The role of head-up cardiopulmonary resuscitation in sudden cardiac arrest: a systematic review and meta-analysis

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Contributions: (I) Conception and design: AFW Ho, ESY Chan, MEH Ong; (II) Administrative support: CXY Goh, MX Han, YK Tan; (III) Provision of study materials or patients: AFW Ho; (IV) Collection and assembly of data: YK Tan, MX Han, AFW Ho; (V) Data analysis and interpretation: MX Han, BYQ Tan, CH Sia, CXY Goh, AST Leow, DJ Hausenloy; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

#These authors contributed equally to this work.

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Background: Head-up cardiopulmonary resuscitation (HU-CPR) is an experimental treatment for sudden cardiac arrest (SCA), where cardiopulmonary resuscitation (CPR) is performed in a ramped position. We evaluated whether HU-CPR improved survival and surrogate outcomes as compared to standard CPR (S-CPR).

Methods: Studies reporting on HU-CPR in SCA were searched for in PubMed, Embase and Cochrane Library from inception to May 1st 2021. Outcomes included neurologically-intact survival, 24-hour-survival, intracranial pressure (ICP), cerebral perfusion pressure (CerPP) and brain blood flow (BBF). Risk of bias was assessed using the GRADE assessment tool and Newcastle Ottawa Scale. Fixed- and random-effects models were used to estimate the pooled effects of HU-CPR at 30 degrees.

Results: Thirteen articles met the criteria for inclusion (11 animal-only studies, one before-and-after human-only study, one study that utilized human- and animal-cadavers). Among animal studies, the most common implementation of HU-CPR was a 30-degree upward tilt of the head and thorax (n=7), while four studies investigated controlled sequential elevation (CSE). Two animal studies reported improved cerebral performance category (CPC) scores at 24-hour. The pooled effect on 24-hour survival was not statistically significant (P=0.37). The lone human study reported doubled return of spontaneous circulation (ROSC) (17.9% versus 34.2%, P<0.0001). The pooled effect on ROSC in three porcine studies was OR =3.63 (95% CI: 0.72–18.39). Pooled effects for surrogate physiological outcomes of intracranial cranial pressure (MD −14.08, 95% CI: −23.21 to −4.95, P=0.003), CerPP (MD 14.39, 95% CI: 3.07–25.72, P=0.01) and BBF (MD 0.14, 95% CI: 0.02–0.27, P=0.03), showed statistically significant benefit.

Discussion: Overall, HU-CPR improved neurologically-intact survival at 24-hour, ROSC and physiological surrogate outcomes in animal models. Despite promising preclinical data, and one human...
Introduction

Sudden cardiac arrest (SCA) is the abrupt loss of cardiac activity leading to a lack of systemic perfusion (1), making it the most devastating and time-critical medical emergency. Successful treatment can potentially avert certain death and allow return to an active life in the community. Early and effective cardiopulmonary resuscitation (CPR) is key to achieving good clinical outcomes (2,3). However, clinical outcomes had remained poor in the past 30 years, with out-of-hospital cardiac arrest (OHCA) survival rates ranging from 4.9% to 18.2% (3). Given the large disease burden exerted by SCA (4), there is an urgent need to discover therapeutics to improve clinical outcomes.

Head-up CPR (HU-CPR) is an experimental technique which involves performing high-quality CPR with the patient's torso and head in an inclined position. There is an expanding body of literature both optimizing the protocol of HU-CPR (e.g., in terms of angle of elevation) and investigating its treatment effects (5,6). It has been purported that HU-CPR improves neurological prognosis in SCA by improving intra-arrest brain perfusion (7). In this postulated mechanism, gravity facilitates drainage of blood from the brain, which lowers ICP and in turn improves cerebral perfusion (7,8). This addresses the unmet need that CPR in its current supine form [hereafter, “conventional or S-CPR”] is only able to attain up to 30% of both normal cerebral and coronary blood flow (6,7,9). One contributing factor is that during the compression phase, concurrent pressure increases in both the right and left sides of the heart leads to increases in intrathoracic pressure (ITP) and hence intracranial pressure (ICP), which compromises cerebral perfusion (10,11).

Despite a paucity of randomized human data to elucidate the efficacy or effectiveness of HU-CPR, a few centres have implemented HU-CPR as standard protocol (e.g., Palm Beach County Fire Rescue, Florida, United States and Rialto Fire Department, California, USA), with astounding preliminary clinical results from their observational data (11,12). At the same time, expert recommendations have been made in support of implementing HU-CPR (12). There is an urgent need to consolidate the literature, both preclinical and clinical data, to clarify the role of HU-CPR in SCA.

In this systematic review and meta-analysis, we synthesized the available evidence for the use of HU-CPR in the treatment of cardiac arrest. The primary hypothesis was that HU-CPR improves survival in cardiac arrest compared to S-CPR. The secondary hypothesis was that HU-CPR improves physiological surrogate markers of clinical outcomes as well as the intermediate clinical outcome of return of spontaneous circulation (ROSC). We present the following article in accordance with the PRISMA (13) reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-21-4984/rc).

Methods

Search strategy

This systematic review has been submitted to PROSPERO (ID: 300352). The search strategy was developed in consultation with a medical information specialist. Employing different keyword combinations [Head up CPR, Head-up CPR, Heads up CPR, Heads-up CPR, resuscitation, CPR, cardiac arrest, cardiopulmonary resuscitation, cardio-pulmonary resuscitation and Chest compress*], a comprehensive search was performed on the bibliometric databases PubMed, Embase and the Cochrane Library from inception to May 1st 2021. The title/abstract screening was performed by two independent reviewers (YKT & AFWH). For articles of interest, full text versions were obtained, with their corresponding reference lists examined for further identification of relevant studies. Any disagreement was resolved by discussion and consensus with a senior author (MEHO).

