

Peer Review File

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Comments	Authors' Reply	Changes in the Text
Reviewer A		
<p>1. The results, although based on low-quality evidence, may be a signal that sets the course for future work.</p>	<p>We thank the reviewer for the kind comments.</p> <p>We acknowledge the paucity of current evidence obtained from human models of study.</p> <p>We agree with the reviewer that the findings from this systematic review and meta-analysis may guide future research into the novel intervention of head-up CPR.</p>	NIL
<p>2. The paper is well written.</p> <p>The selection of references, the description of possible bias and the form of meta-analysis itself are correct.</p> <p>Taking into account the high quality of the manuscript and its high merits, I recommend the publication of the paper without modification.</p>	<p>We express our gratitude to the reviewer for the kind and encouraging comments.</p>	NIL
Reviewer B		
<p>1. This is an important area of research in cardiac resuscitation that is worth analyzing and determining the potential clinical efficacy.</p>	<p>We thank the reviewer for the kind comments.</p>	NIL
<p>2. As the analysis shows the work has been done mostly in animal models with only a single clinical study reported which has the weakness of being a before and after study. Accordingly, it will be very helpful to emphasize from the onset that the findings stem from 12 studies conducted in animal models and that there was only one before and after study in humans.</p>	<p>We thank the reviewer for the comment.</p> <p>We have mentioned in the abstract (Page 4, Lines 12-13) that 11 out of the 13 included studies were animal-only studies.</p> <p>We accept the reviewer's suggestion to emphasise that the sole human study is a before-and-after study.</p> <p>We have also highlighted in the Discussion section (Page 17, Line 3) that the only human data obtained came from a single observational study, despite the numerous porcine studies included in the review.</p>	<p>[Abstract – Results] Page 4 Line 12 We have made the following changes: “...one before-and-after human-only study”.</p>

<p>3. In addition, it is also important to discuss whether any potential efficacy of HU-CPR is contingent on CPR being performed with active compression-decompression and with an impedance threshold device (ITD).</p> <p>This reviewer is not aware of any study showing that HU-CPR works when added to conventional CPR (manual CPR without the ITD), and which could be difficult to perform with the head and torso at 30°.</p> <p>Accordingly, it is critical to clarify whether the data available limits the analysis to when HU-CPR is applied to CPR conducted using active compression-decompression (or with a LUCAS device) and the ITD valve.</p>	<p>We thank the reviewer for the comment.</p> <p>We agree with the reviewer that there is currently no study showing HU-CPR implemented with manual hands-only CPR, to the team’s current knowledge.</p> <p>The closest study to HU-CPR implemented in a conventional manner is Ryu et al’s 2016 study (Ryu HH, Moore JC, Yannopoulos D, Lick M, McKnite S, Shin SD. The Effect of Head Up Cardiopulmonary Resuscitation on Cerebral and Systemic Hemodynamics. Resuscitation. 2016;102:29–34 doi: 10.1016/j.resuscitation.2016.01.033 PMID: 26905388).</p> <p>We take reference from Figure 7 of our paper, which was reproduced from Ryu et al 2016, with permission from Elsevier – As shown by the graph of Cerebral Perfusion Pressure (mmHg) plotted against Time (minutes), the green line denotes the use of HU-CPR applied to conventional CPR without the use of ACD/ITD. While there is an increase in CerPP from 2 to 7 minutes, this benefit tapers off and decreases past the 7-minute mark. This is unlike the ACD and ITD bundled HU-CPR which saw the maintenance of CerPP long after the 7-minute mark.</p> <p>Hence, we are of the opinion that the benefits of HU-CPR are not entirely contingent on ACD/ITD utilization. The ACD, ITD and head-up positioning each has their own benefit and separate mechanism of effect. It is the bundling of the ACD and ITD with HU-CPR that creates newfound synergy and greatly augments the clinical benefit of HU-CPR.</p> <p>We agree with the reviewer to clarify that the analysis done for this research is indeed limited to CPR conducted with ACD/ITD/mechanical compression device, with no manual hands-only experimental arm.</p>	<p>NIL</p> <p>[Limitations] Page 23, Lines 17 to 20 We have added the following sentence to clarify the pertinent point raised by the reviewer.</p> <p>“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.”</p>
<p>4. The opening statement is odd. Is there any other source of blood flow in the body? Please review what mainstream authors have used in the past to describe sudden cardiac arrest.</p>	<p>We thank the reviewer for the comment.</p> <p>We apologise for the odd phrasing and have made a change to the sentence.</p>	<p>[Introduction] Page 6, Lines 2 to 3</p>

