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Improving Post-Cardiac Arrest Cerebral Perfusion Pressure by Elevating the Head and Thorax

Hélène Duhem

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Année : 2020

**L'ÉLEVATION DE LA TÊTE ET DU TRONC AMÉLIORE LA PRESSION DE
PERFUSION CÉRÉBRALE EN POST-ARRÊT CARDIAQUE**

THÈSE
PRÉSENTÉE POUR L'OBTENTION DU TITRE DE DOCTEUR EN MÉDECINE
DIPLOME D'ÉTAT

Hélène DUHEM

[Données à caractère personnel]

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TITLE :

**Improving Post-Cardiac Arrest Cerebral Perfusion Pressure by Elevating the Head and
Thorax**

AUTHORS :

Hélène Duhem^a, Johanna C Moore^{b,c}, Carolina Rojas-Salvador^b, Bayert Salverda^c, Michael Lick^c, Paul Pepe^{d,e}, Jose Labarere^a, Guillaume Debaty^a, Keith G Lurie^{b,c}

^a University Grenoble Alps/CNRS/CHU de Grenoble Alpes/TIMC-IMAG UMR 5525, Grenoble, France

^b Department of Emergency Medicine, Hennepin Healthcare, Minneapolis, MN, USA.

^c Hennepin Healthcare Research Institute, Minneapolis, MN, USA.

^d Dallas County Fire Rescue, Dallas, TX, United States

^e Palm Beach County Fire Rescue, West Palm Beach, FL and Broward Sheriff's Office, Fire Rescue Department Fort Lauderdale, FL, United States

KEYWORDS

Active compression-decompression CPR, Cardiac arrest, Cardiopulmonary Resuscitation, Return of spontaneous circulation, Cerebral perfusion pressure, Head Up CPR, Posture

LIST OF ABBREVIATIONS

ABG: Arterial blood gas

ACD: Active compression decompression

AoP: Aortic blood pressure

BLS: Basic life support

CA: Cardiac arrest

C-CPR: Conventional CPR

CED: Customized head and thorax elevation device

CerPP: Cerebral perfusion pressure

CorPP: Coronary perfusion pressure

CPR: Cardiopulmonary resuscitation

EHT: Elevation of the head and thorax

EtCO₂: End tidal carbon dioxide

ETT: Endotracheal tube

HHRI: Hennepin Healthcare Research Institute

HUP: Highest CED position

ICP: Intracranial pressure

ITD: Impedance threshold device

ITP: Intrathoracic pressure

MAP: Mean aortic pressure

RAP: Right atrial pressure

ROSC: Return of spontaneous circulation

rSO₂: Regional cerebral oximetry

SO₂: Transcutaneous oxygen saturation

VF: Ventricular fibrillation

RÉSUMÉ

Objectif : L'objectif de cette étude était de déterminer si la tête et le tronc doivent rester en position surélevée après le retour d'une activité circulatoire spontanée (RACS) dans un modèle porcin.

Méthode : Nous avons analysé les données originales de deux études contrôlées randomisées. Dans l'étude A, des cochons femelles de 40kg ont été anesthésiés et positionnés en décubitus dorsal, à plat. Après 7,75 minutes de fibrillation ventriculaire (FV) non traitée, les cochons ont été positionnés au niveau le plus bas sur un dispositif automatisé d'élévation de la tête et du tronc. Après 8 minutes de FV non traitée, une réanimation cardiopulmonaire (RCP) avec compression décompression active et valve d'impédance inspiratoire a été réalisée pendant 2 minutes. Les animaux ont été progressivement surélevés au niveau le plus haut du dispositif (HUP, 35° d'élévation) et la RCP poursuivie ainsi pendant 30 minutes. Les cochons ont ensuite été défibrillés. Après le RACS, la tête et le tronc ont été maintenus dans la position HUP pendant 10 minutes puis les animaux ont été randomisés en séquences de 5 minutes successives comme suit : 0°, 35°, 0°, 35° ou inversement. Dans l'étude B, après 6 minutes de FV non traitée, une RCP conventionnelle à plat a été réalisée pendant 6 minutes, après le RACS, les cochons ont été randomisés entre 0° et 35° comme dans l'étude A. Le critère de jugement principal était la pression de perfusion cérébrale (CerPP). Une analyse en MANOVA pour mesures répétées a été utilisée. Les données sont présentées comme moyenne \pm écart type et pourcentage d'augmentation par rapport à la position à plat.

Résultats : Comparée à la position à plat, la pression intracrânienne (PIC) était, en position HUP, $9,5 \pm 1,8$ mmHg ($p < 0,001$) et $8,7 \pm 2,3$ mmHg plus basse ($p < 0,001$), alors que la CerPP était $9,3 \pm 7,0$ mmHg (17%) ($p = 0,004$) et $12,5 \pm 5,9$ (18%) ($p = 0,001$) plus élevée, pour les études A et B respectivement.

Conclusion : Après le RACS, l'élévation de la tête et du tronc était associée avec des pressions de perfusion cérébrale plus élevées et avec des PIC réduites dans un modèle de cochon d'arrêt cardiaque, indépendamment de la durée de la FV et de la méthode de RCP.

ABSTRACT

Aim: The optimal head and thorax position *after* return of spontaneous circulation (ROSC) in cardiac arrest is unknown. The aim of this study was to determine whether head and thorax elevation was beneficial post-ROSC in a porcine model.

Methods: We analysed the original data from two randomized controlled studies. In study A, 40kg anesthetized female pigs were positioned supine and flat. After 7.75 minutes of untreated ventricular fibrillation (VF), pigs were elevated to the lowest customized head and thorax elevation device (CED) position. After 8 minutes of untreated VF, automated active compression decompression (ACD) plus impedance threshold device (ITD) CPR was performed for 2 minutes, then pigs were elevated to the highest CED position (HUP) over 2 minutes. After 30 minutes of HUP ACD+ITD CPR pigs were defibrillated, remained elevated for 10 minutes, and then randomized to 5-minute epochs of Flat, HUP, Flat, HUP or vice versa. Hemodynamics and cerebral oximetry were measured. In study B, after 6 minutes of untreated VF pigs received 6 minutes of conventional (C) CPR flat, and after ROSC were randomized HUP versus Flat as in Study A. The primary endpoint was cerebral perfusion pressure (CerPP). Multivariate analysis-of-variance (MANOVA) for repeated measures was used. Data were reported as mean \pm SD and percentage of increase compare to the flat position.

Results: Compared with flat position, intracranial pressure (ICP) values for HUP were 9.5 ± 1.8 mmHg ($p < 0.001$) and 8.7 ± 2.3 mmHg lower ($p < 0.001$), while CerPP values were 9.3 ± 7.0 mmHg (17%) ($p = 0.004$) and 12.5 ± 5.9 (18%) ($p = 0.001$) higher, in studies A and B, respectively.

Conclusion: In a porcine model of cardiac arrest, post-ROSC head and thorax elevation resulted in significantly higher CerPP and lower ICP values, regardless of VF duration or CPR method.