Study and cohort selection

All study designs (case reports, case series, preclinical studies, randomized controlled trials and observational...
cohort studies) that reported the use of HU-CPR were included during the initial search. We subsequently excluded all studies that reported on other positions during CPR (such as passive leg raise), studies that did not contain primary data, and those without an English translation.

**Data extraction**

Relevant quantitative data were extracted by two authors (YKT & AFWH) in the form of absolute frequencies of events or absolute counts when appropriate. We presented continuous variables as mean and standard deviation (SD). Categorical variables were presented as percentages. Where available, the data included several outcome measures of interest: neurologically-intact survival at 24-hour, survival to 24-hour, ROSC, ICP, cerebral perfusion pressure (CerPP) and brain blood flow (BBF).

**Risk of bias assessment**

The quality and risk of bias of included randomized and non-randomized studies were assessed using the GRADE Assessment Tool (14) and the Newcastle Ottawa Scale (15) respectively. The GRADE Assessment tool assesses quality of evidence in terms of study limitations, inconsistency, indirectness, imprecision and publication bias. The Newcastle Ottawa scale evaluates quality of evidence based on selection of study groups (4 points), comparability of groups (2 points), and ascertainment of exposure and outcomes (3 points). These were graded with the consensus of 3 researchers (AFWH, YKT and MXH).

**Statistical analysis**

In our meta-analysis, fixed- and random-effects models were used in conjunction with the Sidik-Jonkman estimator and Mantel-Haenszel method to estimate the pooled effects of HU-CPR at 30 degrees depending on the presence of substantial between-study heterogeneity. Studies that examined HU-CPR at 30 degrees inclination were selected to be pooled as that represented the most common intervention among all studies. Forest plots displayed individual and pooled odds ratios (OR) and 95% confidence intervals (95% CI) for binary outcomes. Individual and pooled mean difference (MD) and 95% CI were presented for continuous outcomes. Two-tailed statistical significance was set at P value <0.05. Between-study heterogeneity was assessed using the I² statistic. Publication bias was assessed using funnel plots if there were 10 or more studies reporting the same outcome. All data analyses were conducted using the Cochrane Collaboration’s Review Manager (RevMan 5.4) Software Package.

**Results**

**Study selection**

The study identification and selection process were shown in Figure 1. The electronic database search yielded 120 studies, of which 14 studies were removed as duplicates. A further 85 studies were excluded after a screen of title and abstract as they did not report the use of HU-CPR. Then, 8 articles were excluded after full text review. Finally, 13 eligible studies were included in our systematic review and meta-summary (5-8,11,16-23).

**Characteristics of included studies**

The 13 included studies consisted of only one clinical human-only study, 11 animal-only studies and one study that utilized both human cadavers and animals. A meta-summary of included studies was presented in Table 1 (human and human-cadaveric studies) and Table 2 (animal studies).

In terms of study designs, the only human study was an observational before-and-after study, which retrospectively analyzed OHCA cases over 3.5 years, during which the EMS service had implemented HU-CPR as part of their cardiac arrest protocol (11). Specifically, the crew implemented HU-CPR as a reverse Trendelenburg position, as part of a care bundle comprising delayed positive pressure ventilation, ITD and LUCAS mechanical CPR (mCPR).

All 12 animal studies involved porcine models of cardiac arrest where pigs were subjected to a period of untreated VF, which varied from 6 to 15 min across study designs (Table 2).

Regarding experimental interventions and controls, the most common treatment was the bundling of HU-CPR with an active compression-decompression device (ACD) and impedance threshold device (ITD). Across seven animal study protocols, HU-CPR was implemented as a 30-degree upward tilt of the head and thorax (Table 2). Four studies investigated the impact of controlled sequential elevation (CSE), of which one specifically investigated how different time periods of CSE could impact cerebral perfusion (23).
The comparators were homogenous across the studies, all of which used the supine position as the main control for comparison. Eleven studies had a proper control arm while two studies used self-controls within their protocol arms, where each animal served as its own control.

In terms of study outcomes, three studies investigated 24-hour survival and neurologically-intact survival after 24-hour. Eleven studies measured cerebral perfusion (CerPP) and of which only two measured BBF via injection of microspheres. Twelve studies investigated HU-CPR and related manoeuvres as pre-ROSC interventions while one study investigated the effect that HU-CPR would have on subjects after ROSC had been achieved.

Risk of bias

Quality of evidence was found to be low to moderate due to inconsistency of outcomes as evaluated by the GRADE framework and shown in Table 3 (14). The lone human study achieved 7 out of a maximum of 9 points on the Newcastle-Ottawa Scale, signifying high quality and low risk of bias for selection.

Survival

In terms of survival with good neurological status, Moore et al.'s 2016 and 2021 porcine studies (6,18) reported cerebral performance category (CPC) scores assessed at 24-hour post-ROSC. Both studies found that animals subjected to HU-CPR had lower CPC scores and higher rates of favourable neurological survival than the S-CPR arm (6,18).

Pepe et al. 2019's human study reported that the rates of intact neurological survival (modified Rankin score <3, unspecified time frame), collected only for a subset of patients, were similar to the period before HU-CPR interventions were introduced at 35–40% (11).

In terms of 30-day survival or survival to discharge, none of the included studies reported these outcomes.

