



Experimental paper

Tilting for perfusion: Head-up position during cardiopulmonary resuscitation improves brain flow in a porcine model of cardiac arrest[☆]



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ABSTRACT

Introduction: Cerebral perfusion is compromised during cardiopulmonary resuscitation (CPR). We hypothesized that beneficial effects of gravity on the venous circulation during CPR performed in the head-up tilt (HUT) position would improve cerebral perfusion compared with supine or head-down tilt (HDT).

Methods: Twenty-two pigs were sedated, intubated, anesthetized, paralyzed and placed on a tilt table. After 6 min of untreated ventricular fibrillation (VF) CPR was performed on 14 pigs for 3 min with an automated CPR device called LUCAS (L) plus an impedance threshold device (ITD), followed by 5 min of L-CPR + ITD at 0° supine, 5 min at 30° HUT, and then 5 min at 30° HDT. Microspheres were used to measure organ blood flow in 8 pigs. L-CPR + ITD was performed on 8 additional pigs at 0°, 20°, 30°, 40°, and 50° HUT.

Results: Coronary perfusion pressure was 19 ± 2 mmHg at 0° vs. 30 ± 3 at 30° HUT ($p < 0.001$) and 10 ± 3 at 30° HDT ($p < 0.001$). Cerebral perfusion pressure was 19 ± 3 at 0° vs. 35 ± 3 at 30° HUT ($p < 0.001$) and 4 ± 4 at 30° HDT ($p < 0.001$). Brain–blood flow was 0.19 ± 0.04 ml min^{−1} g^{−1} at 0° vs. 0.27 ± 0.04 at 30° HUT ($p = 0.01$) and 0.14 ± 0.06 at 30° HDT ($p = 0.16$). Heart blood flow was not significantly different between interventions. With 0, 10, 20, 30, 40 and 50° HUT, ICP values were 21 ± 2 , 16 ± 2 , 10 ± 2 , 5 ± 2 , 0 ± 2 , -5 ± 2 respectively, ($p < 0.001$), CerPP increased linearly ($p = 0.001$), and CPP remained constant.

Conclusion: During CPR, HDT decreased brain flow whereas HUT significantly lowered ICP and improved cerebral perfusion. Further studies are warranted to explore this new resuscitation concept.

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1. Introduction

Generation of adequate non-invasive circulatory support during CPR remains a complex physiological challenge, with competing demands to provide sufficient venous return to refill the heart after

each compression and enough circulation to the brain to preserve neurological function.^{1–3} Blood flow is highly dependent on the refilling of the heart during the decompression phase and the vascular resistance.

Closed-chest standard (S) manual cardiopulmonary resuscitation (CPR) has traditionally been performed in the 0° supine position. Stimulated by the need to develop better techniques to transport patients in high-rise apartment buildings in small elevators with ongoing CPR in Korea, an international research collaborative was established to examine the impact of CPR in more vertical positions. Little is known about the potential benefit of tilting the head upward or downward during CPR, especially when

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using CPR mechanical devices known to enhance circulation and provide high quality CPR.^{4,5} We hypothesized that use of mechanical adjuncts known to enhance circulation during CPR would improve outcomes when the head and body are tilted upward vs. supine CPR or with feet up and head down.

2. Method

This study was approved by the Institutional Animal Care Committee of the Minneapolis Medical Research Foundation of Hennepin County Medical Center. All animal care was compliant with the National Research Council's 1996 Guidelines for the Care and Use of Laboratory Animals. All studies were performed by a qualified, experienced research team in Yorkshire female farm bred pigs weighing 39.3 ± 0.5 kg. A certified and licensed veterinarian assured the protocols were performed in accordance with the National Research Council's Guidelines.

