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Head and thorax elevation during active compression decompression cardiopulmonary resuscitation with an impedance threshold device improves cerebral perfusion in a swine model of prolonged cardiac arrest

A Thesis

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BY

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FOR THE DEGREE OF
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Advisor: Michelle H Biros, MD

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ABSTRACT

Aim: To compare brain blood flow between the head up (HUP) and supine (SUP) body positions during prolonged cardiopulmonary resuscitation (CPR), using active compression-decompression (ACD) CPR and an impedance threshold device (ITD) in a swine model of cardiac arrest.

Methods: After 8 minutes of untreated ventricular fibrillation (VF), followed by 2 minutes of ACD-CPR+ITD in the SUP position, pigs were randomized to 18 minutes of ACD-CPR+ITD in either 30° HUP or SUP position. Microspheres were injected before VF, and then 5 and 15 minutes after study start.

Results: Brain Blood flow (ml/min/g, mean \pm SD) after 15 minutes of CPR was 0.42 ± 0.05 for HUP (n=8) and 0.21 ± 0.04 for SUP (n=10), ($p < 0.01$). The HUP group also had lower intracranial pressures and higher cerebral perfusion pressures.

Conclusions: Brain blood flow in the HUP position was higher in than the SUP position. This provides pre-clinical support to proceed with a clinical evaluation of head up CPR in humans.

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1. Introduction

The head up (HUP) position during cardiopulmonary resuscitation (CPR), either with a whole body tilt, or elevation of just the head and thorax, has been described as a novel approach to increase cerebral perfusion pressure when compared with CPR in the supine position (SUP) in swine models of cardiac arrest.¹⁻⁴ Additionally, higher cerebral blood flow has been described with the head up whole body tilt versus whole body flat after 5 minutes of mechanical CPR with an impedance threshold device (ITD).¹ However, most clinical CPR efforts last a minimum of 15-20 minutes.⁵ This poses a potential risk of HUP CPR when using a whole-body tilt approach since blood flow to the brain would be anticipated to decrease over time secondary to pooling of blood in the lower extremities. This physiology is known from the use of head-up tilt-table testing to induce syncope.^{6,7} To reduce this potential risk, we previously developed a HUP device that elevates just the head and upper thorax and demonstrated higher cerebral perfusion pressure (CerPP) in the HUP position over a period of 22 minutes with active compression decompression (ACD) + ITD CPR.² With this device the head is elevated about 25 cm and the heart about 5 cm relative to the rest of the body. Building on these studies, in the current investigation we tested the hypothesis cerebral blood flow would be higher with HUP versus SUP during prolonged ACD CPR + ITD.² The primary endpoint of this study was brain blood flow after 15 minutes of CPR in a porcine model of ventricular fibrillation (VF) cardiac arrest. Secondary endpoints included brain blood flow after 5 minutes of CPR, systemic hemodynamics including intracranial pressure, and end tidal CO₂ (ETCO₂) for up to 20 minutes of CPR.

2. Materials and Methods

Study Ethics

This study was approved by the Institutional Animal Care and Use Committee of the Minneapolis Medical Research Foundation (MMRF). Animal care was compliant with the National Research Council's 1996 Guidelines for the Care and Use of Laboratory Animals, and a certified and licensed veterinarian assured protocol performance was in compliance with these guidelines.

Study Design and Measurements

Techniques describing the surgical preparation, anesthesia, microsphere techniques, and data monitoring and recording used in this study have been previously described.^{1,2} Female Yorkshire farm pigs weighing 36-44 kg were fasted overnight after acclimatizing in the animal care facility for three days. Intramuscular ketamine (10 mL of 100 mg/mL) was administered in the holding pen. Animals were transferred to the surgical suite where they were treated with inhaled isoflurane at 1% to 2.5%, then intubated with a 7.5 French endotracheal tube and ventilation was performed using a ventilator (Narkomed, North American Dräger, Telford, PA) with tidal volume 10 mL/kg. ETCO₂ and oxygen saturation were recorded with a CO₂SMO Plus® (Novamatrix Systems, Wallingford, CT). The respiratory rate and FiO₂ were adjusted to keep oxygen saturation above 92% and ETCO₂ between 37 and 43 mmHg. Intravenous access was obtained.. All animals received a normal saline bolus of 1000 ml during preparatory phase to maintain the mean right atrial pressure between 4 and 7 mmHg.