INTRODUCTION

Elevation of the head and thorax (EHT) improves clinical outcomes in critically ill patients with traumatic brain injury, heart failure, and respiratory distress [1–5]. In these conditions gravity helps to lower intracranial pressure (ICP) and improve multiple essential physiological processes including oxygenation, transpulmonary flow, and circulation [6–9].

Recent pre-clinical data have shown that gravity-assisted active compression decompression (ACD), cardiopulmonary resuscitation (CPR) with an impedance threshold device (ITD) improves cerebral perfusion pressures and neurologically-intact survival rates after cardiac arrest (CA), especially when using controlled sequential EHT [10,11]. Preliminary clinical data have shown that gravity-assisted CPR, used with a bundle of care, is safe and results in improved survival to hospital admission rates [12]. This new approach does not work with C-CPR, as forward flow is too limited [12]. However, when used with CPR techniques that augment circulation, EHT harnesses gravity to enhance draining venous blood from the brain, lowers ICP, and improves circulation to the brain, heart and other vital organs. EHT also may protect the brain from abrupt changes in ICP with each chest compression resulting in high pressure arterial and venous waves that simultaneously concuss the brain during CPR [13–17].

While recent evidence supports a clear benefit of gravity-assisted CPR during CA, the optimal position *after* return of spontaneous circulation (ROSC) remains unknown. Lower ICP and higher CerPP after ROSC may decrease reperfusion injuries in the post CA phase and thereby improve outcome [18].

Building upon recent advances with EHT during CPR, we used a porcine model of CA to test the hypothesis that EHT *after* ROSC would enhance cerebral perfusion pressure and lower ICP regardless of the duration of cardiac arrest or method of CPR.

METHODS

Study ethics

The study was approved by the Institutional Animal Care and Use Committee of the Hennepin Healthcare Research Institute (HHRI). A certified and licensed HHRI veterinarian assured that animal care and the study protocol were in compliance with the National Research Council 2011 Guidelines for the Care and Use of Laboratory Animals.

Study design and measurements

We analyzed original data from two experimental studies. Study preparation and surgical techniques were performed as previously described [11,12,17]. Female Yorkshire farm pigs weighing ~40 kg were fasted overnight, received intramuscular ketamine (1000 mg) in the holding pen, and then 5% inhaled isoflurane. Animals were placed on a customized elevation device (CED) (Figure 1), capable of elevating the head and thorax to perform CPR as previously described [19], and then intubated with a 7.5 mm cuffed endotracheal tube (ETT), connected to an anesthesia machine (Narkomed, North American Drager) and ventilated with a tidal volume of 10 mL/kg. Isoflurane was continued for anesthesia at 1%-2.5% until 3 minutes prior to induction of ventricular fibrillation (VF). End tidal carbon dioxide (EtCO₂) and transcutaneous oxygen saturation (SO₂) were measured with a CO₂SMO Plus (Novamatrix Systems). Respiratory rate and FiO₂ were titrated to keep SO₂ > 92% and EtCO₂ between 37-43 mmHg. Intravenous access was then obtained and pigs received normal saline during the preparatory phase to maintain a mean right atrial pressure (RAP) between 4 and 7 mmHg.

Figure 1a

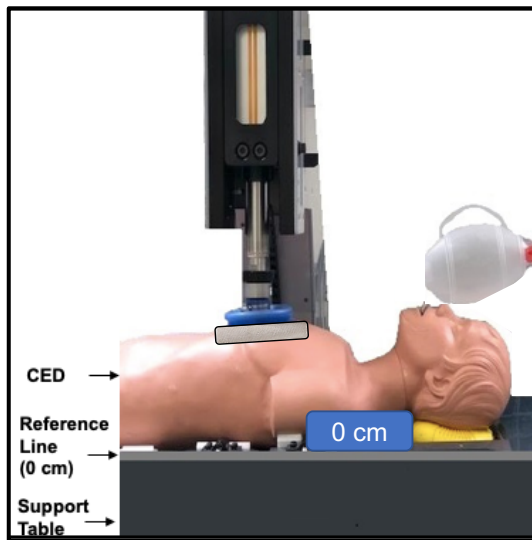


Figure 1b

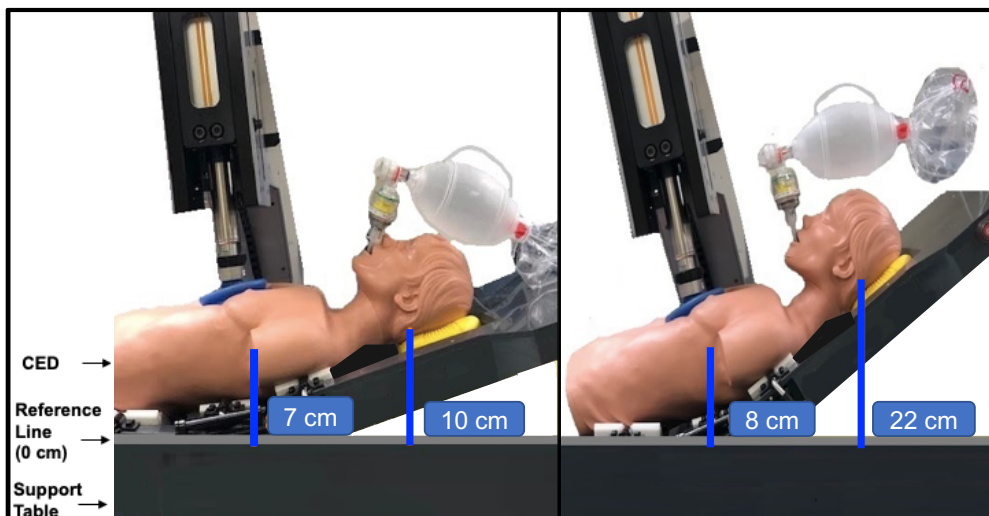


Figure 1: Customized Elevation Device

Figure 1a. Flat position. A washcloth (grey) was placed underneath the suction cup (blue) to allow for full passive chest wall recoil.

Figure 1b. Diagram of the customized elevation device (CED) in the lowest elevation* and highest elevation**

* The heart was elevated 7 cm and the midbrain 10 cm

** The heart was elevated 8 cm and the midbrain 22 cm

Animals received a 100 unit/kg bolus of intravenous heparin every hour. Temperature was continuously measured via esophageal probe and maintained between 37-38°C during the preparatory phase with a heating pad as needed. Proximal airway pressure was measured at the end of the ETT with a differential pressure transducer (TSD160C, Biopac Systems, Inc). RAP

and aortic blood pressure (AoP) were measured with micromanometer-tipped catheters (Mikro-Tip Transducer, Millar Instruments) placed in the femoral vein and artery and advanced to the right atrium and thoracic aorta at the level of the diaphragm, respectively. Catheter placement was confirmed with fluoroscopy. An intracranial bolt was placed in a burr hole in the skull to measure ICP with a micromanometer-tipped catheter. It was positioned approximately 5 mm into cerebral cortex. Regional cerebral oximetry (rSO₂) was measured with near infrared sensors (NONIN Medical, MN) on the pig's forehead. Two paediatric rSO₂ probes (SenSmart 8004CB, Nonin Medical, MN) were placed along a line between the lateral canthus of each eye and the medial portion of the bottom of the ear. For the purpose of these analyses, rSO₂ values were used from the one of two probes that showed the greatest change in rSO₂ pre-arrest to the end of the untreated VF period. Arterial blood gases (ABG) and reference blood samples were acquired through the femoral artery and analyzed using a Gem Premier 3000 device (Instrumentation Laboratory, Lexington, MA).

