to a reduction in cerebral blood flow, thus increasing cerebral ischemia (28). In our model, CPV mode seemed to allow acceptable oxygenation and decarboxylation without hemodynamic impairment. Low MAP level did not allow us
to explore the question of cerebral autoregulation (29), neither the relationship between NIRS and cerebral blood flow or CVP (30). One key point of the influence of ventilation on hemodynamics is the impact of PEEP level during CPR (5). This subject is still controversial; for some authors applying PEEP could impact venous return by increasing intrathoracic pressure and have a negative impact on circulation (31); for others applying PEEP could enhance the airway opening and increase blood flow (32, 33). In our study we did not observe any impact on the right heart of PEEP level in CPV (PEEP 5 cmH2O) nor B-Card (PEEP 5 cmH2O) strategy compared to Standard-group (PEEP 0 cmH2O), and no macro-hemodynamic impairment.

**Limitations**

However, our study has several limitations. First of all, we decided not to use catecholamines during resuscitation in order to avoid their effect on gas exchanges, acid/base balance and hemodynamics. We chose to stop CPR at the end of the experiment with no ROSC goal because we didn’t have the foresight to assess the animal’s prognosis. Secondly, B-CARD strategy tested as permissive hypercapnia was probably put in difficulty with an increased experimental dead space due to the sensors necessary to the experiment. Nevertheless, the major hypercapnia observed did not influence hemodynamic parameters or cerebral perfusion. Finally, in a small pilot study in humans performed during cardiopulmonary resuscitation with an automated mechanical chest compression device, the authors also found a marked hyper-capnia in using a similar device (9). Thirdly, we did not observe any intrathoracic airway closure in our model (34) suggesting that porcine and human respiratory systems may behave differently. Indeed, the rather "peak" shape of the pig chest can also lead to some differences in analysis regarding gas exchanges and the effectiveness of active compression decompression. It would be interesting to be able to assess our hypotheses on revitalized cadavers in order to confirm the reproducibility of our results. Fourthly, choice was made to involve as few animals as possible to achieve research aims because of ethical concerns.

**Conclusion**

Ventilation modalities in this porcine model of prolonged CPR influenced oxygenation and decarboxylation without impairing circulation and cerebral perfusion. Synchronized bi-level pressure-controlled ventilation use avoid hyperoxia and was as efficient as asynchronous volume ventilation to maintain alveolar ventilation and systemic perfusion during prolonged CPR.

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