Temperature was monitored with an esophageal probe, and maintained between 36.5 and 38.5°C. Proximal airway pressure, a surrogate for intrathoracic pressure, was measured with a differential pressure transducer (TSD160C, BioPac Systems, Inc., Goleta, CA).⁸ Central aortic blood pressures were measured with a micromanometer-tipped catheter (Mikro-Tip Transducer, Millar Instruments, Houston, TX) placed through the right femoral artery into the descending thoracic aorta to the level of the diaphragm. A similar Millar catheter was placed in the right femoral vein and advanced to the right atrium (RA) to measure right atrial pressure. A pigtail catheter was positioned in the left ventricle (LV) under fluoroscopic guidance via the left femoral artery. This was used for microsphere injections (see below). The position of all vascular micromanometer-tipped catheters was confirmed by fluoroscopy before induction of VF. Intracranial pressure (ICP) was measured via a burr hole in the skull, and insertion of a Millar catheter into brain as previously described.¹ All animals received a 100 units/kg bolus of heparin intravenously every hour.

Data, including electrocardiographic monitoring, aortic pressure, RA pressure, LV pressure, ICP, and ETCO₂, was continuously recorded using the BioPac computer system (BioPac; BioPac Systems Inc., Goleta CA). All data was stored using the BioPac computer data analysis program. Arterial blood gases (ABG) were acquired through the femoral artery catheter and analyzed with a Gem Premier 3000 device (Instrumentation Laboratory, Lexington, MA).

When the preparatory phase was complete, isoflurane was discontinued, and after 3 minutes VF was induced with delivery of direct electrical current from a pacing wire placed in the right ventricle. ACD CPR + ITD was performed with an automatic piston

device (Pneumatic Compression Controller; Ambu International, Glostrup, Denmark) as described previously.^{2,9} ACD CPR was performed at a rate of 80 compressions/min, with a 50% duty cycle and depth of 22.5% of antero-posterior chest diameter, and the chest was pulled upwards after each compression with a suction cup on the skin at a decompression force of approximately 10 kg. An ITD, (ResQPOD-16, Zoll Medical, Minneapolis, MN) was placed at the end of the endotracheal tube. The HUP CPR device used elevated just the head and shoulders and upper thorax 30°, as previously described.² While transitioning from supine to the HUP CPR was performed in an uninterrupted manner. During CPR, positive pressure ventilation was delivered with oxygen, titrated to a SpO₂ of ≥92%, with a tidal volume of 10 mL/kg. If the animal was noted to gasp during the resuscitation, time at first gasp was recorded. Succinylcholine was administered at a dose of 3mg (0.075/kg) to inhibit gasping after the third gasp.

Microsphere protocol

Blood flow to the heart, brain, kidney, and liver was measured with microsphere injection into the LV under stable baseline conditions 5 min prior to the induction of VF. Neutron activated microspheres (STERISpheres™, BioPAL™: BioPhysics Assay Laboratory, Worcester, MA) 15 microns in diameter containing Samarium (152Sm), Ytterbium (175Yb) and Lutetium (177Lu) were used.

The number of microspheres needed per injection (μ) was determined as follows: $\mu = 1.2 \times 10^6 + ((1.9 \times 10^5) \times \omega)$ where μ is the number of microspheres and ω is the weight of the pig. Then, the volume of microspheres injected at baseline was calculated as follows

$$\text{Volume} = \frac{\mu}{((5 \times 10^8)/20)}.$$

A higher number of microspheres was injected during CPR compared to baseline to account for the low flow state of CPR.¹⁰ Immediately after microsphere injections, reference blood samples were withdrawn continuously over 4 minutes from the descending aorta at a collection rate of 10 ml min⁻¹.^{1, 10}

At the end of the study, animals were sacrificed and then tissue samples from the brain (posterior [pons portion of the brain-stem, hippocampus], left and right cortex), the heart (free left ventricle wall, apex, papillary muscle, and septum), the kidney (cortex), and the liver were obtained. Tissue and blood samples were desiccated and sent to the reference BioPhysics Assay Laboratory for analysis.¹⁰

Organ blood flow could then be calculated in the reference laboratory after performing neutron activation and calculating how many microspheres are in the tissue and reference blood samples by using the following equation:

$$\text{Organ flow (mL/min)} = \frac{\text{Known organ flow (mL/min)} \times \text{No. of microspheres in organ with unknown flow}}{\text{No. of microspheres in organ with known flow}}$$