2.1. Preparatory phase

The surgical preparation, anesthesia, data monitoring, and recording procedures used in this study have been previously described.^{3,6,7} Under aseptic surgical conditions, initial sedation was achieved with intramuscular ketamine (10 mL of 100 mg/mL) followed by inhaled isoflurane at a dose of 0.8–1.2%. Pigs were intubated with a 7.0 French endotracheal tube. The animal's temperature was maintained between 36.5 and 37.5°C with a warming blanket (Bair Hugger, Augustine Medical, Eden Prairie, MN). Central aortic blood pressure was recorded continuously with a electronic-tipped catheter (Mikro-Tip Transducer, Millar Instruments, Houston, TX) placed in the descending thoracic aorta. A second Millar catheter was inserted in the right atrium via the right external jugular vein. An ultrasound flow probe (Transonic 420 series multichannel, Transonic Systems, Ithaca, NY) was placed in the left common carotid artery to measure carotid blood flow (ml min^{-1}). After creating a burr hole, a Millar catheter was then inserted into the parietal lobe to measure intracranial pressure (ICP). In pigs used for the microsphere studies (see below), a second femoral artery cannulation was performed and a 7F pigtail catheter was positioned in the left ventricle under fluoroscopic guidance. All animals received an intravenous heparin bolus (100 units/kg). Animals were fasted overnight and received normal saline solution to maintain the mean right atrial pressure between 3 and 5 mmHg. The animals were ventilated with room air, using an anesthesia machine (Narkomed, Telford, PA), with a tidal volume of 10 mL/kg and a respiratory rate adjusted to continually maintain an end tidal CO_2 (ETCO_2) of 40 mmHg and O_2 saturation of >92%. Arterial blood gases (Gem 3000, Instrumentation Laboratory) were obtained at baseline, and 3 min after each change of CPR position. Surface electrocardiographic tracings were continuously recorded. All hemodynamic data including aortic pressure, right atrial pressure, ETCO_2 , ICP, and carotid blood flow were continuously monitored and recorded with a digital recording system (BIOPAC MP 150, BIOPAC Systems, Inc., CA, USA). Coronary perfusion pressure (CPP) was calculated as the difference between aortic pressure and right atrial pressure during the CPR decompression phase.⁸ Cerebral perfusion pressure (CerPP) was calculated as the difference between mean aortic pressure and mean ICP. Ultrasound derived carotid blood flow velocity was reported in ml min^{-1} . ETCO_2 , tidal volume, minute ventilation, and blood oxygen saturation were continuously measured with a respiratory monitor (COSMO Plus, Novamatrix Medical Systems, Wallingford, CT).

After the surgical preparation was complete, oxygen saturation on room air was greater than 92%, and ETCO_2 was stable between

35 and 42 mmHg for 5 min, VF was induced by delivering direct intra-cardiac current via a temporary pacing wire positioned in the right ventricle. Mechanical CPR was performed using a LUCAS 1TM (Physio-Control, Redmond, WA) compression system at a rate of 100 compressions min^{-1} with a 50% duty cycle. The LUCAS backboard was bolted to a stretcher (Stryker Corporation, Kalamazoo MI) and the pig was tied by its legs to the stretcher as well. The stretcher was attached to a tilt table built to perform CPR with different study angles. In this way the pig, stretcher, and LUCAS could be moved simultaneously while L-CPR was ongoing. An impedance threshold device with a resistance of 16 cmH_2O (ITD-16, ResQPODTM, Advanced Circulatory Systems, Roseville, MN) was attached to the endotracheal tube. Asynchronous positive pressure ventilations with supplemental oxygen at a flow of 10 l min^{-1} were delivered with a manual resuscitator bag. The tidal volume was maintained at ~ 10 mL/kg and the respiratory rate was 10 breaths min^{-1} . In addition, prior to inducing VF succinylcholine ($93.3 \text{ mcg kg}^{-1} \text{ min}^{-1}$) was administered intravenously to prevent spontaneous gasping during CPR.

Angle positions were confirmed after each change of position with a digital protractor (Mitutoyo Pro 360).

2.1.1. Protocol A

Hemodynamics and calculated coronary and cerebral perfusion pressures were the focus of Protocol A. After 6 min of untreated VF, CPR was initiated on 14 pigs with L-CPR + ITD in a 0° supine position for 3 min. This interval provided time for the hemodynamic parameters to stabilize after reperfusion. L-CPR + ITD continued thereafter without interruption for multiple sequential interventions as follows: 5 min epochs at 0°, 30° head up, and 30° head down position, an additional 2 min of L-CPR + ITD in the 30° head up position and then L-CPR alone, without the ITD, for 2 additional min while still in the 30° head up position. Pigs were then placed in the 0° supine position and defibrillated with up to three 275 joule biphasic shocks (Lifepak 15, Physio-control, Redmond, WA). Animals were then sacrificed with a 10 ml injection of saturated potassium chloride.