In terms of 24-hour survival, a total of 37 subjects across two porcine RCTs (6,18) were assessed based on pooled 24-hour
<table>
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<tr>
<th>Study, year (country)</th>
<th>Study design and sample size (N)</th>
<th>Population/model</th>
<th>Outcome measures</th>
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<tr>
<td>Moore et al. 2018 (USA)</td>
<td>Experimental trial (N=18); 9 pigs and 9 human cadavers; findings from the porcine protocols are reported in Table 2</td>
<td>6 female and 3 male human cadavers with average age 84±10 years, average weight 70±14 kg, average height 1.7±0.1 m, and average interval since death of 3.7±2 days</td>
<td>CerPP; ICP</td>
<td>HC protocol: 6 min of untreated VF; CPR performed for 1 min epochs as follows: standard (S)-CPR supine (SUP), ACD+ITD CPR SUP, then ACD+ITD HUP CPR</td>
<td>Mean CerPP in human cadaver: 1.3±4 for ACD+ITD SUP; 11.3±5 for ACD+ITD HUP (P=0.007); mean ICP was significantly lower in the ACD+ITD HUP group versus the ACD+ITD SUP group in all three CPR models</td>
<td>HU-CPR decreased ICP while increasing CerPP in HC CPR models</td>
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<td>Pepe et al. 2019 (USA)</td>
<td>Observational study (N=2,322)</td>
<td>Human, out-of-hospital cardiac arrest (all presenting rhythms)</td>
<td>Primary outcome: resuscitation rate; defined as hospital arrival with ROSC sustained for 5 min; Secondary outcome: intact neurological status (modified Rankin Score &lt;3)</td>
<td>Pre-intervention: ITD + LUCAS mCPR with pit-crew approach Additional measures during intervention period: (I) Delayed positive pressure ventilations after application of oxygen (II) Strengthening of the team set-up for fast LUCAS placement (III) Positioning of patient in reverse Trendelenburg (20 degrees) by raising the angle of the whole stretcher, after the placement of LUCAS and advanced airway insertion connection to an ITD</td>
<td>Mean resuscitation rate pre-intervention vs. post-intervention: 17.87% (range, 14.81–20.13%; n=806) vs. 34.22% (range, 29.76–39.42%; n=1,356, P&lt;0.0001)</td>
<td>Bundled intervention doubled resuscitation rates in out-of-hospital cardiac arrest</td>
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ICP, intracranial pressure; CerPP, cerebral perfusion pressure; HC, human cadaver; ACD, active compression-decompression device; SUP, standard (S)-CPR supine; HUP, head-up position; ITD, impedance threshold device; LUCAS, chest compression system.
Table 2 Characteristics of the 12 included animal or animal-cadaveric studies