Here, the known organ flows were from the reference blood samples, and the number of microspheres in the organ with unknown flow calculated in each organ by neutron activation. Therefore, the blood flow to each organ could then be calculated in mL/mg/g tissue.¹¹

Experimental Protocol

The experimental protocol is outlined in Figure 1. After 8 minutes of untreated VF, ACD CPR + ITD was performed with a 30:2 compression: ventilation ratio, and positive pressure ventilation with room air was provided while all pigs were in the SUP to simulate basic life support (BLS).¹² After 2 minutes of CPR, animals were randomized either HUP CPR or SUP CPR and continuous asynchronous ACD CPR+ITD CPR was continued for 18 minutes with a 10:1 compression: ventilation ratio to simulate advanced life support (ALS).¹³ Randomization was performed with block randomization in groups of 4 prior to the study start. All members of the research study team were unaware of the randomization until 1 minute into CPR, when an unmarked envelope was opened with the randomized body position. . Microsphere injections were performed after 5 and 15 minutes of CPR and 20 ml of blood were collected over 4 minutes (see above). After 19 total minutes of CPR, 0.5 mg of adrenaline was administered intravenously followed by 25 mg of amiodarone. One minute later, pigs were defibrillated with up to three 200 J biphasic shocks (X-series, Zoll Medical, Chelmsford MA). If return of spontaneous circulation (ROSC) was not obtained, CPR was resumed and a shock was delivered every 2 minutes together with 0.5 mg of adrenaline every 4 minutes. If spontaneous circulation was not restored after a total of 3 shocks, CPR was stopped. If ROSC was obtained, animals were euthanized with an intravenous injection of KCl 20 minutes later.

2.3 Data Analysis

The sample size calculation was based on previous studies. We estimated the brain blood flow would be approximately 25% higher in the HUP ACD CPR + ITD

group.¹ Assuming an alpha level of 0.05 and 80% power, 11 animals were needed per group to detect an 80% difference.

Hemodynamic data were analyzed at baseline just prior to the microsphere injection, and then after 5, 15, 19, and 20 minutes of CPR. Airway, aortic, right atrial, and intracranial pressures measurements were made from 3 sequential compression-decompression cycles between positive pressure breaths. These values were averaged for each of the compression-decompression cycle measurements for each time point in each animal study. The coronary perfusion pressure (CPP) was calculated as the difference between the decompression phase aortic and right atrial pressures, and represents the aortic to right atrial pressure gradient during the relaxation phase of cardiopulmonary resuscitation. As with previous studies, our target CPP during CPR was at a minimum of 15 mmHg since CPP of at least 15-20 correlates with ROSC in animals and humans, and is a marker of high quality CPR.^{14, 15} In addition, when calculating the mean CerPP we used the mathematical difference between aortic and intracranial pressure over a 15 second interval at each time point.

Data are expressed as mean \pm standard deviation (SD). Statistical analysis was performed using SPSS 21 (IBM Corporation, USA). An unpaired Student's t-test was used to determine significance between HUP and SUP for the primary outcome of blood flow at 15 minutes, and also for secondary hemodynamic outcomes. A Fisher's exact test was used to compare ROSC rate. All statistical tests were two-sided, and a p value of less than 0.05 was required to reject the null hypothesis. Unadjusted p values are presented for the secondary analyses. Studies where technical difficulties were encountered due to either dislodgment of the left ventricular catheter, or inability to

compress the chest 22.5% of the antero-posterior diameter, did not meet study inclusion criteria and were therefore not included in the results.

3. Results

Eighteen pigs weighing 39.5 ± 8.2 kg randomized to CPR in HUP (n=8) or SUP (n=10) met study inclusion criteria. Results showing the blood flow to the brain, heart, kidney, and liver before VF and then 5 and 15 minutes after the start of CPR are provided in Table 1 and Figure 2. The blood flow to the brain after 15 minutes of CPR, the primary study endpoint, was higher in the HUP group at 0.42 ± 0.05 ml/min/g versus 0.21 ± 0.04 in the SUP group, respectively ($p < 0.01$). When compared with pre-VF values, blood flow to the brain after 15 minutes of CPR was 25% of baseline in the SUP versus 50% in the HUP. Regional brain blood flow before cardiac arrest and after 5 and 15 minutes of HUP and SUP CPR are shown in Figure 2.

