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# Does 'Heads-Up' Positioning Cardiopulmonary Resuscitation Improve Outcomes for Patients in Out of Hospital Cardiac Arrest? A Systematic Review

## Introduction

Paramedics in the UK have been trained in the delivery of advanced life support (ALS) since 1979, with techniques being refined and updated over time in an attempt to improve survival to discharge for out of hospital cardiac arrest (OHCA) patients (College of Paramedics, 2015). Despite these changes, data from National Health Service (NHS) England (2018) show that in August of that year, the survival to discharge of all-cause OHCA patients treated by UK ambulance services was 10.4%, with even fewer than this discharged with favourable neurological outcome (exact percentage unlisted within these statistics). The earliest available comparable statistics from NHS England (2011) show OHCA survival to discharge rates have remained largely unchanged over the last seven years and it is clear that more research is needed to identify areas of improvement for treatment of OHCA by ambulance services.

Presently, 1% of the guidelines for treatment of OHCA are based on data derived from multiple randomised controlled trials (RCTs), with the remaining 99% based on non-randomised trials, or expert opinion (American Heart Association, 2018). Whilst RCTs are widely regarded as the highest level of research (Oxford Centre for Evidence Based Medicine, 2011), conducting a RCT to research treatment of OHCA is inherently difficult owing to the heterogeneous nature of OHCA; the cause of cardiac arrest, environment, chance of bystander CPR or defibrillation and attending practitioners are different for every OHCA and therefore make it difficult to formulate and implement a clinically robust trial. Furthermore, the nature of cardiac arrest is extremely distressing; proposals for prehospital trials must be thoroughly researched and evidenced prior to acceptance.

An EMS (emergency medical service) system in Florida, America, have implemented a HUPCPR (heads up CPR) protocol as part of a package of measures and are claiming an increase in survival of all-cause OHCA from 17.4% to 36% across 2014-2015 (Pepe *et al.* 2016). However, this information was delivered at an EMS conference and is now only available as an abstract, meaning that there is virtually no information available for critical analysis other than their observed increase in survival with HUPCPR and adjunctive therapies (namely use of an active compression-decompression and impedance threshold device). No subsequent data have been released disclosing further information on this doubling of survival rates, neither has ‘increased survival’ been given more exact definition. NHS England (2018) measure success rates in OHCA by ‘survival to discharge from hospital’ and measure the quality of discharge by neurological outcome. Whilst this abstract offers little in terms of tangible research or evidence to critique, the possibility of doubling survival rates in OHCA patients is worthy of further investigation.

This systematic review sets out to find out if HUPCPR improves patient survival to discharge and neurological outcomes in OHCA by critically analysing the supporting literature of the ‘Heads-Up’ CPR technique.

Aims

To discern if HUPCPR improves patient survival to discharge for OHCA and improves patient neurological outcomes compared to supine position CPR.

Objectives

- To explore if HUPCPR improves patient survival to discharge compared to supine position CPR.
- To explore if HUPCPR improves neurological outcome for survivors of OHCA compared to supine position CPR.
- To explore if HUPCPR can be recommended for UK paramedic practice.

Methodology

PICO Tool

- Population: adult OHCA patients.
- Intervention: 'Heads-Up' elevated cardiopulmonary resuscitation.
- Comparison: standard supine CPR.
- Outcome: Identification of improved patient survival to discharge with particular focus on improved neurological outcome for patients.

A pilot search was conducted based upon the PICO criteria exploring the available literature around HUPCPR, but generated results containing only animal studies and abstracts from conferences containing too little detail to benefit this systematic review. This research was of a lower level than anticipated in accordance with the hierarchy of research (Oxford Centre for Evidence Based Medicine, 2011). Therefore the inclusion criteria built from the PICO Tool warranted adaptation.

A systematic search of literature dating the past ten years from the databases AMED, CINAHL Plus and PubMed was conducted from 15th January to 19th February of 2019. The search terms used were “heads up” or “elevat*” (a truncated search term) or “patient positioning” and “cardiopulmonary resuscitation”.

Grey literature was also explored, with several articles found on American EMS websites. This exploration confirmed that identified within the pilot search, further sculpting the inclusions/exclusion criteria.