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<th>Study, year (country)</th>
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<td>Debaty et al. 2015 (USA)</td>
<td>Experimental trial (N=30)</td>
<td>Female Yorkshire farm-bred pigs weighing 39.3±0.5 kg</td>
<td>CoPP, CerPP, ICP, BBF</td>
<td>Preparation: 6 min of untreated VF; 3 min of LUCAS mCPR + ITD in supine position Protocol A: 5 min each of LUCAS mCPR + ITD at 0, 30 deg HUP and 30 deg HDT; 2 min of LUCAS mCPR+ITD at 30 deg HUP; 2 min of LUCAS mCPR at 30 deg HUP Protocol B: interventions as per Protocol A but with microspheres injected before induction of VF and during CPR Protocol C: 1 min each of LUCAS mCPR + ITD at 0, 10, 20, 30, 40 and 50 deg HUP</td>
<td>CoPP: 19±2 at 0° vs. 30±3 at 30° HUT (P&lt;0.001); 10±3 at 30° HDT (P&lt;0.001) CerPP: 19±3 at 0° vs. 35±3 at 30° HUT (P&lt;0.001); 4±4 at 30° HDT (P&lt;0.001) ICP: 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&lt;0.001) BBF: 0.19±0.04 mL/min/g at 0° vs. 0.27±0.04 at 30° HUT (P&lt;0.001); 0.14±0.06 at 30° HDT (P=0.16) CPC ≤2 at 24-hour: 62/62 (100%) vs. 60/62 (96.8%) HUT during LUCAS mCPR + ITD lowered ICP significantly and also improved cerebral perfusion; HDT reduced brain blood flow CSE in Protocol C: CerPP increased linearly while CoPP remained constant</td>
<td>Elevating the head and thorax after ROSC resulted in higher CerPP levels and lower ICP levels in a porcine model of cardiac arrest</td>
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<td>Duhem et al. 2021 (USA)</td>
<td>Randomised experimental trial (N=15)</td>
<td>Female Yorkshire Primary outcome: CerPP</td>
<td>Farm-bred pigs weighing approximately 40 kg</td>
<td>Protocol A: 7.75 min of untreated VF; 30 min of HUP CPR followed by defibrillation and ROSC; 10 min in HUP; randomised to four 5-min epochs of HUP or flat position Protocol B: 6 min of untreated VF 6 min of S-CPR followed by defibrillation and ROSC; 10 min in SUP; randomised to four 5-min epochs of HUP or flat position</td>
<td>ICP: significantly lower after ROSC with HUP position vs. SUP position (8.1±5.5 vs. 18.5±5.1, P&lt;0.001) CerPP: significantly higher after ROSC with HUP position vs. SUP position (62.5±19.9 vs. 53.2±18.1, P=0.004)</td>
<td>CerPP increased with consistently greater head up position; CoPP was peak at 30 degrees HUP</td>
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<td>Kim et al. 2017 (South Korea)</td>
<td>Randomised Experimental Trial (N=12)</td>
<td>Female pigs weighing 42±3 kg</td>
<td>CerPP; CoPP</td>
<td>Preparation: 6 min of Untreated VF; 3 min of LUCAS mCPR at supine position Intervention: 5 min each of mCPR at three different positions, each with varying angles (I) Head Down Tilt (HDT): −30, −45, −60 degrees; (II) Supine: 0 degrees; (III) Head Up Tilt (HDT): 30, 45, 60 degrees; pigs were randomized to 1 of 2 tilt sequences: HDT Supine HUT or HUT Supine HDT</td>
<td>CerPP: means (SDs) of CerPP increased consistently: 2.4 (0.4), 9.3 (1.6), 16.5 (1.6), 27.0 (1.5), 35.1 (0.4), 39.4 (0.6), and 39.9 (0.3) mmHg, as angles changed from HDT (−60 degrees) to HUT (60 degrees); CerPPs peaked at HUT 60 degrees CoPP: peaked at HUT 30 degrees ROSC: 100% for all protocols after subjects were defibrillated ICP: means (SDs) of ICP decreased consistently 59 (0.7), 51.3 (1.8), 41.4 (1.2), 27.8 (1.8), 8.9 (0.3), −3.8 (0.5), −7 (0.2) as angles changed from HDT (−60 degrees) to HUT (60 degrees)</td>
<td>CerPP increased with consistently greater head up position; CoPP was peak at 30 degrees HUP</td>
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<td>Moore, 2016 (abstract experimental trial only) (USA)</td>
<td>Randomised Pigs (N=21); HUP =12; SUP =9</td>
<td>CPC Score at 24-hour; Neurological Deficit Score (NDS) at 24-hour</td>
<td>CPC ≤2 at 24-hour: ACD+ITD CPR for 1.5 min</td>
<td>Survival to 24-hour: • HUP: 8/12 • SUP: 6/9 CPC ≤2 at 24-hour: • HUP: 6/12 • SUP: 3/9 Mean CPC score at 24-hour: • HUP: 1.6±0.3 • SUP: 2.5±0.6 Control Group: ACD+ITD CPR in SUP position for 6.5 min Mean NDS score at 24-hour: • HUP: 44±22 • SUP: 88±45</td>
<td>Higher rate of intact neurological survival for HUP group</td>
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Table 2 (continued)
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<tr>
<th>Study, year (country)</th>
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<td>Moore et al. 2017 (United States)</td>
<td>Randomised experimental trial (N=18); HUP =8; SUP =10</td>
<td>Female Yorkshire farm-bred pigs weighing 36–44 kg</td>
<td>Primary outcome: BBF</td>
<td>Preparation: 8 min of untreated VF; 2 min of ACD+ITD CPR in the SUP position</td>
<td>BBF: 0.42±0.05 HUP (n=8); 0.21±0.04 SUP (n=10)</td>
<td>Brain blood flow was 2-fold higher for ACD+ITD CPR in HUP position versus SUP position</td>
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<td>Moore et al. 2020 (USA)</td>
<td>Randomised experimental trial (N=30); N=18 for Study A; N=6 for each sequence in Study B</td>
<td>Female Yorkshire farm-bred pigs weighing approximately 40 kg</td>
<td>Primary outcome: CerPP</td>
<td>Preparation: 8 min of untreated VF in pigs; Study A: different angles (20, 30, 40 deg) were assessed, each randomized over 5-min periods of ACD+ITD CPR</td>
<td>CerPP in Study A: equivalent for 30 degrees and 40 degrees; 20±25 versus 38±18, P=0.002; CerPP in Study B at 17 min: higher CerPP in the 20°–30°–40° sequence: 60±17 versus 33±18 (P=0.035)</td>
<td>No optimal HUP CPR angle was observed. However, controlled progressive elevation of the head and thorax during CPR is more beneficial than an absolute angle or height to maximise CerPP</td>
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<td>Moore et al. 2021 (USA)</td>
<td>Randomised experimental trial (N=16)</td>
<td>Female Yorkshire farm-bred pigs weighing approximately 40 kg</td>
<td>Primary outcome: Neurologically Intact Survival (CPC Score)</td>
<td>Preparation: sedation, intubation and anaesthesia followed by 10 min of untreated VF</td>
<td>ROSC: 8/8 (100%) with ACD + ITD CSE; 3/8 (25%) for C-CPR (P=0.026)</td>
<td>Bundled resuscitation approach of CSE with ACD+ITD CPR increased favourable neurological survival versus C-CPR in a porcine model of cardiac arrest</td>
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### Table 2 (continued)