Key hemodynamic variables for the two treatment groups are shown in Table 2. Pigs treated with HUP CPR had significantly lower intracranial pressure (ICP) and higher CerPP after 5, 15, 19, and 20 minutes of ACD CPR + ITD versus SUP. One minute after adrenaline, the CerPP values remained higher in the HUP group. The time to first gasp was 282 ± 51 seconds in the HUP group versus 437 ± 185 seconds in the SUP group ($p = 0.045$).

The ROSC rate and ABG values were similar between the two treatment groups. With HUP CPR 5/8 pigs achieved ROSC versus 3/10 in the SUP group ($p = 0.34$). The arterial blood gases were similar at baseline and in the animals that had ROSC, as shown in Table 3.

Discussion

The evaluation of any new approach in the treatment of patients in cardiac arrest requires preclinical proof of safety and effectiveness. This translational process is ongoing in regard to the potential benefits of elevating the head and thorax during CPR. Building upon recent studies demonstrating proof-of-concept of HUP CPR in multiple animal laboratories,^{1, 2, 16} the current study was designed to determine if elevation of the head and thorax was effective, safe, and consistent with previous work during a prolonged CPR effort in pigs. The experimental protocol lasted 20 minutes, the average duration of many CPR efforts. Two questions were assessed in this protocol: are the beneficial physiological effects of HUP CPR sustained over time and can this new approach be safely applied in a prolonged resuscitation? ACD CPR + ITD was used based upon prior animal studies demonstrating that conventional CPR did not provide enough forward flow to pump blood “uphill” to the brain during HUP CPR, whereas a longer-term hemodynamic benefit was observed with HUP ACD+ITD CPR.²

These results show for the first time that blood flow can be maintained at levels of 50% of baseline values in this animal model of prolonged CPR. By contrast, ACD CPR + ITD in the flat position provided only 25% of normal brain flow after 8 minutes of untreated VF and 15 minutes of CPR. The microsphere blood flow studies parallel the hemodynamics findings of higher CerPP throughout the resuscitation effort, and results from the current study confirmed prior hemodynamic studies. Two hemodynamic factors contributed to the higher and sustained CerPP in the HUP group; a gradual reduction in ICP in the HUP group over time and a sustained mean aortic pressure. By comparison, ICP remained relatively high and constant and aortic pressure relative low and constant in

the SUP group. An earlier study demonstrated a similar improvement in CerPP, but such measurements are calculated by the difference between the arterial driving pressures and the resistance generated by ICP. This calculated CerPP has the potential to overestimate the actual delivery of blood to brain tissues as the arterial pressure cannot be easily measured in the cerebral arteries, due to technical limitations.² This limitation of the previous work highlighted the need to also demonstrate increased brain blood flow with HUP CPR in a prolonged CPR effort as shown in the current study.

Blood flow to the brain is needed to preserve and maintain brain function. Gasping is also dependent upon brain blood flow.¹⁷ Pigs treated with HUP CPR took their first spontaneous gasp earlier compared with the SUP group. This may be of clinical significance as gasping is associated with brain stem functionality and better clinical outcomes in patients in cardiac arrest. As such, time to first gasp may be a useful clinical endpoint when evaluating HUP CPR in human patients.¹⁷⁻²¹

The increase in brain blood flow and shorter time to first gasp are a direct result of HUP CPR. These observations are most likely due to the multiple effects of gravity and ACD CPR + ITD on intracranial and right heart pressures and trans-pulmonary blood flow.¹⁻³ With HUP CPR, venous blood flow to the thorax and right heart is enhanced from the brain and paravertebral plexus; this decreases ICP and increases cardiac preload.^{1-3, 22} This reduction in ICP lowers resistance to forward brain flow. The reduction in ICP and right-sided venous pressures in combination with the factor of pumping blood “uphill” with compression during HUP CPR also reduces the concussive forces that simultaneously strike the brain with each chest compression from a combination of simultaneous high arterial and venous high pressure waves. In these recent studies ACD

CPR + ITD was used to generate high enough aortic pressures to overcome the challenge of pumping arterial blood “uphill”.² Without the ITD there was less of a clinically meaningful benefit with HUP CPR.¹

Previous studies have demonstrated that ACD CPR + ITD is superior to conventional CPR in terms of blood pressure, brain flow to the heart and brain, and long-term survival with favorable neurological function.^{3, 5, 23} In this study, ACD CPR + ITD in both positions resulted in similar aortic pressures and ABGs. Right atrial pressures tended to be lower in the HUP group but these differences were not significant. The current study suggests that when ACD CPR + ITD is performed continuously, first SUP, during the transition from SUP to HUP, and then HUP for a prolonged period of time, there is no increased risk of harm.