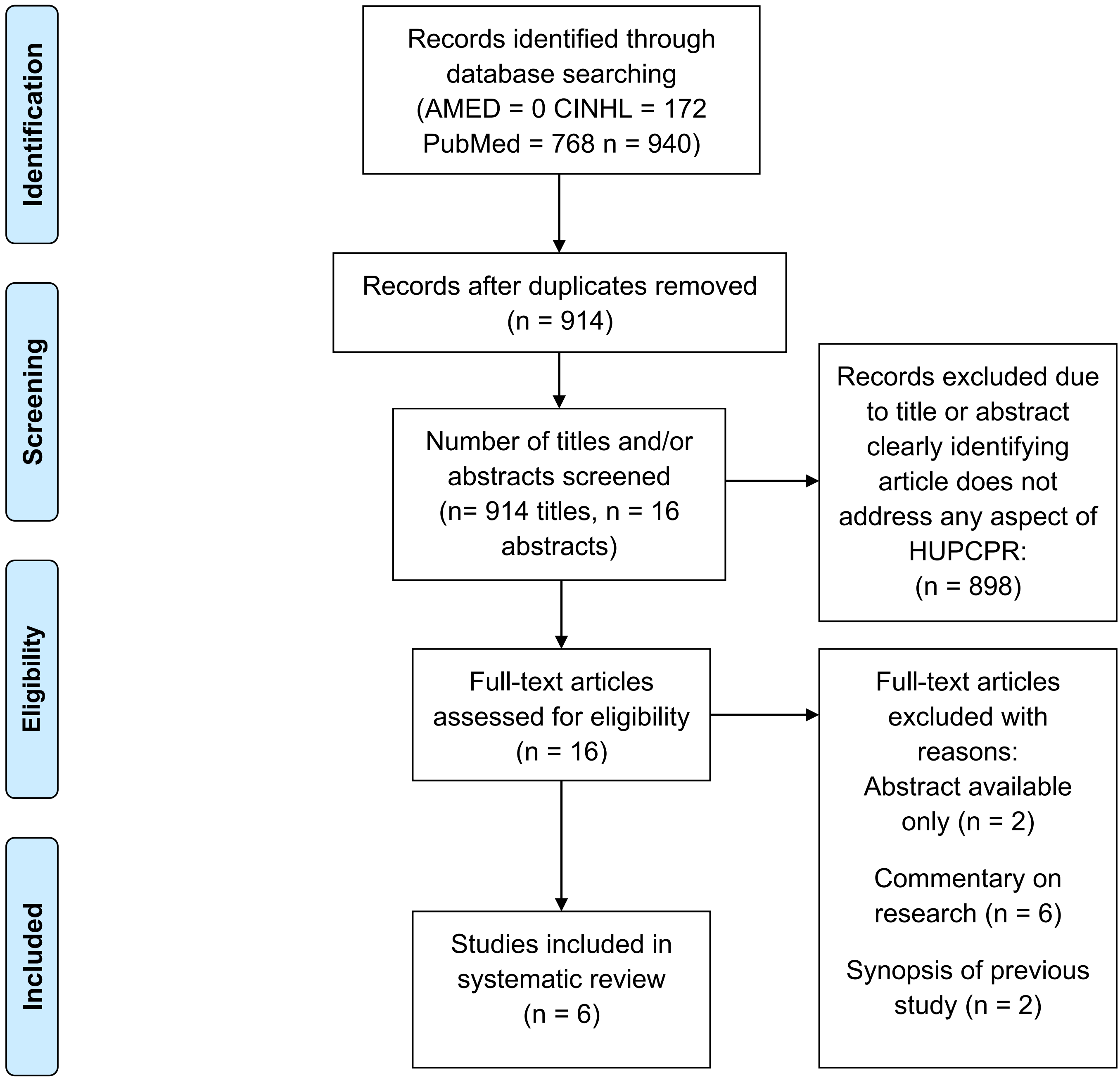
Inclusion Criteria (Revised based upon the pilot search)

- Studies monitoring the affect of heads up positioning on outcome of cardiac arrest (with particular interest to survival with neurological outcome).
- Animal model of cardiac arrest studies.
- Human cadaver model of cardiac arrest studies.

Exclusion Criteria

- Full text not available (full critical analysis is required of the articles; hence abstracts will not be included owing to their lack of data available for critique).
- Foreign language paper with no available translation.