Data were continuously monitored during the study, including electrocardiographic monitoring, EtCO₂, ICP, RAP, AoP, intrathoracic pressure using the BioPac data acquisition system (BioPac MP150; BioPac Systems Inc) and then stored and analyzed using the BioPac Acqknowledge 4.2 software.

Experimental protocols

Study A:

As outlined in Figure 2, VF was induced via direct current from a pacing wire placed in the right ventricle under fluoroscopy. After 7.75 minutes the CED was raised completely flat to the lowest elevation position (Figure 1). After 8 minutes of untreated VF, ACD CPR was performed with an automatic piston device (Caztek Engineering, St. Paul, MN). ACD CPR was performed

at a rate of 100 compressions/minute, with a 50% duty cycle and depth of 22.5% antero-posterior chest diameter. Decompression was performed with a suction cup at an approximate force of 10 kg. An ITD (ResQPOD-16, ZOLL Medical) was attached to the endotracheal tube at the initiation of CPR. Manual positive pressure ventilation was delivered with a tidal volume of 10 mL/kg and a 30:2 compression:ventilation ratio, without oxygen to simulate basic life support (BLS) [19,20] and to prime the cardio-cerebral circuit. After 2 minutes of BLS ACD+ITD CPR in the lowest CED position, ACD+ITD CPR was performed continuously with a 10:1 compression/ventilation ratio and the head and thorax were progressively elevated at a rate of 6 cm/minute over 2 minutes to the highest level of the CED was achieved. After 30 minutes of CPR in this highest CED position, 0.25 or 0.5 mg of adrenaline was administered intravenously if the decompression phase arterial blood pressure was 20-30 mmHg, or <20 mmHg, respectively. IV amiodarone (25 mg) was administered at that time. Animals were then defibrillated with up to three 200 J biphasic shocks (X-series, ZOLL Medical). After ROSC, animals received isoflurane (1.0%). The head and thorax were maintained at the highest CED level for 10 minutes before randomization into one of the following sequences for 5-minutes epochs: Flat, head up position (HUP), Flat, HUP (group 1) or HUP, Flat, HUP, Flat (group 2). Pigs completing the protocol were included in the study. They were then euthanized with an intravenous injection of KCl.

Study B: After 6 minutes of untreated VF, automated C-CPR was performed in the supine and flat position, with the device shown in Figure 1, at 100 compressions per minute, a depth of 22% of the antero-postero-diameter, and a 50% duty cycle. Manual positive pressure ventilation was performed with room air with a 30:2 compression: ventilation ratio. After 5 minutes of CPR, medications, defibrillation, and euthanasia were delivered in a sequence and manner similar to Study A. If ROSC was not achieved, additional CPR was performed using ACD+ITD

and pigs were defibrillated again. After ROSC, animals received isoflurane as in Study A. The head and thorax were maintained flat for 10 minutes before randomization to one of two 5-minutes epoch sequences: Flat, HUP, Flat, HUP (group 1) or HUP, Flat, HUP, Flat (group 2). HUP was achieved with the device shown in Figure 1.

Study outcomes

The mean CerPP was the primary study endpoint. Secondary outcomes were mean arterial pressure, RAP, ICP, coronary perfusion pressure (CorPP), EtCO₂ and rSO₂. AoP, RAP, ICP, airway pressures, heart rate, SpO₂ and rSO₂ were measured and then averaged during the last minute of each 5-minutes epoch. CorPP was calculated as decompression phase, or diastolic, AoP minus RAP. CerPP was calculated as mean aortic pressure (MAP) minus ICP.

Sample size

We estimated that a sample size of 6 pigs would achieve 80% power to detect a mean difference of 10 mmHg with an estimated standard deviation of 2 in CerPP between the HUP and Flat ACD+ITD groups, with significance level (alpha) of 0.05, using a two-sided t-test.

Statistical analysis

Data are expressed as mean \pm standard deviation. We fit multivariate analysis-of-variance (MANOVA) with the repeated measures appearing as dependent variables and time and head position entered as main effects. A first-order interaction involving time and head position was assessed for statistical significance. A paired t-test was also performed to compare the first two 5-minutes epoch interventions. All statistical tests were two-sided, and a p-value of <0.05 was required to reject the null hypothesis. P-values for all secondary outcomes were adjusted for

multiple comparisons using the Bonferroni method. Statistical analysis was performed using the SPSS software (SPSS Statistics, Version 24.0. Armonk, NY: IBM Corp).

RESULTS

Study A

ROSC was achieved in 7 out of 9 pigs. After 29 minutes of CPR, the mean CerPP and CorPP were 36.2 ± 24.4 and 25.3 ± 29.6 mmHg for all 9 pigs. Arterial pH and lactates levels were 7.1 ± 0.1 and 7.5 ± 1.4 mmol/L. One pig had multiple broken ribs and a pneumothorax and did not achieve ROSC and one had refractory VF without ROSC. Additionally, one pig was profoundly hypotensive post-ROSC and died half way through the HUP/flat protocol.