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<tr>
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<tr>
<td>Park et al. 2019 (South Korea)</td>
<td>Randomised Experimental Trial (N=18)</td>
<td>Female Yorkshire farm-bred pigs weighing 42±3 kg</td>
<td>Primary outcome: 24-hour survival</td>
<td>Preparation: 2 hr of surgical preparation involving sedation, intubation and paralysis; 15 min of untreated VF</td>
<td>ROSC: lower in HUP (1/8) vs. SUP (6/8) P=0.04</td>
<td>HUP positioned CPR with a 30 deg angle showed lower rate of survival to 24-hour and lower ROSC rate than CPR in supine position in a porcine cardiac arrest model</td>
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<td>Secondary outcome: ROSC Rate after 6 min of BLS</td>
<td>Control Group: 6 min of ACD+ITD CPR in supine position</td>
<td>24-hour survival: 0 in HUP vs. 6/8 in SUP</td>
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<td>Experimental Group: 6 min of ACD+ITD CPR in HUP 30 deg position</td>
<td>ICP: −4.8±3.1 in HUP vs. 19.7±3.9 in SUP (P&lt;0.01)</td>
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<td>Post-intervention: defibrillation (if shockable rhythm) at 200 J</td>
<td>CerPP: 22.9±7.2 in HUP vs. 17.1±5.0 in SUP (P=0.08)</td>
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<td>• if ROSC: additional hydration and adrenaline for up to 90 min</td>
<td>CoPP: 10.6±7.9 in HUP vs. 18.4±11.0 in SUP (P=0.12)</td>
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<td>• if no ROSC: additional 20 min of ACD+ITD CPR in previous position with adrenaline every 3 min and defibrillation every 2 min</td>
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<td>Putzer et al. 2018 (Austria)</td>
<td>Randomised Experimental Trial (N=19)</td>
<td>12- to 16-week-old local pigs, weighing 31–45 kg each</td>
<td>Primary outcomes: ICP; CerPP</td>
<td>Preparation: 8 min of untreated VF</td>
<td>ICP at 5 min: significantly lower in HUP vs. SUP (18.0±4.5 vs. 24.1±5.2, P=0.033)</td>
<td>HUP did not lead to improvements in cerebral oxygenation or metabolism</td>
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<td>Secondary outcomes: rSO₂, PbrO₂, Svo₂</td>
<td>Control Group: LUCAS mCPR in SUP Position for 20 min</td>
<td>ICP at 20 min: significantly lower in HUP vs. SUP (12.0±3.4 vs. 17.8±4.3, P=0.023)</td>
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<td>Experimental Group: LUCAS mCPR in HUP Position (30 deg) for 20 min</td>
<td>CerPP at 5 min: significantly higher in HUP vs. SUP (3.4±6.4 vs. −3.8±2.8, P=0.023)</td>
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<td>Post-intervention: defibrillation (if shockable rhythm) at 200 J</td>
<td>CerPP at 20 min: significantly higher in HUP vs. SUP (11.2±9.5 vs. 1.0±9.2, P=0.045)</td>
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<td>• if ROSC: additional hydration and adrenaline for up to 90 min</td>
<td>CoPP: 10.6±7.9 in HUP vs. 18.4±11.0 in SUP (P=0.12)</td>
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<td>• if no ROSC: additional 20 min of ACD+ITD CPR in previous position with adrenaline every 3 min and defibrillation every 2 min</td>
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<td>Time to 50% BL CerPP: significantly lower in 4- vs. 10-min group in Protocol A (53±14.4 vs. 38.5±3.6 mmHg respectively, P=0.03); significantly higher in 2-min (P=0.031) and 4-min groups (P=0.032) vs. 24-sec group</td>
<td>With CSE and ACD+ITD interventions, CerPP values attained half of baseline values within 2.5 min of CPR; and &gt;80% of baseline values after 7 min of CPR</td>
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<td>Protocol A: ACD+ITD CPR with CSE (to maximum CED height) over either 4 or 10 min</td>
<td>Time to 50% BL CerPP: significantly lower in 4- vs. 10-min group (2.5±1.2 vs. 6±3.1 min, P=0.03)</td>
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<tr>
<td>Rojas-Salvador et al. 2020 (United States)</td>
<td>Randomised Experimental Trial (n=24)</td>
<td>Female Yorkshire farm-bred pigs weighing approximately 40 kg</td>
<td>Primary outcome: CerPP</td>
<td>Preparation: 8 min of untreated VF; 2 min of automated ACD+ITD CPR</td>
<td>CerPP after 7 min of CPR: significantly higher in 4- vs. 10-min groups in Protocol A (53±14.4 vs. 38.5±3.6 mmHg respectively, P=0.03); significantly higher in 2-min (P=0.031) and 4-min groups (P=0.032) vs. 24-sec group</td>
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<td>Protocol A: ACD+ITD CPR with CSE (to maximum CED height) over either 4 or 10 min</td>
<td>CerPP at 5 min: significantly lower in HUP vs. SUP (18.0±4.5 vs. 24.1±5.2, P=0.033)</td>
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<td>Protocol B: ACD+ITD CPR with CSE (to maximum CED height) over 2 min</td>
<td>CerPP at 20 min: significantly lower in HUP vs. SUP (12.0±3.4 vs. 17.8±4.3, P=0.023)</td>
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<td>Protocol C: ACD+ITD CPR with CSE (to maximum CED height) over 24 seconds, without initial 2 min of ACD+ITD CPR</td>
<td>CerPP at 5 min: significantly higher in HUP vs. SUP (11.2±9.5 vs. 1.0±9.2, P=0.045)</td>
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<td>Time to 50% BL CerPP: significantly lower in 4- vs. 10-min group (2.5±1.2 vs. 6±3.1 min, P=0.03)</td>
<td>CerPP at 20 min: significantly higher in HUP vs. SUP (3.4±6.4 vs. −3.8±2.8, P=0.023)</td>
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<td>Protocol A: ACD+ITD CPR with CSE (to maximum CED height) over either 4 or 10 min</td>
<td>CerPP at 5 min: significantly lower in HUP vs. SUP (18.0±4.5 vs. 24.1±5.2, P=0.033)</td>
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<td>Protocol B: ACD+ITD CPR with CSE (to maximum CED height) over 2 min</td>
<td>CerPP at 20 min: significantly lower in HUP vs. SUP (12.0±3.4 vs. 17.8±4.3, P=0.023)</td>
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<td>Protocol C: ACD+ITD CPR with CSE (to maximum CED height) over 24 seconds, without initial 2 min of ACD+ITD CPR</td>
<td>CerPP after 7 min of CPR: significantly higher in 4- vs. 10-min groups in Protocol A (53±14.4 vs. 38.5±3.6 mmHg respectively, P=0.03); significantly higher in 2-min (P=0.031) and 4-min groups (P=0.032) vs. 24-sec group</td>
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**Table 2 (continued)**
Table 2 (continued)