Flow Diagram 1 (adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Flow Chart, 2009)



Analysis

A brief summary of each paper identified by the search is presented within Table 1:

| Authors, date. | Study aim and design. | Outcomes measured. | Key results. |
|---|---|---|---|
| **Debaty *et al.* (2015).** | Examines potential benefits of heads-up positioning compared to supine and heads-down positioning during CPR respectively.<br><br>22 female Yorkshire pigs were sedated, intubated, ventilated and secured on a table designed to tilt the whole body according to the position required. Ventricular fibrillation (VF) was induced and left untreated for 6 minutes prior to interventions outlined in the adjacent protocols.<br><br>CPR was implemented with an active compression-decompression (ACD) device that pulls the chest wall up after each compression rather than allowing passive recoil, and an impedance threshold device (ITD) that lowers intrathoracic pressure during the decompression phase, thereby improving blood return to the heart. | Protocol A: To observe how CPR augmented with ACD and an ITD affects coronary perfusion pressure (CoPP) and cerebral perfusion pressure (CerPP) comparatively as the patient changes position: supine, head up tilt $+30^{o}$ (HUT) or head down tilt at $-30^{o}$(HDT) receiving 5 minutes of ACD+ITD CPR in each position. Secondary objective of protocol A: to determine the importance of ITD by removing it whilst continuing CPR. 14 pigs examined.<br><br>Protocol B: 8 pigs randomly selected from Protocol A. Blood flow to heart and brain measured via four injected microspheres into the left cardiac ventricle (LV); the first to gain baseline information 5 minutes prior to induced VF, 4 minute after ACD+ITD CPR initiated, 1 minute after HUT and HDT respectively.<br><br>Protocol C: 8 pigs randomly selected from Protocol A. Observe impact increasing levels of heads up ACD+ITD CPR from $+0^{o}$ to $+50^{o}$ in $10^{o}$ increments has on CoPP and CerPP. | Protocol A: CerPP increased with HUT ($p<0.05$). No definitive increase in CoPP. Secondary outcome observed immediate drop in SBP, DBP and CoPP.<br><br>Protocol B: Brain-blood flow 42% higher in HUT compared with supine (decrease by 26% in HDT). No statistically significant difference in blood flow to heart across positions.<br><br>Protocol C: Linear decrease in ICP and increase in CerPP as HUT angle increased ($p<0.001$ for both values respectively). CoPP remained constant throughout positional changes. |

| Authors, date. | Study aim and design. | Outcomes measured. | Key results. |
|---|---|---|---|
| **Ryu *et al.* (2016)** | Observe if head and thorax elevation has similar effect on systemic haemodynamics during CPR previous study by Debaty *et al.* (2015) involving full body-tilt.<br><br>30 female Yorkshire pigs. VF induced and left untreated for 8 minutes prior to interventions outlined in the two study groups adjacent.<br><br>Subjects were randomized into the groups outlined in the following column. | CerPP and CoPP were the primary outcomes measured for each group.<br><br>Group A: 14 pigs in supine position (SUP) experienced 2 minutes of conventional automated CPR (C-CPR) where chest compressions were delivered via a piston device and allowed passive chest recoil. Subjects were then randomized to either $30^{o}$ head up (HUP) or SUP without interruption in C-CPR for 20 minutes.<br><br>Group B: 16 pigs with resuscitation cycle and randomisation of positions identical to Group A. ACD+ITD CPR used as opposed to C-CPR in A.<br><br>After 22 minutes of CPR, subjects were defibrillated with up to three 275J biphasic shocks. If return of spontaneous circulation (ROSC) was not achieved, 0.5mg adrenaline and 25mg amiodarone were administered. If ROSC was not achieved, CPR resumed with defibrillation every 2 minutes and 0.5mg adrenaline every 4 minutes for up to a total of 15 minutes. If ROSC was not achieved CPR was stopped. If ROSC was achieved subjects were then euthanized. | Group A: CerPP was significantly higher ($p=0.016$) in HUP group. CoPP was not significantly different.<br><br>Group B: CerPP was significantly higher in the HUP group ($p=0.006$). CoPP was not significantly different.<br><br>Mean CerPP in ACD+ITD HUPCPR group was far higher than all other groups ($p<0.0001$).<br><br>No subjects in group A were resuscitated. 8/16 subjects from group B achieved ROSC, 6 from each sub-group. |