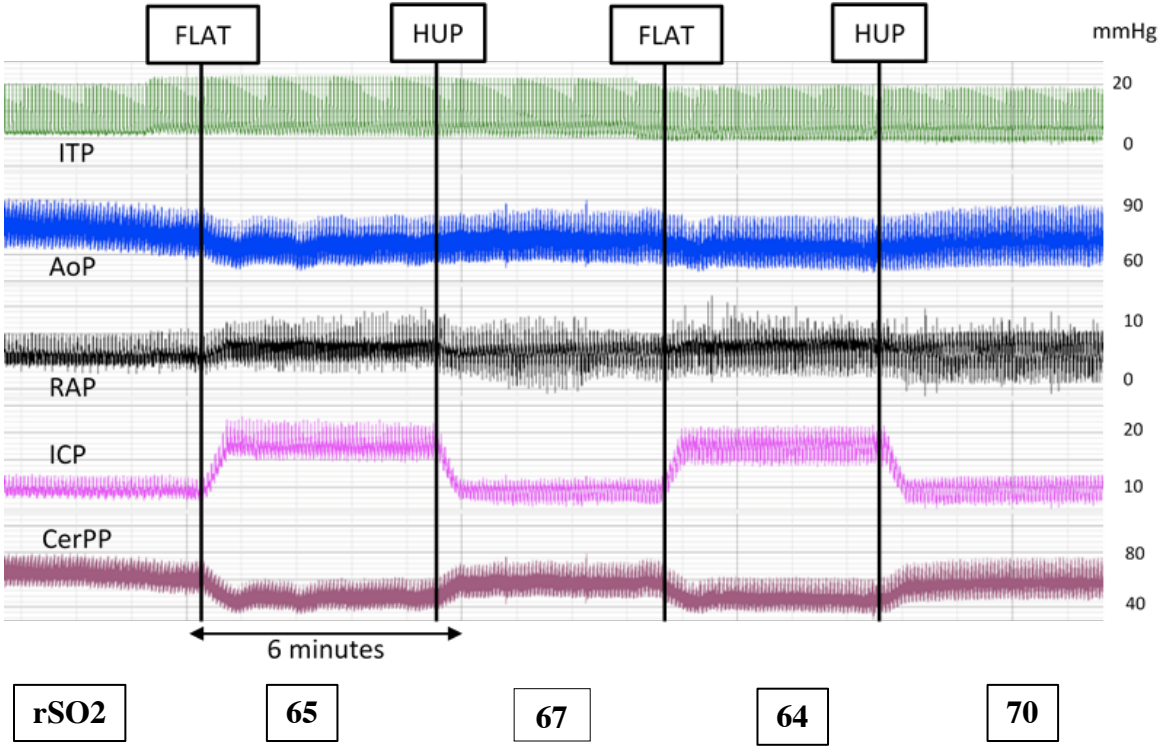


Figure 2: Representative haemodynamic tracings post-ROSC. ITP: Intrathoracic pressure, AoP: Aortic pressure, RAP: Right atrial pressure, ICP: Intracranial pressure, CerPP: Cerebral perfusion pressure.

Hemodynamic variables, as well as arterial blood gas and serum lactate values for the 6 out of 9 pigs that survived the entire protocol, are shown in Table 1. After 29 minutes of ACD+ITD HUP CPR the mean CorPP and CerPP of the 6 survivors were 40.6 ± 20.5 mmHg and 50.5 ± 15.6 mmHg, respectively. Arterial pH values were 7.1 ± 0.1 and lactate levels were 6.9 ± 1.9 mmol/L.

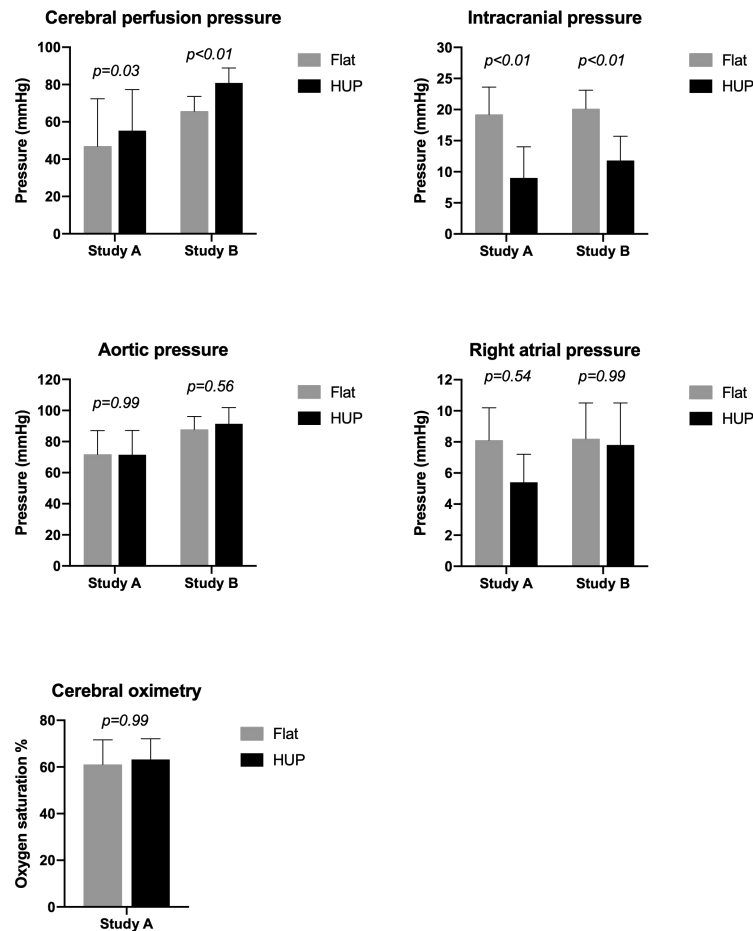


Figure 3: Main haemodynamic parameters and cerebral oximetry of HUP versus Flat for the whole post-ROSC period.

rSO₂ values were measured continuously in all 9 pigs in study A. Prior to VF induction the mean rSO₂ values were $73.9 \pm 3.1\%$. These values decreased to $57.8 \pm 4.4\%$ just prior to CPR. Over 30 minutes of CPR, rSO₂ increased to a maximal level of $63.1 \pm 5.8\%$ and were $59.1 \pm 6.4\%$ just prior to defibrillation.

After 29 minutes of CPR, rSO₂ values were 61.8±5.1% in the 6/9 pigs with a sustained ROSC versus 53.7±5.2% in the 3/9 pigs without ROSC or sustained ROSC. Arterial lactate and pH values were 7.1±0.1 and 6.9±1.9mmol/L in the 6/9 pigs with a sustained ROSC versus 7.2±.02 and 7.4±0.1mmol/L in the 3/9 pigs without ROSC or sustained ROSC, respectively.

| Protocol A | All Interventions | | | | |
|-----------------------------|-------------------|--------------------|--------------|--------------|-------|
| | At baseline | After 29min of CPR | Flat | HUP | P |
| Intrathoracic pressure | 2.0 (0.2) | -2.4 (1.3) | 1.8 (0.6) | 1.5 (0.3) | .99 |
| Mean arterial pressure | 82.4 (8.9) | 59.4 (17.2) | 71.8 (15.2) | 71.6 (15.6) | .99 |
| Mean right atrial pressure | 7.4 (1.8) | 41.0 (10.2) | 7.1 (2.0) | 4.6 (1.3) | .54 |
| Intracranial pressure | 16.5 (0.9) | 8.9 (3.8) | 18.6 (5.1) | 9.1 (5.5) | <.001 |
| Cerebral perfusion pressure | 65.9 (8.4) | 50.5 (15.6) | 53.2 (19.1) | 62.5 (19.9) | .004 |
| Coronary perfusion pressure | 66.9 (9.2) | 40.6 (20.5) | 58.9 (14.7) | 60.5 (15.1) | .99 |
| Cerebral oximetry | 74.8 (3.3) | 61.8 (5.1) | 61.0 (10.6) | 63.2 (8.9) | .99 |
| End-tidal CO ₂ | 39.4 (3.0) | 34.3 (10.9) | 22.9 (6.1) | 20.4 (3.4) | .99 |
| Oxygen saturation | 95.6 (1.4) | 82.2 (10.0) | 73.0 (26.9) | 73.9 (28.5) | .99 |
| Heart rate | 92.3 (12.1) | 100.0 (0.0) | 148.4 (28.0) | 148.4 (16.3) | .99 |
| Arterial pH | 7.46 (0.03) | 7.10 (0.08) | 7.09 (0.13) | 7.09 (0.14) | .99 |
| Arterial lactate | 0.9 (0.3) | 6.9 (1.9) | 8.3 (3.6) | 8.3 (3.5) | .99 |