2.1.2. Protocol B

Cerebral and myocardial perfusion were assessed under different experimental CPR positions in Protocol B. Blood flow to the heart and brain was measured with microspheres injected into the left ventricle under baseline pre-VF conditions and during CPR as previously described.^{9–11} In the current study 15 μm diameter neutron activated Lanthanum (^{140}La), Gold (^{198}Au), Ytterbium (^{175}Yb), and Lutetium (^{177}Lu) microspheres (STERISpheresTM, BioPALTM: BioPhysics Assay Laboratory, Worcester, MA) were used. Microspheres were randomly assigned for each of the respective four interventions with one type of microsphere per intervention. Microspheres were injected into a total of 8 pigs during CPR under different experimental CPR positions. The microspheres were first injected into the left ventricle under stable baseline conditions 5 min prior to the induction of VF. Then, following 6 min of untreated VF CPR was performed continuously with L-CPR + ITD for the different time intervals and using the 3 different CPR positions as described in Fig. 1. After 4 min of CPR a second microsphere was injected while the pig remained in the 0° supine position. The pig was then tilted upwards to the 30° head up position and 1 min later a third microsphere was injected. After 4 min the pig was tilted downwards in the 30° head down position and 1 min later the last microsphere was injected. The number of microspheres injected for each intervention was computed as follow:

$$\mu = 1.2 \cdot 10^6 + ((1.9 \cdot 10^5) \cdot \omega)$$

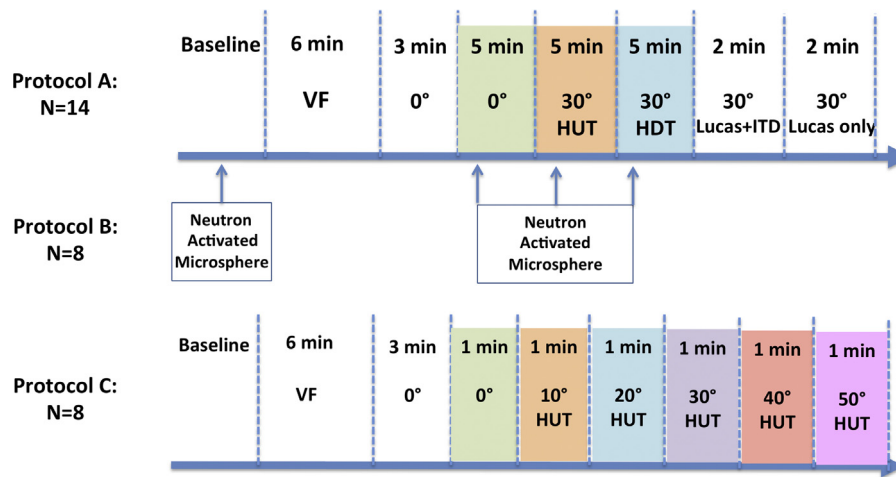


Fig. 1. Study protocol. VF: ventricular fibrillation, HUT: Head up tilt, HDT: Head down tilt

where μ = required number of microspheres; ω = pig weight.

$$\text{Baseline injection volume} = \frac{\mu}{(5 \cdot 10^8)/20}$$

$$\text{Intervention injection volume} = \frac{\mu}{((5 \cdot 10^8)/20) \cdot (5/3)}$$

Concurrently with the microsphere injections, reference blood samples were withdrawn continuously from the descending aorta at a collection rate of 10 ml min⁻¹. At the end of the procedure animals were sacrificed with potassium chloride as described above and then tissue samples from the brain (pons portion of the brainstem, hippocampus, left and right cortex) and heart (left ventricular apex, papillary muscle, free wall) samples were obtained. Samples were desiccated and sent to the reference BioPhysics Assay Laboratory for analysis.¹¹ Data for each organ, using pooled data from the portions sampled, were reported in Section 3.

2.1.3. Protocol C

This protocol was used to determine the effect of incremental increases in the head-up angle on key hemodynamic measures. The angle-response relationship for the different hemodynamic parameters assessed was determined in 8 additional pigs as follows: after 6 min of untreated VF, L-CPR+ITD was initiated and following a 3 min stabilization period in the 0° supine position hemodynamic measurements were recorded for 1 min intervals at 0°, 10°, 20°, 30°, 40°, 50° head up tilt position. Animals were then sacrificed as described above.