| Authors, date. | Study aim and design. | Outcomes measured. | Key results. |
|---|---|---|---|
| **Kim *et al.* (2017)** | Assess ideal angle of tilt for optimal CerPP and CoPP using a whole-body tilt table.<br><br>12 female farm pigs underwent similar procedural preparation to previous studies (change only in sedative administered). Subjects were left untreated in VF for 6 minutes followed by 3 minutes of ACD+ITD CPR prior to protocol implementation. | CerPP and CoPP measured at heads up tilt (HUT) of $+30^{o}$, $+45^{o}$ or $+ 60^{o}$, supine position (SUP) and heads down tilt (HDT) of $-30^{o}$, $-45^{o}$ or $-60^{o}$. 4 pigs were randomly assigned to each angle of tilt in two groups:<br><br>Group 1: 5 minutes at HUT, 5 minutes supine, 5 minutes HDT.<br><br>Group 2: 5 minutes HDT, 5 minutes supine, 5 minutes HUT.<br><br>After 18 total minutes of ACD+ITD CPR subjects were administered defibrillated with a 200J biphasic shock. | Peak CoPP was found at $+30^{o}$. Peak CerPP was found at $+45^{0}$ and $+60^{o}$.<br><br>CerPP increased significantly between each change in position from $-60^{o}$ to $+45^{o}$ across the angles tested ($p<0.001$ for each respective change).<br><br>CoPP increased significantly between each change in position from $-30^{o}$ to $+45^{o}$ across the angles tested ($p<0.001$ for each respective pchange).<br><br>All animals achieved ROSC post defibrillation. |
| **Moore *et al.* (2017)** | Compares brain blood-flow between head and thorax elevation (HUP) and supine (SUP) positioning during a prolonged resuscitation effort.<br><br>18 female Yorkshire pigs underwent identical preparation as outlined in the first two studies. VF and left untreated for 8 minutes, followed by 2 minutes of SUP ACD+ITD CPR. Brain blood-flow was measured by microspheres injected into the LV. | Subjects were randomised into either SUP or HUP for 18 minutes of continuous ACD+ITD CPR.<br><br>Primary outcome measured was blood flow to the brain after 15minutes of CPR.<br><br>Secondary outcomes measured after 5 minutes of CPR was blood flow to the brain, ICP and end tidal $CO_2$ for up to after 20 minutes of CPR.<br><br>After 19 minutes of CPR 0.5mg adrenaline and 25mg amiodarone were administered, and defibrillated with 200J 1 minute later. If ROSC wasn't achieved CPR was continued, with defibrillation every 2 minutes and 0.5mg adrenaline administered every 4 minutes. After the third shock, resuscitation was terminated if ROSC was not achieved. If ROSC was achieved, subjects were then euthanized. | Primary outcome: brain blood-flow was 25% of pre-VF baselines rate in the SUP group compared to 50% in the HUP group.<br><br>Secondary outcome: Blood flow was only slightly higher in HUP group. ICP remained fairly constant throughout the study for SUP group, and steadily declined in HUP ($p\leq 0.001$ after 15 minutes of CPR). End tidal $CO_2$ gradually reduced at an equal rate in both groups.<br><br>5/8 pigs were successfully resuscitated from the HUP group compared to 3/10 for the SUP group. |