| Protocol B | All Interventions | | | | |
|-----------------------------|-------------------|-------------------|--------------|--------------|-------|
| | At baseline | After 6min of CPR | Flat | HUP | P |
| Intrathoracic pressure | 1.9 (0.2) | -0.8 (0.4) | 1.8 (0.4) | 1.4 (0.7) | .99 |
| Mean arterial pressure | 84.7 (7.8) | 42.7 (6.9) | 87.7 (8.4) | 91.4 (10.4) | .56 |
| Mean right atrial pressure | 10.0 (1.5) | 30.8 (7.0) | 7.6 (2.3) | 7.1 (2.6) | .99 |
| Intracranial pressure | 19.1 (1.9) | 25.3 (4.3) | 19.7 (3.0) | 11.0 (4.3) | <.001 |
| Cerebral perfusion pressure | 65.6 (9.5) | 17.3 (4.1) | 68.0 (6.2) | 80.4 (7.3) | <.001 |
| Coronary perfusion pressure | 66.0 (8.0) | 19.3 (3.1) | 72.2 (8.2) | 75.7 (11.1) | .56 |
| End-tidal CO ₂ | 37.6 (1.7) | 4.6 (3.2) | 35.8 (7.5) | 31.4 (8.9) | .99 |
| Heart rate | 110.5 (19.6) | 100.0 (0.0) | 150.5 (32.6) | 154.0 (35.2) | .99 |

Table 1: Haemodynamic measurements at baseline, at the end of CPR and in the post-ROSC period for the two studies. Values are mean (standard deviation). P values are comparing HUP vs Flat during post-ROSC for the whole experiment. All secondary outcome's P values are adjusted for multiple comparisons using the Bonferroni method.

Key outcomes are shown in Figures 3-5 and Table 1. For all 4 epochs studied, ICP values during HUP were 9.1±5.5mmHg and 18.6±5.1mmHg Flat (p<0.001) and CerPP was 62.5±19.9mmHg

HUP and 53.2 ± 19.1 mmHg Flat ($p=0.004$). As demonstrated in Figure 2, a representative pressure tracing from one animal, changes in body position resulted in rapid changes in ICP, RAP, CerPP, and rSO₂ and no change in AoP. Randomization order did not alter the changes observed with the HUP and Flat positions. Specifically, with a MANOVA, no significant first-order interaction involving time and head position was observed for CerPP ($P=0.46$). CerPP was 9.3 ± 7.0 mmHg higher with HUP compared with Flat corresponding to a 17.4% higher CerPP levels ($p=0.004$, Supplementary Table 2) but did not differ according to time of measurement ($P=0.96$) (Figures 3 and 4 and Table 1). ICP values were 9.5 ± 1.8 mmHg lower with HUP ($P<0.001$, Supplementary Table 2).

Arterial lactate, rSO₂, RAP and pH and transcutaneous SaO₂ values were not significantly altered by the position of the head and thorax post-ROSC when comparing values across all 4 epochs.

Outcomes were generally similar when data for the first two 5-minute epoch interventions were analysed separately. Each time the head and thorax were elevated, RAP and ICP decreased, and CerPP increased, as shown in Figure 4. More specifically, for the first two 5-minute epoch interventions, CerPP increased with HUP 7.4 ± 7.3 mmHg (a relative 14% change) ($p=0.07$), and ICP decreased 9.9 ± 1.8 mmHg (a relative 52% decrease) ($p<0.001$). However, RAP values were significantly higher in the first two interventions (HUP/Flat) versus the second HUP/Flat sequence ($P=0.029$), suggesting a real decrease in RAP over time. These changes were reproducible, both in terms of the rate and magnitude of change when comparing HUP versus Flat. In addition, rSO₂ values were higher with HUP versus Flat in 5/6 pigs (for the last pig, values were equal) during epochs 1 and 2 (uncorrected $p=0.032$) but lost statistical

significance with the Bonferonni correction. Two pigs with a sustained ROSC and low SO_2 values throughout the experiment had severe lung injuries on necropsy.

Epinephrine was administered intravenously during the post-ROSC phase when the MAP was less than 55 mmHg. In the subgroup of 6 pigs with a sustained ROSC that completed the protocol, epinephrine was required in 2/6 pigs to achieve ROSC and 3/6 for at least some portion of the post-ROSC period. Use of epinephrine did not impact the changes in ICP, RAP, CerPP, MAP or rSO_2 observed with a change in body position post-ROSC (data in Supplement).