<table>
<thead>
<tr>
<th>Study, year (country)</th>
<th>Study design and sample size (N)</th>
<th>Species/model</th>
<th>Outcome measures</th>
<th>Intervention type and controls for comparison</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ryu et al. 2016 (USA)</td>
<td>Randomised Experimental Trial (N=30)</td>
<td>Female Yorkshire farm-bred pigs weighing 39.3±0.5 kg</td>
<td>Primary outcome: CerPP</td>
<td>Preparation: 8 min of untreated VF in Group A at 22 min: 6±3 in the HUP arm versus −5±3 in the SUP arm (P=0.016)</td>
<td>CerPP was significantly improved by the HUP positional intervention in both C-CPR and ACD+ITD CPR in a porcine model of cardiac arrest</td>
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<td>Group B (2 arms): 2 min of ACD+ITD CPR in SUP position; 20 min of ACD+ITD CPR randomized to either HUP 30 deg or SUP positions</td>
<td>CerPP in Group B at 22 min: 51±8 in HUP arm versus 20±5 in SUP arm (P=0.006)</td>
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<td>Group A (2 arms): 2 min of C-CPR in SUP position; 20 min of C-CPR randomized to either HUP 30 deg or SUP positions</td>
<td>ROSC in Group A: 6/8</td>
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<td>ICP in Group A during compression and decompression at 22 min: compression: 14±1 in the HUP arm versus 23±1 in the SUP arm (P&lt;0.001); decompression: 12±1 in the HUP arm versus 20±1 in the SUP arm (P=0.001)</td>
<td>ROSC in Group B: 6/8</td>
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<td>ICP in Group B during compression and decompression at 22 min: compression: 20±2 in the HUP arm versus 26±2 in the SUP arm (P=0.019); decompression: 15±1 in the HUP arm versus 20±1 in the SUP arm (P&lt;0.001)</td>
<td>ICP in Group A during compression and decompression at 22 min: compression: 14±1 in the HUP arm versus 23±1 in the SUP arm (P&lt;0.001); decompression: 12±1 in the HUP arm versus 20±1 in the SUP arm (P&lt;0.001)</td>
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ACD, active compression-decompression device; BBF, brain blood flow; C-CPR, conventional CPR; CED, customised head and thorax elevation device; CerPP, cerebral perfusion pressure; CoPP, coronary perfusion pressure; HUP, head-up position; HUT, head-up tilt; HDT, head-down tilt; ICP, intracranial pressure; ITD, impedance threshold device; LUCAS, chest compression system; mCPR, mechanical CPR; NDS, neurological deficit score; PbO2, brain tissue oxygen tension; ROSC, return of spontaneous circulation; rSO2, cerebral regional oxygen saturation; ScvO2, cerebral venous oxygen saturation; SUP, supine position.

Table 3 GRADE Assessment framework (14)

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication bias</th>
<th>Events, n</th>
<th>Individuals, n</th>
<th>Rate (95% CI)</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>Randomised controlled trial</td>
<td>Not serious</td>
<td>Serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Undetected</td>
<td>13</td>
<td>53</td>
<td>1.14 (0.04–32.49)</td>
<td>☀️Receipt</td>
<td>Critical</td>
</tr>
<tr>
<td>Cerebral perfusion pressure (assessed with mean difference; scale from: −100 to 100)</td>
<td>Randomised controlled trial</td>
<td>Not serious</td>
<td>Serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Undetected</td>
<td>–</td>
<td>69</td>
<td>14.39 (3.07–25.72)</td>
<td>☜️Receipt</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

☀️Receipt, very low certainty; ☜️Receipt, low certainty; ☜️Receipt, moderate certainty; ☜️Receipt, high certainty.

Survival outcomes. Meta-analytic estimates for 24-hour survival showed no statistically significant benefit for animals where HU-CPR was conducted in comparison to animals that underwent S-CPR, as shown in Figure 2 (OR =3.93, 95% CI: 0.20–77.08, P=0.37, I²=71%). However, it is worth noting that meta-analytic estimates in Figure 2 showed a trend favouring HU-CPR. There was high between-study heterogeneity (I²=71%).

**ROSC**

Sustained ROSC of five min with hospital arrival was reported as the primary outcome in Pepe et al.’s human study, which they termed “successful resuscitation” (11). After HU-CPR was introduced, there was a two-fold increase in the rates of successful resuscitation from 17.87% (range, 14.81–20.13%; n=806) to 34.22% (range, 29.76–39.42%; n=1,356, P<0.0001).

Two studies using porcine VF models reported that all subjects achieved ROSC after defibrillation in both intervention and control arms, regardless of the angle of elevation (17,23).

With regards to pooled ROSC outcomes, a total of...
50 animal subjects across three porcine RCTs (6,7,19) were assessed. Meta-analytic estimates for ROSC showed no statistically significant benefit for animals where HU-CPR was conducted in comparison to animals that underwent C-CPR, as shown in Figure 3 (OR: 3.63, 95% CI: 0.72–18.39, P=0.12). There was low heterogeneity (I^2=28%).

**ICP**

Consistently across seven animal studies, HU-CPR significantly lowered ICP. Moreover, Moore et al’s 2018 study demonstrated this finding consistently across human-cadaveric, porcine and porcine-cadaveric models (20).

With regards to the pooled outcome of ICP after 20 min of CPR, a total of 53 animal subjects across three porcine RCTs (19,21,22) were assessed. Meta-analytic estimates for ICP showed a statistically significant benefit in animals where HU-CPR was conducted in comparison to animals that underwent S-CPR, as shown in Figure 4 (MD: −14.08, 95% CI: −23.21 to −4.95, P=0.003). High heterogeneity was reported (I^2=97%).