| Authors, date. | Study aim and design. | Outcomes measured. | Key results. |
|---|---|---|---|
| **Moore *et al.* (2018)** | Tests hypothesis that similar changes in systemic haemodynamics would be witnessed across porcine models, pig cadaver (PC) models and human cadaver (HC) models when comparing SUP and HUP CPR.<br><br>The HC were prepared within 24-48hrs post mortem in preparation for the study which occurred at a later date. | CerPP and mean systolic and diastolic ICP was continuously monitored in each the 3 groups.<br><br>9 pigs were prepared identically as in the articles discussed previously; VF was induced and left untreated for 6 minutes before initiating CPR for 2 minute epochs in the following sequence: C-CPR, SUP ACD+ITD CPR and finally HUP ACD+ITD CPR. They were then defibrillated with up to three 200J biphasic shocks. If ROSC was not achieved, CPR was continued and 0.5mg of adrenaline and 25mg of amiodarone were administered IV until ROSC. Subjects were then euthanized.<br><br>3hrs later the PC were exsanguinated and filled with heparinised saline. The above epochs were then repeated.<br><br>The HC underwent 1 minute epochs of the same sequence. | Consistent increase in CerPP and decrease in ICP across the three cardiac arrest models ($p=0.007$ for all values when comparing HUP with SUP ACD+ITD CPR).<br><br>Little or no change was witnessed in the HC when comparing CerPP and ICP between C-CPR and SUP ACD+ITD CPR. |
| **Putzer *et al.* (2018)** | Aims to determine the effects of HUP verses SUP CPR on cerebral oxygenation and metabolism.<br><br>20 pigs prepared to allow study outcomes to be measured. VF was induced and left untreated for 8 minutes. Pigs were then randomised to either HUP or SUP. CPR was commenced, simulating basic life support (BLS) by a mechanical device. | Mean arterial pressure (MAP), ICP (and consequently CerPP), cerebral regional oxygenation ($rSO_2$), brain tissue partial oxygen pressure ($P_{bt}O_2$) and cerebral venous oxygenation ($S_{cv}O_2$) at five minute intervals from 0-20 minutes of CPR. | MAP increased after 5 minutes of CPR in both groups, slightly favouring HUP.<br><br>ICP increased significantly in SUP, but remained largely unchanged in the HUP group.<br><br>CerPP was significantly higher in the HUP group during CPR throughout the study.<br><br>$rSO_2$, $P_{bt}O_2$ and $S_{cv}O_2$ were virtually identical in both groups during CPR. |

As previously described, the literature for HUPCPR was of a lower level than anticipated (Oxford Centre for Evidence Based Medicine, 2011); rather than prehospital focused RCTs, only porcine animal studies investigating HUPCPR were found as a result of the literature search. The NICE appraisal checklist for quantitative intervention studies (2012) was deemed most appropriate with which to critique the literature.

The first 5 papers listed in Table 1 share conflicts of interest. Author Laurie is inventor of the ITD and ACD and is consultant to the company that authors Metzger and Lick are employed by. Funding for the research was provided by the same company. The repeated involvement of the aforementioned across these studies may have biased the validity of results obtained.

All six of the papers clearly addressed a focused issue, with virtually identical study protocols observed across the first four. Sample sizes, whilst small at face value, were deemed appropriate by all investigators when assuming an alpha level of 0.05 to reject the null hypothesis and a power of 95%. Samples were increased to accommodate for potential drop-outs in experimental procedure (due to dislodged monitoring equipment as in one pig studied by Putzer *et al.*, 2018).

The investigative processes described in five of the papers (excluding Moore *et al.,* 2018) required an element of randomised selection, which was largely well documented. However, Debaty *et al.* (2015) constructed three investigation protocols (see Table1) for which the recruitment process was not described. This poor methodological recording is unlikely to have impacted upon the results in group A, as each subject experienced HUT, supine and HDT positioning, but may bias results within groups B and C, where eight pigs per group were selected for further testing.

Ryu *et al.* (2016) similarly did not describe the randomisation process for the two groups observed within their study. These errors potentially bias results, with no indication given as to whether the randomisation process was blinded, potentially introducing selection bias. This dilutes the validity of these two papers with respect to answering the research question.

Each study measured outcomes in a largely similar way, yet due to the nature of tilting the patient thereby altering arterial pressures at which the probes are sited, CerPP calculations can vary significantly in HUP positioning if MAP is measured at the foramen of Monro rather than the right cardiac atria and experts have yet to agree on which site is optimal (Harris, 2016). If this method is later found to be less accurate it may reduce the reliability of the results garnered. However, should studies of HUPCPR develop to the prehospital setting, measurement at the foramen of Monro would be less practical (requiring a more complicated, invasive neurosurgical procedure) than obtaining central venous access to the right cardiac atria. Whilst it is unknown which method is more reliable, measurement at the right atria is more likely to be achievable in the prehospital environment. Furthermore, should it be established that measuring MAP is more accurate at the foramen of Monro, Harris (2016) states that the estimated difference may be that of 15mmHg less at the atria – this can be easily remedied mathematically by allowing for an overestimation of the same value when analysing results. Translational processes are limited within these experiments, as acknowledged in each of the papers, due to their nature as animal studies. Authors acknowledge this by building an argument for potential benefit of HUPCPR over the course of their investigations, with prior conclusions preparing the next phase of experimentation and by integrating procedural nuances in an attempt to bridge the gap between the laboratory and the prehospital environment. Subjects are untreated in VF for 6-8 minutes prior to commencing control interventions; a reasonably accurate representation of OHCA, making results more transferable to paramedic practice. Also, in acknowledging anatomical differences between humans and pigs, namely that the lower limbs of a pig are far smaller proportionally to humans, Moore *et al.* (2018) created a translational HC study (described more fully in Table 1). However, detrimentally and without explanation, catheters were inserted into the HC's renal arteries to restrict flow of saline (blood replacement in the cadaver cardiac arrest model) to the extremities, therefore restoring the previously identified discrepancy between subject and target patient anatomy. This, accompanied by the incoagulable saline blood-replacement, which removes comparison not only to potential ongoing coagulation due to reduced blood flow, but also of potential thromboembolic cause of OHCA, and nature of HC makes the results from this experiment virtually unusable in answering the question set by this systematic review. As such, it cannot meaningfully contribute to this review's conclusion. However, despite its flawed methodology, the paper, remains included within this review for the reasoning that such a novel approach, with regards to bridging the gap between the porcine and human model of cardiac arrest, may be vital if repeated with more rigorous study technique in identifying the potential benefit of HUPCPR in OHCA.