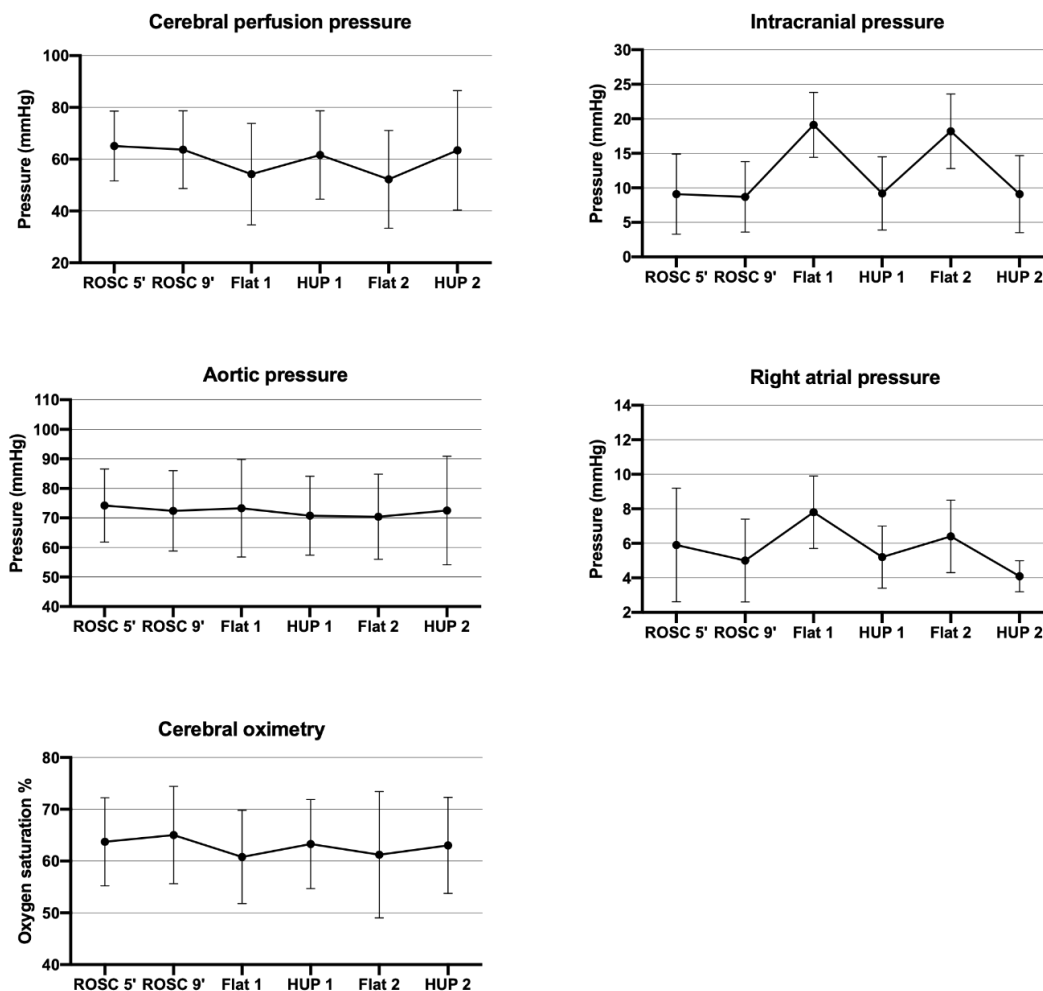


Figure 4: Evolution over time of the main haemodynamic parameters and of cerebral oximetry during the post-ROSC period in study A.

Study B

Results from Protocol B, shown in Table 1 and Figures 3 and 5, were generally similar to those observed in Protocol A. ROSC was achieved in a total of 5/6 pigs after 6 minutes of untreated VF and 6 minutes of standard CPR. Additional CPR with ACD+ITD was needed in 1/6 pigs for achieving ROSC.

The CerPP, CorPP, and other key hemodynamic variables after 6 minutes of standard CPR and prior to defibrillation are shown in Table 1. After 6 minutes of CPR, the mean CorPP and CerPP were 19.3 ± 3.1 mmHg and 17.3 ± 4.1 mmHg, respectively. Unfortunately, rSO₂ values could not be obtained as part of Protocol B as sensors with adhesive were not available at the time of the experiments.

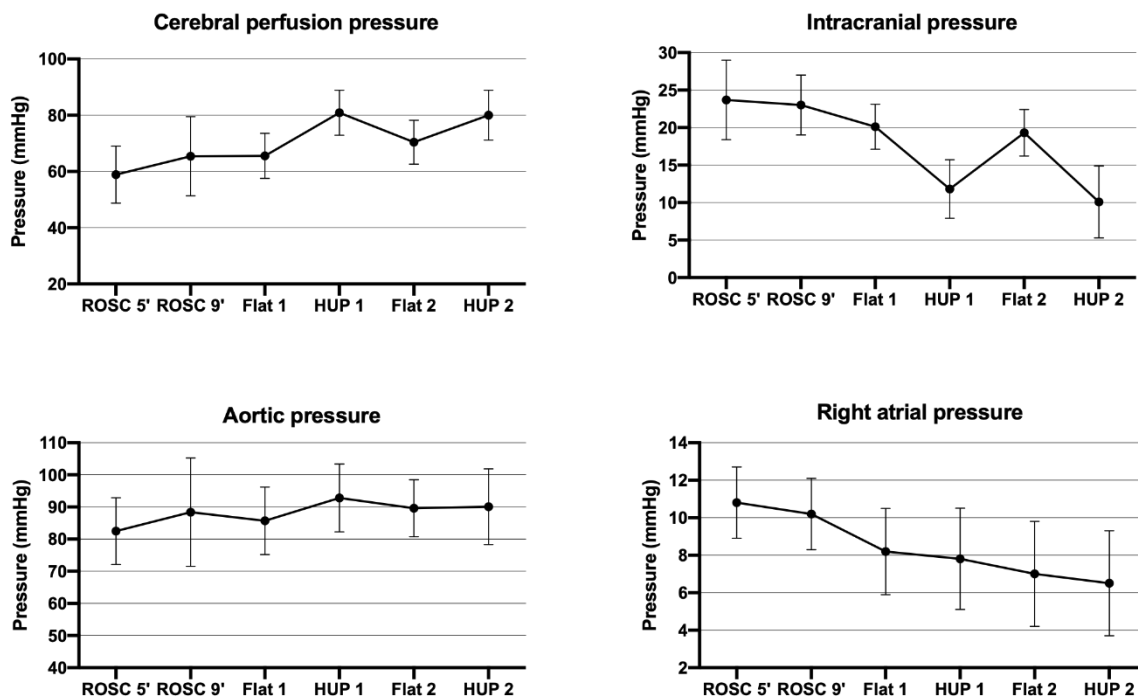


Figure 5: Evolution over time of the main haemodynamic parameters and of cerebral oximetry during the post-ROSC period in study B.

Key outcomes are shown in Figures 3 – 5 and table 1. For all 4 epochs studied ICP values during HUP were 11.0 ± 4.3 mmHg and 19.7 ± 3.0 mmHg Flat ($p < 0.001$) and CerPP was 80.4 ± 7.3 mmHg HUP and 68.0 ± 6.2 mmHg Flat ($p = 0.001$). In MANOVA, no significant first-order interaction involving time and head position was observed for CerPP ($p = 0.18$). CerPP was 12.5 ± 5.9 mmHg higher with HUP compared with Flat, corresponding to 18.3% higher CerPP levels ($p < 0.001$, Supplementary table 3) but did not differ according to time ($P = 0.96$) (Figure 3 – 5 and Table 1). ICP values were 8.7 ± 2.3 mmHg lower with HUP ($p < 0.001$).

Outcomes were similar when the data for the first two 5-minutes epoch interventions were analysed separately. Each time the head and thorax were elevated RAP and ICP decreased and CerPP increased, as shown in Figure 5. More specifically, for the first two 5-minutes epoch interventions, CerPP increased with HUP 15.3 ± 6.2 mmHg (a relative 23.4% increase) ($p = 0.003$) and ICP decreased 8.3 ± 2.4 mmHg (a relative 41% decrease) ($p < 0.01$). In contrast to Protocol A results, there were no differences in RAP depending on the time of intervention.

Epinephrine was required in 4/6 pigs to achieve ROSC and 1/6 for at least some portion of the post-ROSC period.

DISCUSSION

The goal of this study was to use an animal model of cardiac arrest to determine if elevation of the head and thorax after ROSC would be of hemodynamic benefit when compared with the conventional approach of leaving the body in the horizontal plane. Using a randomized controlled study design, we demonstrated that each time the head and thorax were elevated CerPP increased and ICP decreased, with two different methods of CPR and two different durations of untreated VF. MAP, on average, remained constant with a change in position.

These new findings are supportive of a modest elevation the head and thorax *after* ROSC to lower ICP and improve CerPP, as long as the MAP is stable. The findings were consistent, for ACD+ITD CPR in the HUP position during resuscitation for 30 minutes prior to defibrillation and for C-CPR in the flat position for a shorter duration of VF and CPR. The overall observations are similar to what has been reported for the routine treatment of traumatic brain injury [21].