2.2. Statistical analysis

Data are expressed as mean ± standard error of mean (SEM). For the primary hypotheses, mean values were compared using a Student's paired *t* test with the 0° supine reference position.

One-Way Repeated Measures Analysis of Variance with linear trend was used to compare continuous data within the different angles in Protocol C. All statistical tests were two-sided, and a *p* value of less than 0.05 was required to reject the null hypothesis. Statistical analysis was performed using IBM SPSS Statistics 21.

3. Results

3.1. Protocol A: hemodynamic parameters and perfusion pressures

Results from Protocol A are shown in Table 1 and supplementary Fig. 1. During CPR in the 30° head up position mean ICP values were nearly immediately reduced by 75% compared with the 0° supine position (7 ± 1 vs. 28 ± 2 , $p < 0.001$). By contrast, the mean aortic pressure decreased by about 17% in the 30° head up position (42 ± 4 vs. 48 ± 4 , respectively, $p < 0.001$). Consequently, the CerPP was significantly higher with 30° head up tilt (35 ± 3 vs. 19 ± 3 , respectively, $p < 0.001$). Placement of the pig in the 30° head up position resulted in 140% reduction in decompression phase right atrial pressure relative to the 0° supine position (-4.3 ± 1 vs. 10.1 ± 1 , respectively, $p < 0.001$) and an increase in the calculated CPP, as shown in Table 1 and supplementary Fig. 1. By contrast, with the 30° head down position ICP was significantly higher, while CPP and CerPP were significantly lower compared with the 0° supine position (42 ± 2 vs. 28 ± 2 , 10 ± 3 vs. 19 ± 2 , 4 ± 4 vs. 19 ± 3 , respectively, $p < 0.001$ for each comparison). Representative pressure curves recorded during the three different positions are shown in Fig. 2. A total of 9/14 pigs were successfully defibrillated at the end of the protocol.

3.2. Protocol B: cerebral and cardiac blood flow

Protocol B was used to assess instantaneous blood flow during three L-CPR+ITD positions. Cerebral blood flow (ml min⁻¹ g⁻¹ of

Table 1

Hemodynamic parameters at baseline and between 0, 30° head up and 30° head down L-CPR+ITD.

	Baseline	CPR angle		
		0°	30°	-30°
SBP	106 ± 4	94 ± 6	83 ± 5*	90 ± 6
DBP	71 ± 4*	30 ± 3	26 ± 3*	27 ± 4
RA max	8 ± 1*	157 ± 16	123 ± 14*	172 ± 13*
RA min	0 ± 1*	10 ± 1	-4 ± 1*	17 ± 1*
CBF max	613 ± 32*	377 ± 41	329 ± 43*	327 ± 46*
CBF min	223 ± 31*	-138 ± 21	-132 ± 32	-131 ± 32
ICP max	23 ± 1*	45 ± 5	15 ± 2*	65 ± 4*
ICP min	19 ± 1*	15 ± 2	-2 ± 2*	24 ± 1*

SBP: systolic blood pressure, DBP: diastolic blood pressure, RA: right atrial pressure, CBF: carotid blood flow; ICP: intracranial pressure (maximum and minimum value during compression and decompression).

* $p < 0.05$ compared with to 0° supine CPR.