Follow-up of subjects was short and for reasons undisclosed (either study design oversight or gaining favourable ethical opinion) subject follow-up never progresses beyond ROSC, when subjects were then euthanized. Therefore, unless ethics permit extended observational periods to assess neurological status, conclusions made by Ryu *et al.* (2016) cannot be extended to simulated survival to discharge for OHCA patients in this porcine model of cardiac arrest.

## Discussion

The results of this systematic search are congruent; illustrating an emergent school of thought that 'Heads-Up' positioning during the porcine model of cardiac arrest reduces ICP and increases CerPP.

Putzer *et al.* (2018) identify that HUPCPR alone, whilst statistically significantly reducing ICP and increasing CerPP, does not increase cerebral tissue oxygenation. Debaty *et al.* (2015) and Ryu *et al.* (2016) also previously demonstrated that CerPP values were significantly lower when comparing C-CPR to ACD+ITD HUPCPR. On the basis of these three papers, it is reasonable to conclude that HUPCPR without augmentation of ACD+ITD would be of unlikely benefit in OHCA patients, although further research in human cardiac arrest would be required to form a true conclusion.

Patients in cardiac arrest lose haemodynamic autoregulation, commonly causing cerebral oedema (Brule *et al.*,2018), resulting in raised ICP, reducing CerPP (as CerPP = MAP-ICP) and thus inducing hypoxic brain injury. Management of ROSC patients in hospital involves close monitoring and pharmaceutical control of their ICP to nullify this pathology (Malaguit *et al.*, 2017). Consistently, as displayed in Table 1, ICP has been documented to decrease with elevating the patient, whether by a full body tilt or by elevating the head and thorax (Ryu *et al.*, 2016). The ideal angle of elevation was shown to be 30$^{o}$ (Kim *et al.,* 2017). Therefore ACD+ITD HUPCPR has the potential to improve patient outcomes given its documented ability to reduce ICP in the porcine model of cardiac arrest. Left unanswered however is whether or not this method reduces ICP and raises CerPP in human OHCA significantly enough to improve survival to discharge and neurological outcome.

Furthermore, whilst ROSC rates appeared higher for subjects given ACD+ITD HUPCPR (as observed by Ryu *et al*., 2016 and Moore *et al.*, 2017), differences in drug dosages, energy delivered during defibrillation, length of time in altered positions of HUP, SUP and HDT as well as timings of interventions between the studies render their findings difficult to compare with each other. They are also difficult to translate to OHCA. The UK Resuscitation Council (2017) and AHA (2015) recommend immediate defibrillation for OHCA when the patient is found in a shockable rhythm. This extreme heterogeneity and variance from standard treatment make it difficult to determine even at what stage initiation of HUPCPR would be most beneficial, if at all. Additionally, Kim *et al.* (2017) displayed ROSC for all subjects involved in their study, each of which experienced HUT, SUP and HDT positioning.