These investigations build upon recent studies demonstrating that controlled sequential elevation of the head and thorax during ACD+ITD CPR was synergistic, with near normalization of CerPP values after prolonged CPR and a 6-fold increase in neurologically-intact survival in animals [19]. The natural question that arose from those studies was, should the head and heart remain elevated post ROSC? Our results demonstrate that CerPP increased by nearly 20% after ROSC after 30 minutes of ACD+ITD HUP CPR by maintaining HUP versus lowering the pigs to a flat position. The impact of gravity was profound, immediate, reproducible, and may be of significant clinical benefit. Each time the head and thorax were elevated 22cm and 10cm, respectively, from the horizontal plane, ICP decreased on average 10mmHg. In the setting of potential brain injury, a 10-mmHg reduction in ICP may be clinically relevant [22]. Experimental models of cardiac arrest support the pathophysiological hypothesis of a worsening in vital organs during the reperfusion phase and extend over the first hours. Improving cerebral perfusion in the early post-ROSC phase could be of critical importance to limit reperfusion injuries.

This study was not designed to compare ACD+ITD CPR HUP versus C-CPR flat. However, it is noteworthy that after 8 minutes of untreated VF and 30 minutes of ACD+ITD HUP CPR the CerPP was 50.5 ± 15.6 mmHg and only 17.3 ± 4.1 mmHg after 6 minutes of untreated VF and 6

minutes of C-CPR, consistently with previous reports [12,16]. Interestingly, post-ROSC CerPP values were approximately 20mmHg higher both HUP and flat after C-CPR in comparison with ACD+ITD HUP CPR. Further, in contrast to the ACD+ITD HUP CPR treatment group, there was no change in RAP with a change in body position post-ROSC in the C-CPR group. We speculate that these differences may reflect differences in autoregulation as well vascular and cardiac compliance as a result of the different CPR methods (e.g., more post-ROSC cerebral hyperaemia with C-CPR).

Although no adverse effects of HUP were observed in this study, there is a theoretical harm associated with HUP in the setting of significant hypotension, especially if the head is elevated too rapidly or too high. In patients with traumatic brain injury, 30° HUP is routinely used in the intensive care unit as it provides significant clinical benefit and improves clinical outcomes, but only when the MAP with HUP is adequate to pump blood ‘uphill’ [21].

This study has some limitations. First brain blood flow was not directly measured, nor were short term or long-term clinical outcomes. However, prior studies on head and thorax elevation during CPR have shown a close relationship between blood flow, CerPP and coronary perfusion pressure [11, 23]. Our finding that post-ROSC HUP results in higher CerPP and lower ICP is therefore promising. Second, our study was powered to test the primary hypothesis but some of the differences in the secondary endpoints did not achieve statistical significance. The data demonstrating a rise in rSO₂ when the head and thorax were elevated is intriguing but the study was underpowered to demonstrate this observation conclusively. This was likely due to the relatively limited effective sample size and inter-individual variability. Third, we used healthy pigs, without any co-morbidities commonly seen in human cardiac arrest.

CONCLUSION

The results from this animal study demonstrate that head and thorax elevation post-ROSC significantly increases CerPP and lowers ICP. These preclinical data are a first step towards implementation of a new post-resuscitation intervention that could be synergistic with other head and thorax elevation manoeuvres during CPR and after ROSC to improve neurological survival, by decreasing the likelihood of brain injury.

THÈSE SOUTENUE PAR : HÉLÈNE DUHEM

**L'ÉLEVATION DE LA TÊTE ET DU TRONC AMÉLIORE LA PRESSION DE
PERFUSION CÉRÉBRALE EN POST-ARRÊT CARDIAQUE**

CONCLUSION :

L'objectif de notre étude était de déterminer l'effet de la surélévation de la tête et du tronc après retour à une activité circulatoire spontanée (RACS) dans un modèle porcin d'arrêt cardiaque par fibrillation ventriculaire pris en charge avec deux techniques différentes de réanimation cardiopulmonaire (RCP). Le critère de jugement principal était la pression de perfusion cérébrale (CerPP) après RACS.

Notre principal résultat est que la CerPP post-RACS était significativement plus élevée en cas de surélévation de la tête et du tronc post-RACS qu'en cas de maintien en position à plat stricte (+ 17%, $p=0.004$ et +18%, $p=0.001$ respectivement dans les deux techniques de RCP). Par ailleurs, les pressions intracrâniennes étaient également réduites par la surélévation de la tête et du tronc. Ces bénéfices étaient indépendants de la durée de la fibrillation ventriculaire et de la méthode de RCP.

Les résultats de cette étude animale pré-clinique permettent d'envisager une nouvelle prise en charge des patients post arrêt cardiaque, potentiellement en synergie avec d'autres manœuvres d'élévation de la tête et du tronc en per-RCP, l'objectif étant d'améliorer la survie et le pronostic neurologique en diminuant la survenue de lésions cérébrales.

VU ET PERMIS D'IMPRIMER

Grenoble, le : 3/09/10

LE DOYEN



Pr. Patrice MORAND
Président
et par délégation
Le Doyen de la Faculté de Médecine
Pr. Patrice MORAND