**CerPP**

Consistently across six animal studies, CerPP was significantly higher with HU-CPR. Moore et al’s 2018 study demonstrated this finding consistently across human-cadaveric, porcine and porcine-cadaveric models (20). Moore et al’s 2020 study also specified that it was the 20→30→40 deg sequence in CSE that led to the significant increases in CerPP, which attained doubling of baseline values after 17 min of CPR (5). In addition, Rojas-Salvador et al. 2020 reported that CerPP was significantly higher for CSE over four min as compared to a 10 minute rise (23).
With regards to the pooled outcome of CerPP after 20 min of CPR, a total of 69 animal subjects across four porcine RCTs (7,19,21,22) were assessed. Meta-analytic estimates for CerPP showed a statistically significant benefit for animals where HU-CPR was conducted in comparison to animals that underwent C-CPR, as shown in Figure 5 (MD: 14.39, 95% CI: 3.07–25.72, P=0.01). High heterogeneity was reported (I²=93%).

Despite significant heterogeneity (I²=93%), it is worth noting that all four animal studies in the meta-analysis showed a significant effect favouring HU-CPR.

The animal RCTs assessed in the meta-analyses for ICP and CerPP differed slightly in their methodologies. Three studies allocated 8 min for untreated VF as the baseline, with Park et al. being the only study delaying interventions by 15 min. Physiological parameters were measured regularly throughout the intervention periods, which were 20 min in Moore et al. and Putzer et al., and 22 min in Ryu et al. Park was the only study that measured parameters every minute to a maximum of six min which represented the entirety of their intervention period. The longer delay of treatment and subsequent shorter time period allocated for CPR could account for the absence of statistical significance in Park’s findings, with respect to CerPP. All four RCTs defined HU-CPR as elevation of the head and thorax by a 30-degree angle, with Putzer et al. being the only study that administered compressions without the use of an ITD.

**BBF**

With regards to BBF, a total of 40 animal subjects from 2 RCTs (16,19) were assessed. Meta-analytic estimates for BBF showed a statistically significant benefit for animals where HU-CPR was conducted in comparison to animals that underwent S-CPR, as shown in Figure 6 (MD: 0.14, 95% CI: 0.02–0.27, P=0.03). High heterogeneity was reported (I²=95%).

Both porcine RCTs used similar time periods for their interventions. Debaty et al. 2015 allocated a total of 19 min for CPR (ACD and ITD) while Moore et al. 2017 allocated 18 min for CPR (LUCAS mCPR and ITD). Microspheres to measure blood flow were injected at four instances in Debaty et al. 2015’s protocol, namely at 5 min prior to VF induction, after four min of CPR, after 1 min of HUT (9 min of CPR) and after 1 min of HDT (14 min of CPR). Moore et al. 2017 measured BBF at two instances post-VF, namely after 5 and 15 min of CPR.

**Publication bias**

Funnel plots could not be assessed as there were fewer than ten studies reporting each outcome.

**Discussion**

In this systematic review and meta-analysis, several main...
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improve ROSC rate independently (25,26). In the three animal studies pooled, the outcome ROSC, despite being statistically significant, is less clinically important because the determinants of ROSC in experimental induced-VF models were probably different from that in real-life.

Of note, Park et al. was the only study that reported a significantly worse rate of ROSC and 24-hour survival. The reason for this anomaly was unknown, but was possibly related to protocol design. Importantly, the studies’ protocols differed in the length of time pigs were left untreated after inducing VF. While Moore et al.’s protocols subjected pigs to 10–12 min of untreated VF, Park et al. used 15 min. Across all other included studies, the period of untreated VF ranged from 6 to 8 min. This additional delay to HU-CPR could have impacted on haemodynamic parameters and therefore reduced survival rate (27,28). The duration of untreated VF is a possible effect modifier of the benefit of HU-CPR, and hence a possible source of clinical heterogeneity in our study. It is also important to note that Park et al. was the only study that did not prime the pump before doing HUCPR compared to other studies, lacking a suction cup to allow for passive recoil. Not priming the pump could have thus affected the rate of ROSC and survival rate, as shown in other studies (29). The speculation that the benefit of HU-CPR was limited to patients with short downtime is hypothesis generating.

Besides simply ascertaining the efficacy of HU-CPR, a few studies examined additional research questions: (I) interaction effects with ACD and ITD; (II) optimal angle of inclination; (III) CSE. Firstly, some included studies found a positive interaction between HU-CPR and ACD/ITD (6,11,19,20). The ACD is a suction cup integrated into the piston of the mCPR device, which, exerts an active decompressive force after each compression (9,19). The ITD attaches to the airway adjunct and lowers ITP by preventing passive gas exchange during chest wall recoil (9). Figure 7 (11) shows that the effect of ACD/ITD and HU-CPR on CerPP were more than additive. In addition, the inclusion of ACD/ITD to HU-CPR prevented a downward decay in CerPP over time, as compared to HU-CPR with solely a mechanical compression device. It is also important to note that Putzer et al. 2018, as the only study which did not utilise ITD, had demonstrably worse outcomes compared to the rest of the other studies included in the forest plots (Figures 4,5).

Secondly, some included animal studies investigated the optimal angle of elevation. Kim et al. 2017 found that coronary perfusion pressure (CoPP) peaked at 30 degrees,
similar to CerPP which rose linearly until 30 degrees and thereafter plateaued (17). Debaty et al. 2015 concluded that while the optimal HUT angle is unknown, it demonstrated that a head-down tilt reduced BBF (16). While the pooled effect of 30-degree inclination was beneficial, these were all found in porcine models and may not be directly translatable to humans.