The limitations of the data found cannot be understated. Firstly, there were no human clinical trials found during the time this systematic review was conducted. Secondly, the attempt at creating a translational HC model by Moore *et al.* (2018) was thwarted by poor investigative technique. Thirdly, the pool of data is almost exclusively from the same bank of authors, with acknowledged conflicts of interest rooted in finance and employment. Fourthly, discrepancies between advanced life support procedure observed and heterogeneity of results make these papers harder to directly compare than one would have anticipated given the overlap in authorship across five of the research endeavours. These weaknesses mean that, however conclusively these papers identify that ACD+ITD HUPCPR reduces ICP and increases CerPP and CoPP in the porcine model of cardiac arrest, the results are difficult to extrapolate to OHCA patients and therefore this procedure cannot yet be recommended for implementation in paramedic practice.

Whilst the research analysed cannot answer the question set by this systematic review, it strongly suggests the next steps required to identify the potential benefits of augmented HUPCPR in OHCA, namely re-evaluating a translational cadaver model as initially attempted by Moore *et al.* (2018).

The novel approach demonstrated by Moore *et al.* (2018) at establishing a translational cadaver model to overcome the inherent physiological differences in vasculature between pigs and humans requires a more robust investigation. The two main areas of improvement would be identifying a more realistic substitute for blood than saline (one of equal viscosity) and refraining from diverting the blood-replacement from the extremities of the cadavers.

Furthermore, current prehospital resuscitation guidelines should be observed during the attempted drug resuscitation portion of the experiment to allow greater comparison to OHCA. For example, porcine subjects, left in induced VF and untreated for a 6-7 minutes to represent a realistic OHCA without bystander CPR (time-frame in line with ambulance response times according to guidance from NHS England, 2017), should be subjected to immediate defibrillation, followed by initiation of augmented HUPCPR whilst following recognised resuscitation guidelines either from UK Resuscitation Council (2015) or American Heart Association guidelines (2018) etc.

Building upon the study by Putzer *et al.* (2018), a further study into cerebral tissue oxygenation should be conducted but with augmented HUPCPR rather than standard HUPCPR. This would further evidence whether or not augmented HUPCPR increases CerPP to a great enough extent to improve cerebral tissue oxygenation and potentially improve neurological outcome post ROSC.

Finally, should favourable ethical opinion be gained, it would be beneficial to facilitate an investigation to study the quality of neurological outcome of porcine subjects following successful resuscitation from augmented (ICD+ACD) HUPCPR by allowing subjects to recover and be observed for a set period of time. International Liaison Committee on Resuscitation (ILCOR, 2015) state the Utstein criteria for assessment of successful resuscitation is quality of life measured at 12 month survival, this may be unrealistic at this early stage of clinical trials, however this should influence the decision at what length of time the porcine subjects be re-evaluated. Also, as Ryu *et al.* (2016) demonstrated equal ROSC rate between augmented HUPCPR and augmented supine CPR, subject assessment a suitable time post ROSC would help establish the quality of ROSC achieved and elucidate the benefit of augmented HUPCPR against augmented supine CPR. Given Moore *et al.* (2017) found a greater ROSC rate in their HUPCPR compared with their supine CPR groups, both receiving ACD and ITD augmentation, gives reason to expect results in favour of augmented HUPCPR, but without thorough investigation these remain hypothesised results.

Should these studies identify a promising rise in CerPP, human trials may be the next logical step in the development of augmented HUPCPR.

## Conclusion

HUPCPR has been demonstrated to effectively increase CerPP and CoPP in the porcine model of cardiac arrest by each of the six sources analysed.

Putzer *et al.* (2018) have identified that HUPCPR without augmentation of ACD+ITD increases CerPP, but does not increase regional cerebral tissue oxygenation and therefore is unlikely to be of any benefit in OHCA patients. According to the research evaluated, it appears HUPCPR must be augmented with ACD and ITD in order to increase CerPP to a greater degree.

It is the recommendation of this systematic review that further research is required to ascertain if HUPCPR is of likely benefit to patients in OHCA.

<u>Limitations</u>

The authors of this systematic review acknowledge two main limitations to this body of work.

Firstly, the literature discussed, whilst clearly of a lower level than that expected in answering the research question, is complex in its number of variables measured. In depth analysis was thereby restricted by the word count, leaving some aspects of the literature unexplored. The heterogeneity of the subject studied further increases the difficulty of drawing a clear conclusion from the literature.

Secondly, the number of authors of this work (two) may limit exploratory abilities. As mentioned above, the papers analysed are intensely heterogeneous and may have benefited from additional authorship.

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