LE PRÉSIDENT DE LA THÈSE



Pr. Gérald VANZETTO

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Supplementary material

| Protocol A | | | | | | | | |
|--|-------------|--------|--------------------|--------|-------|--------|-------|--------|
| | At Baseline | | After 30min of CPR | | Flat | | HUP | |
| Intrathoracic pressure Epinephrine | 2.6 | (0.9) | -2.3 | (0.8) | 1.5 | (0.8) | 1.6 | (0.2) |
| Intrathoracic pressure No Epinephrine | 2.0 | (0.3) | -2.8 | (1.5) | 1.8 | (0.3) | 1.4 | (0.3) |
| Mean arterial pressure Epinephrine | 78.7 | (10.2) | 40.8 | (13.1) | 54.4 | (21.5) | 53.2 | (19.5) |
| Mean arterial pressure No Epinephrine | 84.4 | (4.8) | 73.5 | (6.4) | 78.8 | (13.8) | 80.8 | (12.0) |
| Mean right atrial pressure Epinephrine | 6.7 | (1.7) | 36.3 | (16.0) | 7.9 | (2.8) | 4.8 | (1.7) |
| Mean right atrial pressure No Epinephrine | 8.1 | (1.2) | 39.4 | (5.2) | 7.0 | (0.1) | 5.2 | (1.1) |
| Intracranial pressure Epinephrine | 16.2 | (0.8) | 6.0 | (1.5) | 20.1 | (5.9) | 9.7 | (6.6) |
| Intracranial pressure No Epinephrine | 17.1 | (0.6) | 12.3 | (2.1) | 17.1 | (0.1) | 8.1 | (0.4) |
| Cerebral perfusion pressure Epinephrine | 62.5 | (10.1) | 34.8 | (14.4) | 34.3 | (25.0) | 43.5 | (23.2) |
| Cerebral perfusion pressure No Epinephrine | 67.2 | (4.2) | 61.2 | (8.4) | 61.7 | (13.7) | 72.8 | (12.4) |
| Coronary perfusion pressure Epinephrine | 64.1 | (10.7) | 21.0 | (8.2) | 46.2 | (21.9) | 42.8 | (17.2) |
| Coronary perfusion pressure No Epinephrine | 68.2 | (4.7) | 59.3 | (7.3) | 72.2 | (13.9) | 70.1 | (11.8) |
| Cerebral oximetry Epinephrine | 76.0 | (3.4) | 57.8 | (6.6) | 51.5 | (7.7) | 55.5 | (9.2) |
| Cerebral oximetry No Epinephrine | 72.3 | (0.9) | 63.7 | (2.6) | 69.2 | (4.1) | 68.7 | (2.2) |
| End-tidal CO ₂ Epinephrine | 36.3 | (7.7) | 23.0 | (4.0) | 12.6 | (7.5) | 16.1 | (7.0) |
| End-tidal CO ₂ No Epinephrine | 38.5 | (1.7) | 44.7 | (0.8) | 29.0 | (0.6) | 20.9 | (3.6) |
| Heart rate Epinephrine | 94.9 | (14.9) | 100.0 | (0.0) | 121.4 | (59.1) | 129.6 | (45.8) |
| Heart rate No Epinephrine | 81.8 | (5.4) | 100.0 | (0.0) | 146.6 | (14.9) | 141.8 | (15.7) |
| Arterial pH Epinephrine | 7.46 | (0.02) | 7.11 | (0.08) | 6.96 | (0.03) | 6.96 | (0.01) |
| Arterial pH No Epinephrine | 7.46 | (0.03) | 7.11 | (0.00) | 7.23 | (0.04) | 7.22 | (0.02) |
| Arterial lactate Epinephrine | 0.9 | (0.2) | 7.5 | (1.6) | 11.8 | (1.0) | 10.0 | (2.6) |
| Arterial lactate No Epinephrine | 1.0 | (0.4) | 5.5 | (0.0) | 4.8 | (0.3) | 4.7 | (0.4) |

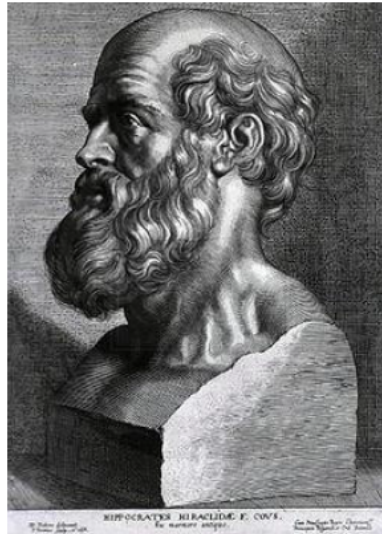
Supplementary Table 1: Comparison of the main haemodynamic parameters between the pigs that received epinephrine and the pigs that didn't in study A and B.

| Protocol A | All Interventions | | | | |
|----------------------------------|--------------------------|------------------------|--------|----------|-----------|
| | Absolute Value | Mean difference | | % | P* |
| Intrathoracic pressure Flat | 1.8 | | | | |
| Intrathoracic pressure HUP | 1.5 | -0.3 | (0.7) | -18.6 | .99 |
| Mean arterial pressure Flat | 71.8 | | | | |
| Mean arterial pressure HUP | 71.6 | -0.2 | (6.9) | -0.3 | .99 |
| Mean right atrial pressure Flat | 7.1 | | | | |
| Mean right atrial pressure HUP | 4.6 | -2.4 | (2.3) | -34.4 | .54 |
| Intracranial pressure Flat | 18.6 | | | | |
| Intracranial pressure HUP | 9.1 | -9.5 | (1.8) | -51.0 | <.001 |
| Cerebral perfusion pressure Flat | 53.2 | | | | |
| Cerebral perfusion pressure HUP | 62.5 | 9.3 | (7.0) | 17.4 | .004 |
| Coronary perfusion pressure Flat | 58.9 | | | | |
| Coronary perfusion pressure HUP | 60.5 | 1.6 | (6.9) | 2.6 | .99 |
| Cerebral oximetry Flat | 61.0 | | | | |
| Cerebral oximetry HUP | 63.2 | 2.2 | (4.3) | 3.6 | .99 |
| End-tidal CO ₂ Flat | 22.9 | | | | |
| End-tidal CO ₂ HUP | 20.4 | -2.5 | (8.9) | -11.1 | .99 |
| Heart rate Flat | 148.4 | | | | |
| Heart rate HUP | 148.4 | 0.0 | (17.3) | 0.0 | .99 |
| Arterial pH Flat | 7.09 | | | | |
| Arterial pH HUP | 7.09 | 0.01 | (0.02) | -0.01 | .99 |
| Arterial lactate Flat | 8.3 | | | | |
| Arterial lactate HUP | 8.3 | 0.0 | (0.4) | -0.01 | .99 |

Supplementary Table 2: Difference in absolute values shown as mean (standard deviation) and percentage change between HUP and Flat position for the main haemodynamic parameters in study A.

| Protocol B | All Interventions | | | | |
|----------------------------------|-------------------|------------------|--------|-------|-------|
| | Absolute Values | Mean differences | | % | P |
| Intrathoracic pressure FLAT | 1.8 | -0.4 | (0.9) | -26.5 | .99 |
| Intrathoracic pressure HUP | 1.4 | | | | |
| Mean arterial pressure FLAT | 87.7 | 3.7 | (6.8) | 4.3 | .56 |
| Mean arterial pressure HUP | 91.4 | | | | |
| Mean right atrial pressure FLAT | 7.6 | -0.4 | (1.9) | -5.6 | .99 |
| Mean right atrial pressure HUP | 7.1 | | | | |
| Intracranial pressure FLAT | 19.7 | -8.7 | (2.3) | -44.3 | <.001 |
| Intracranial pressure HUP | 11.0 | | | | |
| Cerebral perfusion pressure FLAT | 68.0 | 12.5 | (5.9) | 18.3 | <.001 |
| Cerebral perfusion pressure HUP | 80.4 | | | | |
| Coronary perfusion pressure FLAT | 72.2 | 3.5 | (6.7) | 4.9 | .56 |
| Coronary perfusion pressure HUP | 75.7 | | | | |
| End-tidal CO ₂ FLAT | 35.8 | -4.5 | (11.1) | -12.4 | .99 |
| End-tidal CO ₂ HUP | 31.4 | | | | |
| Heart rate FLAT | 150.5 | 3.5 | (8.1) | 2.3 | .99 |
| Heart rate HUP | 154.0 | | | | |

Supplementary Table 3: Difference in absolute values shown as mean (standard deviation) and percentage change between HUP and Flat position for the main haemodynamic parameters in study B.



SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.

Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.