The current study provides additional support for the concept of HUP CPR but does have some limitations. First, this study is in an animal model of VF cardiac arrest, using young healthy swine without cardiac disease. The current VF model is widely used in cardiac arrest research, however may not necessarily translate to humans. Additionally, many prolonged arrests have an initial presenting rhythm of pulseless electrical activity (PEA), or asystole. However, the VF prolonged arrest model is commonly used.²⁴⁻²⁷ While this study provides definitive evidence of an increase in blood flow to the brain during prolonged HUP CPR, it is unknown if this benefit will translate into an increase in long-term survival with favorable brain function. Further study is needed in this regard. Another limitation is that given the higher than anticipated effect size we stopped randomizing and performing studies on pigs after 18 pigs. Different from the first study that was used to estimate the sample size¹, in the current study we used an ACD CPR that

pulled upwards with 10 kg versus 1.5 kg, and we only elevated the head and thorax rather than whole body head up tilt. Finally, we did not examine the potential risks and harm of maintaining HUP in pigs in cardiac arrest without ongoing CPR. We suspect that long pauses during cardiac arrest could be potentially harmful in the HUP due to pooling of blood in the abdomen and lower extremities without ongoing circulatory effort.

4. Conclusion

After prolonged ACD CPR + ITD with elevation of the thorax and head, blood flow of the brain was 2-fold higher versus controls treated with the same method of CPR in the supine position. These findings provide additional strong pre-clinical support to proceed with a clinical evaluation of elevation of the head and thorax during ACD CPR + ITD in humans in cardiac arrest.

ml/min/g	Baseline		5 min CPR		15 min CPR	
	SUP	HUP	SUP	HUP	SUP	HUP
n	10	8	10	8	10	8
Brain	0.84 ± 0.17	0.86 ± 0.14	0.33 ± 0.06	0.45 ± 0.07	0.21 ± 0.04	0.42 ± 0.05 *
Heart	1.37 ± 0.19	1.57 ± 0.17	0.51 ± 0.11	0.42 ± 0.09	0.33 ± 0.12	0.34 ± 0.06
Kidney	2.51 ± 0.29	2.32 ± 0.24	0.28 ± 0.08	0.38 ± 0.07	0.21 ± 0.06	0.31 ± 0.07
Liver	0.59 ± 0.11	0.76 ± 0.23	0.10 ± 0.02	0.08 ± 0.02	0.05 ± 0.02	0.08 ± 0.02

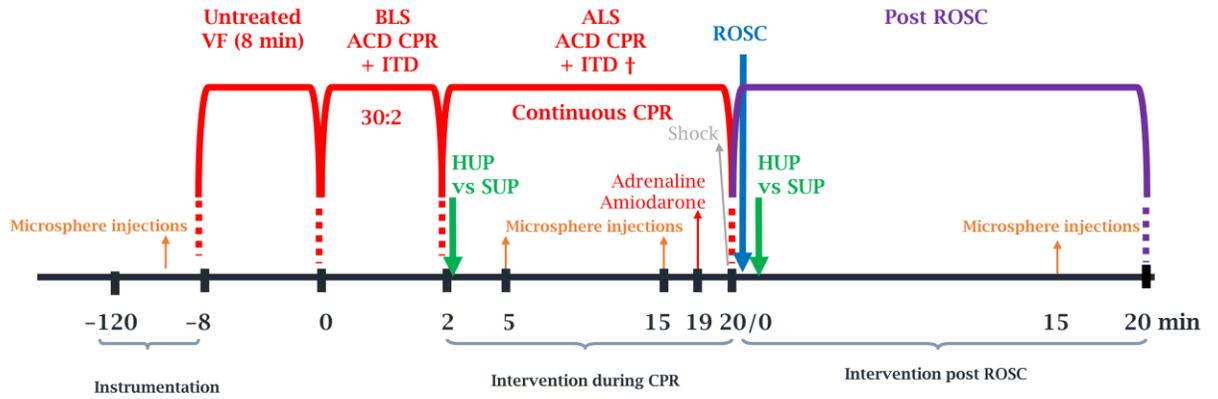
Table 1: Blood flow (ml/min/g) to various organs during cardiopulmonary resuscitation (CPR) in animals randomized to head and thorax elevation (HUP) or supine (SUP) positions. Values are presented as mean ± standard deviation; *p=0.01 compared to the 15 min SUP CPR value.