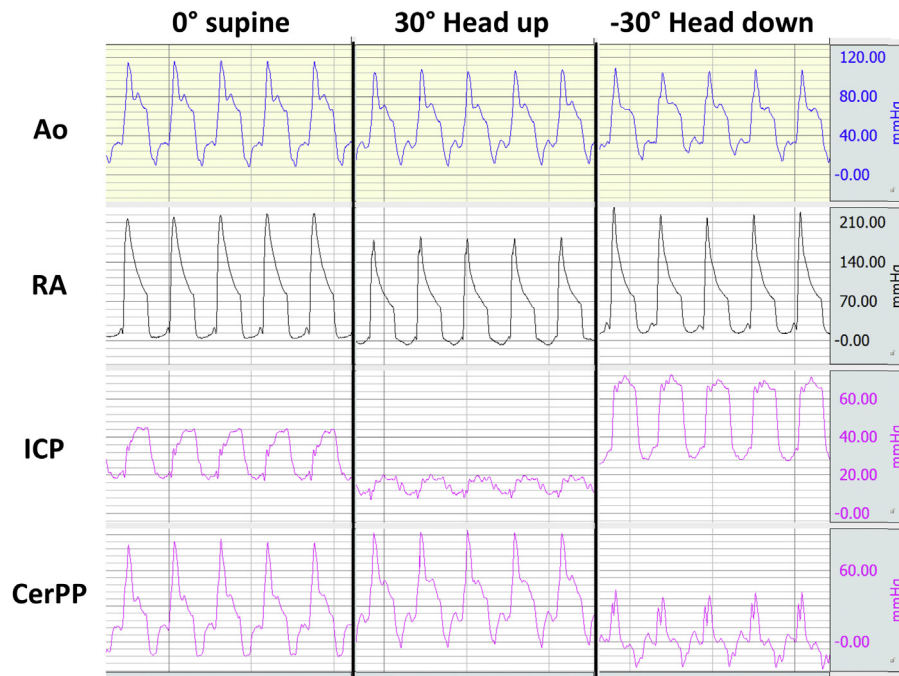


Fig. 2. Representative pressure curve of aortic pressure (AO), right atrial pressure (RA), intracranial pressure (ICP), coronary perfusion pressure (CPP) and cerebral perfusion pressure (CerPP) during 0° CPR, 30° Head up CPR and 30° head down CPR (−30°).

tissue) during 0° supine L-CPR + ITD was 35% of baseline (0.19 ± 0.04 vs. 0.54 ± 0.07 , $p = 0.03$) and cardiac blood flow was 28% of baseline value (0.28 ± 0.09 vs. 0.99 ± 0.14 , $p = 0.01$). Brain–blood flow with 30° HUT was 42% higher compared with the 0° supine position 0.27 ± 0.04 vs. 0.19 ± 0.04 ($p = 0.01$). With 30° HDT brain flow was reduced by 26% to 0.14 ± 0.06 compared to supine 0° values ($p = 0.16$). Heart blood flow was 0.28 ± 0.09 at 0° vs. 0.26 ± 0.06 at 30° HUT ($p = 0.48$) and 0.22 ± 0.07 at 30° HDT ($p = 0.23$) (Fig. 3).

3.3. Blood gas analysis

During L-CPR + ITD the arterial PO_2 was significantly higher with 30° HUT compared with 0° CPR at the same inspired oxygen fraction (175 ± 30 vs. 120 ± 14 , $p = 0.009$) (Table 2). In addition, peak inspiratory pressure was lower with 30° HUT compared with the 0° supine position, 28.7 ± 1.8 mmHg vs. 37.8 ± 1.9 , respectively ($p < 0.001$).

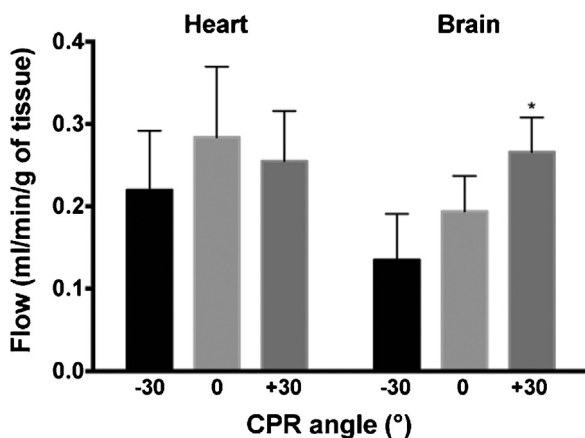


Fig. 3. Blood flow to the heart and brain with supine, 30° head up and 30° head down CPR. CPP: coronary perfusion pressure (CPP), cerebral perfusion pressure (CerPP). * $p < 0.05$ compared with 0°.

3.4. LUCAS alone vs. LUCAS + ITD

To determine the potential importance of the L-CPR + ITD combination vs. L-CPR only, at the end of Protocol A the ITD was removed. We observed an immediate and significant decrease in systolic blood pressure (78 ± 4 vs. 58 ± 7 mmHg, $p = 0.011$), diastolic blood pressure (19 ± 3 vs. 17 ± 2 mmHg, $p = 0.002$), and CPP (25 ± 2 vs. 23 ± 2 mmHg, $p = 0.012$) as soon as the ITD was removed.