Thirdly, a few studies implemented a CSE protocol. This meant a sequential elevation of the head and thorax from smaller to larger angles over a specified time frame. Moore et al.’s 2020 study found that CerPP was highest when HUT was increased sequentially from 20 to 40 degrees (5,17). Specifically, it was a 2-minute sequential elevation that produced the most favourable neurological outcome, as reported in Moore et al.’s 2021 study. It was assumed that CSE augmented right to left pulmonary flow and improved autoregulation of systemic vasculature (5).

An additional variation in HU-CPR protocol is of interest. The configuration of a full-body tilt (reverse Trendelenburg) as compared to a head-and-thorax-only (above waist) tilt warrants further deliberation. It was suggested that a full-body tilt leads to greater pooling of blood in the lower extremities, which worsens brain perfusion (19). This might be supported by Pepe et al. 2019’s findings that HU-CPR delivered as a reverse Trendelenburg position resulted in similar rates of neurologically intact survival pre- and post-intervention (11). Ryu et al. 2016’s study had instead created and implemented a head-up device that tilts just the head and upper thorax, resulting in higher CerPP over a 22-min period of ACD+ITD HU-CPR (7). This suggests that elevation of the head and thorax could be preferable over a full-body tilt in HU-CPR.

The transferability of experimental findings from healthy, young pigs to real-life human SCA is a common concern across the included studies. While porcine models of cardiac arrest had been extensively developed and used in SCA research over decades, they were not without limitations (30). For example, the lower limbs of swine differ significantly from human equivalents in terms of the smaller blood volume. A systematic review of 490 studies employing animal models of cardiac arrest revealed that swine were most commonly used due their advantages of similarities to human cardiovascular and neurological physiology (31). Porcine models hence have higher fidelity than rodent models which were less preferred due to higher heart and respiratory rates which complicated compression-ventilation timings (31). While primate models could be superior to porcine models, there is limited collective experience with it in SCA research, where it has only been successfully reported in the field of cardiac xenotransplantation (32).

The accuracy of CerPP, ICP, BBF and rSO2 as surrogates for predicting neurological outcomes should also be evaluated. The studies included in this review reported their findings based on these parameters: CerPP (nine studies), ICP (ten studies), BBF (two studies), rSO2 (one study). In cardiac arrest, cerebrovascular homeostasis is disrupted due to primary ischemia, leading to cerebral oedema and increased ICP, which in turn decreases cerebral blood flow (33,34). Upon ROSC, hypoxic ischaemic encephalopathy, also termed as global ischaemia-reperfusion injury, interferes with cerebral blood flow and perfusion (35-37). CPP may therefore become dependent upon blood pressure or MAP (35). Considering this pathophysiology, it seems valid for CerPP, ICP and BBF to be used as surrogate markers of neurological outcomes. Specifically, BBF has been used to prognosticate neurological status post-cardiac arrest and to inform research in targeted temperature management (37). On the other hand, rSO2 has limited predictive potential for neurological outcomes after SCA (38,39).

There was substantial uncertainty over whether these laboratory findings can be replicated in real life, due to implementation challenges. Firstly, it is generally difficult to implement intra-arrest interventions, due to cardiac arrest care being already complex and the pre-hospital care environment already chaotic. The value of the novel intervention of HU-CPR is present only if the rudimentary criteria of high-quality chest compressions are met (10,12,40). Incremental encumbrance of paramedic resuscitative workflow during SCA may lead to compromise in the quality of key interventional processes (e.g., reducing interruption in CPR and early defibrillation) (12,40).

Furthermore, given that there were suggestions that the benefit of HU-CPR was attenuated (or even becomes harmful) when HU-CPR is instituted late, this becomes an implementation challenge because the ambulance response time in many health systems can be very variable (41,42). In addition, the ability to maintain a HU-CPR position while navigating tight urban spaces and bumpy road conditions is yet another challenge. A possible solution is the EleGARD device which has been mentioned in some literature (23,43), although further research into its specific use in human models of cardiac arrest is needed.

**Limitations**

The limitations of this systematic review and meta-analysis...
should be acknowledged. Firstly, the findings from this report are informed by a predominance of animal studies and hence limited by the paucity of randomized human data. The only observational human study had adopted a pre-post implementation design, which has inherent causal limitations due to the lack of a contemporaneous control group. Further, that study examined HU-CPR as part of a bundle of multiple interventions, which means it is difficult to infer the treatment effect attributable to HU-CPR alone. Secondly, further research is needed to examine the use of HU-CPR with manual hands-only compressions since the findings of this review are limited to CPR conducted with ACD, ITD and mechanical compression devices. Manual hands-only compressions could be challenging to perform in a head-up position. Thirdly, although the use of porcine VF models is common, key anatomical differences remain. Moreover, the swine used in porcine studies were young and healthy, which is not representative of cardiac arrest patients who are likely to present with multiple comorbidities. Fourthly, while CerPP, ICP and BBF have been consistently used as surrogate parameters for neurological outcomes, their accuracy requires future corroboration by future research. Finally, the benefits of HU-CPR in the real-world are dependent heavily on the dynamic and unpredictable nature of the pre-hospital environment and its influence on cardiac arrest management. The certainty of its actual benefit upon implementation is therefore intrinsically linked with paramedic competencies and team cohesiveness during resuscitation, factors which are bound to vary across EMS systems and geographical contexts.

Conclusions

There was an absence of human experimental trials. Overall, HU-CPR improved neurologically-intact survival at 24-hour, ROSC and physiological surrogate outcomes in animal models. Despite promising preclinical data, and one human observational study, clinical equipoise remains surrounding the role of HU-CPR in SCA, necessitating clarification with future randomized human trials.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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