N SUP=10 HUP=8	Baseline		5 min CPR		15 min CPR		19 min CPR		20 min CPR	
	SUP	HUP	SUP	HUP	SUP	HUP	SUP	HUP	SUP	HUP
ITP diastole	2.3 ± 1.2	2.0 ± 0.6	-5.3 ± 3.0	-5.8 ± 1.8	-5.7 ± 2.8	-6.0 ± 0.8	-5.6 ± 3.4	-5.1 ± 1.5	-5.1 ± 3.9	-5.4 ± 1.3
Ao systole /diastole	96 ± 12 / 73 ± 10	86 ± 14 / 65 ± 13	56 ± 11 / 24 ± 5	58 ± 10 / 24 ± 5	53 ± 14 / 21 ± 6	59 ± 8 / 23 ± 4	45 ± 17 / 16 ± 8	53 ± 9 / 20 ± 5	52 ± 22 / 21 ± 12	58 ± 13 / 23 ± 7
RA systole/ diastole	7.4 ± 2.2 / 5.9 ± 2.3	7.1 ± 1.9 / 5.1 ± 1.7	60 ± 17 / 6.1 ± 4.9	49 ± 16 / 2.8 ± 3.6	52 ± 15 / 5.7 ± 4.2	48 ± 14 / 2.7 ± 3.4	48 ± 14 / 5.1 ± 4.5	43 ± 14 / 2.0 ± 3.7	51 ± 11 / 6 ± 6	46 ± 16 / 4 ± 5
ICP mean	18.8 ± 2.5	16.8 ± 3.6	18.3 ± 6.4	10.0 ± 7.0 *	17.7 ± 5.5	7.7 ± 5.5 ***	15.7 ± 4.2	6.1 ± 5.1 ***	14 ± 2	2 ± 2 ***
CPP diastole	66 ± 10	58 ± 13	18 ± 8	21 ± 6	15 ± 8	20 ± 5	11 ± 11	18 ± 6	15 ± 15	20 ± 6
CerPP mean	65 ± 11	60 ± 14	13 ± 7	26 ± 7 ***	11 ± 9	28 ± 5 ***	8 ± 10	27 ± 5 ***	6 ± 11	20 ± 7 **
EtCO₂ mean	42 ± 2	42 ± 2	34 ± 16	40 ± 6	28 ± 15	32 ± 14	24 ± 11	28 ± 12	23 ± 10	26 ± 11

Table 2: Hemodynamic measurements in animals randomized to the head up (HUP) or supine (SUP) position during a prolonged cardiopulmonary resuscitation (CPR) effort. Values are presented as mean ± standard deviation. Abbreviations: Intrathoracic pressure (ITP), Aortic pressure (Ao), right atrial pressure (RA), intracranial pressure (ICP), Coronary Perfusion Pressure (CPP), Cerebral Perfusion Pressure (CerPP), end-tidal CO₂ (ETCO₂), active compression decompression (ACD), impedance threshold device (ITD), *** p≤0.001 ; ** p<0.01 ; * p<0.05, compared to the SUP CPR value at the same CPR time point.

	Baseline		ROSC	
	SUP	HUP	SUP (n=3)	HUP (n=4)
pH	7.46 ± 0.02	7.46 ± 0.03	7.02 ± 0.03	6.97 ± 0.03
PaCO2	42 ± 3	44 ± 1	57 ± 5	73 ± 21
PaO2	85 ± 10	93 ± 16	80 ± 10	91 ± 18
HCO³⁻	30 ± 2	30 ± 1	15 ± 1	16 ± 4
BE	6 ± 3	6 ± 1	-16 ± 1	-10 ± 4
SaO2	96 ± 2	97 ± 1	86 ± 5	83 ± 11

Table 3: Arterial blood gases results of the head up (HUP) and supine (SUP) cardiopulmonary resuscitation (CPR) groups. Values are presented as means ± standard deviation; Abbreviations: Return of spontaneous circulation (ROSC), base excess (BE)



† SC: succinylcholine (0.20 mg/kg IV bolus if gasp >3 in 30s)

Figure 1: Study timeline. Abbreviations: Head Up CPR (HUP), supine (SUP), active compression decompression (ACD) plus impedance threshold device (ITD) cardiopulmonary resuscitation (CPR), ventricular fibrillation (VF), basic life support (BLS), advanced life support (ALS), return of spontaneous circulation (ROSC), adrenaline.