3.5. Protocol C

With 0, 10, 20, 30, 40 and 50° HUT, mean ICP decreased linearly as follows: 21 ± 2 , 16 ± 2 , 10 ± 2 , 5 ± 2 , 0 ± 2 , -5 ± 2 respectively, ($p < 0.001$). During the compression phase of CPR the maximum ICP decreased also linearly with 0, 10, 20, 30, 40 and 50° HUT: 30 ± 2 , 24 ± 2 , 16 ± 2 , 12 ± 2 , 7 ± 2 , 4 ± 2 respectively, ($p < 0.001$), whereas CerPP increased linearly ($p = 0.001$), and CPP remained constant (Fig. 4).

Table 2

Respiratory parameters at baseline and between 0, 30° head up and 30° head down CPR.

	Baseline	CPR angle		
		0°	30°	−30°
pH	$7.43 \pm 0.01^*$	7.23 ± 0.02	7.21 ± 0.02	$7.13 \pm 0.03^*$
PCO ₂	$41 \pm 1^*$	49 ± 3	46 ± 2	$58 \pm 4^*$
PO ₂	104 ± 6	120 ± 14	$175 \pm 30^*$	113 ± 18
HCO ₃ [−]	$27 \pm 1^*$	20 ± 1	$18 \pm 1^*$	$18 \pm 1^*$
BE	$2.9 \pm 0.7^*$	-7.4 ± 0.6	$-9.4 \pm 0.4^*$	$-11.1 \pm 0.6^*$
ETCO ₂	40 ± 1	35 ± 2	33 ± 2	31 ± 4
ITP max	$3.6 \pm 0.1^*$	7.6 ± 0.7	7.5 ± 0.8	8.7 ± 1.2
ITP min	$2.3 \pm 0.1^*$	-10.3 ± 0.8	-10.3 ± 0.8	$-9.2 \pm 0.9^*$
PIP	$18.7 \pm 0.6^*$	37.8 ± 1.9	$28.7 \pm 1.8^*$	42.7 ± 2.2

ITP: Intrathoracic pressure during chest compression; PIP: peak inspiratory pressure during positive pressure ventilation. Pressures are in mmHg.

* $p < 0.05$ compare to 0° CPR.

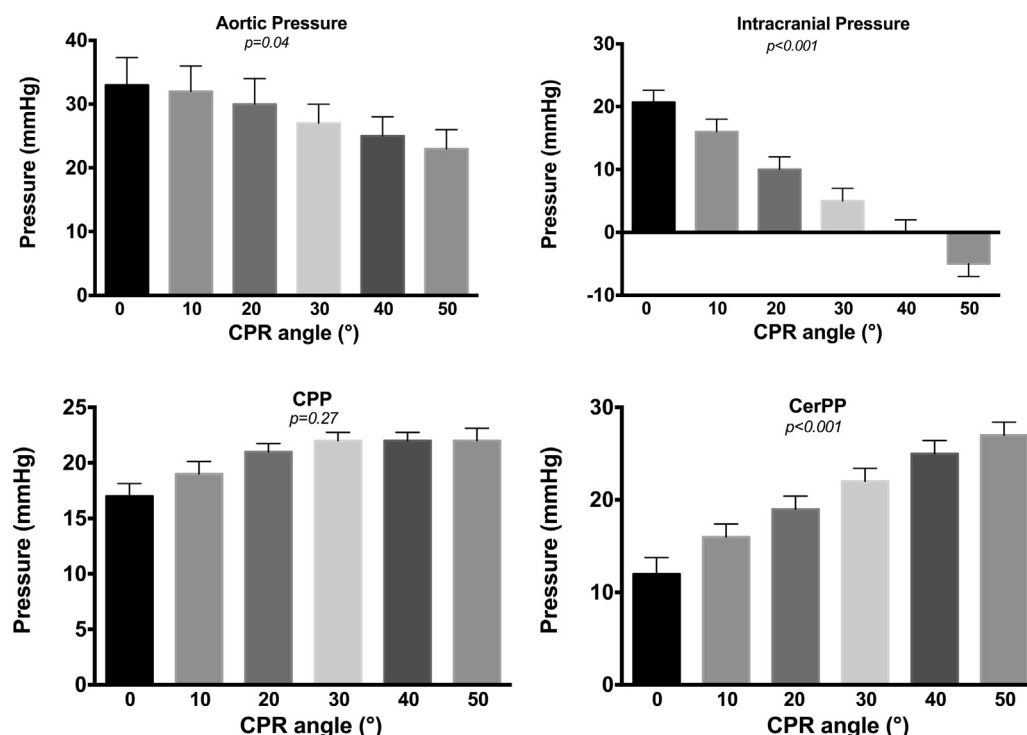


Fig. 4. Dose angle relationships with mean aortic pressure and intracranial pressure, coronary perfusion pressure (CPP) and cerebral perfusion pressure (CerPP). p value are reported for linear trend.