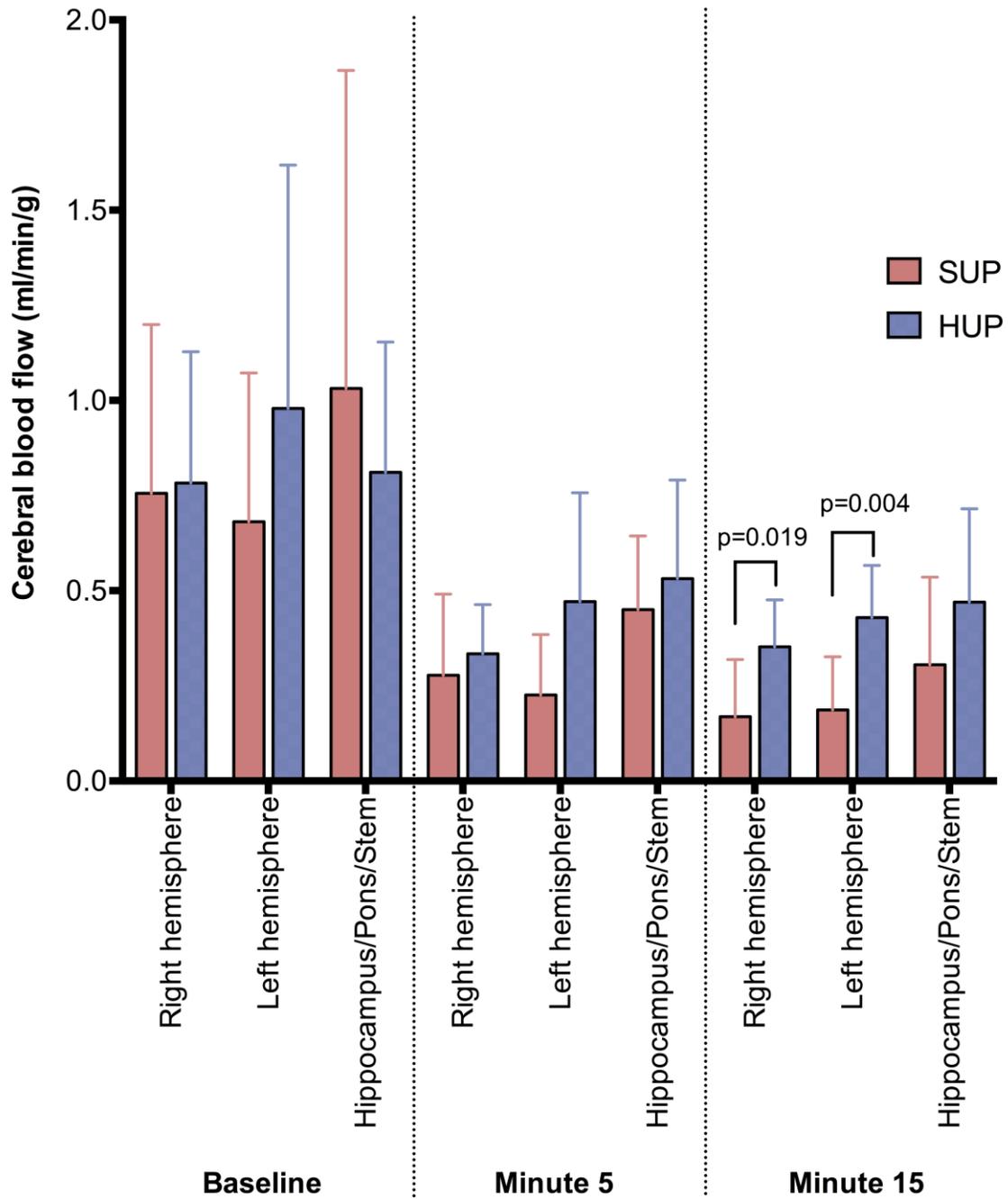


Figure 2: Blood flow to the various areas of the brain with head up (HUP) and supine (SUP) cardiopulmonary resuscitation (CPR)

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