4. Discussion

An inherent limitation to systemic and cerebral perfusion during conventional CPR is the high resistance generated in the venous circulation with each chest compression, which reduces or eliminates the forward flow pressure gradient to the heart and often to the brain.¹² Results from the current study demonstrate that L-CPR + ITD performed in the head up position (reverse Trendelenberg) significantly increases cerebral perfusion pressure, oxygenation, and cerebral blood flow, compared with either 0° supine or HDT. The shift in the position of the head and body to the upright position immediately reduced ICP and venous pressures, thereby rapidly reducing resistance to forward blood flow generated by L-CPR + ITD. As such, the combination of L-CPR + ITD in the novel HUT position may provide a new way to overcome some of the most fundamental challenges associated with the generation of sufficient circulation to the heart and brain.

During standard CPR in the 0° supine position, arterial and venous pressure rise to a similar degree with each chest compression. This increase in venous pressure is nearly instantaneously transmitted to the brain through venous structures including the paravertebral venous plexus.¹² As shown in Fig. 2, when CPR was performed in the horizontal plane, each compression is associated with a rise in ICP and a concurrent decrease in the aortic minus ICP cerebral perfusion gradient: in some pig studies ICP during the compression phase was >80 mmHg. The findings from the current study, for the first time to our knowledge, demonstrate that tilting the head and body upward during the chest compression and decompression phases reduces venous and ICP pressures thereby significantly increasing brain perfusion and calculated perfusion pressure.

The optimal head up angle is not currently known. From a mechanistic perspective, the results from the current study demonstrate that with each 10° increase in the HUT angle the peak, trough and mean compression phase ICP and right atrial pressure decreased significantly, thus generating a much larger cerebral vascular

pressure gradient between the arteries and veins. The decreases in ICP and right atrial pressure were linear, with a 0.3–0.4 mmHg decrease with each 1° increase in HUT. This resulted in a linear increase in cerebral perfusion pressure. By contrast, HDT resulted in a striking increase in ICP and a decrease in coronary and cerebral perfusion pressures. The absolute ICP values during the compression phase of head down suggest that such an approach may cause significant harm.

In order to consistently perfuse the brain in the elevated head position, it is important to maintain sufficient central blood volume and forward flow. This was accomplished in the current study with L-CPR + ITD, a device combination that harnesses the intrathoracic vacuum generated during the decompression phase of CPR to enhance circulation and further reduce ICP.^{6,10} In this study, without the ITD the systolic and diastolic blood pressure as well as calculated CPP decreased immediately.

This first study on the potential impact of head up position was limited by the experimental design: different interventions were performed in sequential rather than randomized order. In prior studies coronary perfusion pressures have been shown to decrease over time so the absolute increase in these parameters with head-up position may be underestimated.¹³ In addition, this new concept has resulted in a number of currently unanswered questions including: what is the optimal CPR head-up angle, what is the impact of HUT on pulmonary function and circulation, should the entire body be tilted upward or just part of the body, how long can CPR be performed in the head up position, and will survival rates be increased HUT. Studies are currently ongoing to address these important issues.

5. Conclusion

CPR with head up positioning provides a novel way to easily, rapidly, and significantly augment cerebral perfusion during CPR without impairing perfusion to the heart. Mean ICP values

decreased and CerPP increased linearly until 50° head-up positioning. Further studies are warranted to explore this new approach.

Source of funding

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Conflicts of interest statement

Keith Lurie is the inventor of the Impedance Threshold Device and is the medical director of Advanced Circulatory System (Roseville, MN). Anja Metzger, and Michael Lick are employees of Advanced Circulatory System.

There are no other conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.resuscitation.2014.11.019>.

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