		“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.”
5. Please provide the pertinent reference to the sentence that ends discussing the range of survival rates from out of hospital cardiac arrest (Page 6, Line 7).	<p>We thank the reviewer for the comment.</p> <p>We apologise for the oversight. The reference in-question is: Sasson C, Rogers MA, Dahl J, Kellermann AL. Predictors of survival from out-of-hospital cardiac arrest: a systematic review and meta-analysis. <i>Circulation: Cardiovascular Quality and Outcomes</i>. 2010 Jan;3(1):63-81. We have since added the in-text citation.</p>	<p>[Introduction] Page 6, Line 8</p> <p>Added in-text citation [3] to the end of the sentence.</p>
6. Please be thorough with your references. There are several statements lacking the required references. One example is the sentence that ends on Line 13 (Page 6).	<p>We thank the reviewer for the comment.</p> <p>We apologise for the oversight. The references in-question are:</p> <p>Moore JC, Salverda B, Lick M, et al. Controlled progressive elevation rather than an optimal angle maximizes cerebral perfusion pressure during head up CPR in a swine model of cardiac arrest. <i>Resuscitation</i>. 2020;150(C):23-8.</p> <p>Moore JC, Salverda B, Rojas-Salvador C, Lick M, Debaty G, G Lurie K. Controlled sequential elevation of the head and thorax combined with active compression decompression cardiopulmonary resuscitation and an impedance threshold device improves neurological survival in a porcine model of cardiac arrest. <i>Resuscitation</i>. 2021;158:220-7.</p> <p>Ryu HH, Moore JC, Yannopoulos D, Lick M, McKnite S, Shin SD. The Effect of Head Up Cardiopulmonary Resuscitation on Cerebral and Systemic Hemodynamics. <i>Resuscitation</i>. 2016;102:29-34</p>	<p>[Introduction] Page 6, Line 14</p> <p>Added in-text citations [5] and [6], corresponding to Moore et al 2020 and Moore et al 2021.</p> <p>Page 6, Line 15</p> <p>Added in-text citation [7], corresponding to Ryu et al 2016.</p>
7. The sentence on page 7 stating that “guideline recommendations have been made in support of implementing HU-CPR11” is incorrect. The authors cited a study proposing a comprehensive strategy that includes among many other interventions HU-	We thank the reviewer for the comment and have made a change to the sentence in-question.	<p>[Introduction] Page 7, Line 5</p>

<p>CPR by a group of well recognized research experts, but it is not the same as a guideline.</p> <p>The most recent AHA guidelines on advanced life support states that “there is insufficient evidence concerning the cardiac arrest bundle of care with the inclusion of “heads-up” CPR to provide a recommendation concerning its use. (Panchal AR et al. Circulation 2020 Oct 20;142(16_suppl_2):S366-S468. doi: 10.1161/CIR.0000000000000916. Epub 2020 Oct 21. PMID: 33081529).</p>		<p>“...guideline recommendations ...” has been changed to “...expert recommendations...”</p>
<p>8. Results: At the onset of this section, please emphasize that there was only one clinical study identified, which was a before and after (Pepe et al.).</p>	<p>We thank the reviewer for the comment and have since made the changes.</p>	<p>[Results – Characteristics of included studies]</p> <p>Page 11, Lines 10 to 11</p> <p>The sentence has been re-ordered to emphasise the one clinical human study.</p> <p>“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.”</p>
<p>9. At the same time, point that the analysis that follows includes 12 animal studies, and avoid combining the clinical with the animal findings.</p>	<p>We thank the reviewer for the comment and we apologise for the lack of clarity in the organisation of results.</p> <p>We have since separated the findings of the animal and human studies by paragraphing, and have ensured that sentences reporting any findings specified the studies as “animal” or “human”.</p>	<p>[Results – Survival]</p> <p>Page 13, Lines 3 to 4</p> <p>“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-hours post-ROSC.”</p> <p>New paragraph added for Lines 8-10. “Pepe et al 2019's human study reported that the rates of intact neurological survival (modified</p>

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)”

Page 13, Lines 15 to 16

“In terms of 24-hour survival, a total of 37 animal subjects across two porcine RCTs (6,18) were assessed based on pooled 24-hour survival outcomes.”

[Results – ROSC]

Page 14, Line 9

“With regards to pooled ROSC outcomes, a total of 50 animal subjects across three porcine RCTs (6,7,19) were assessed.”

[Results – ICP]

Page 14, Line 16

“Consistently across seven animal studies, HU-CPR significantly lowered ICP.”

Page 14, Lines 20 to 21

“With regards to the pooled outcome of ICP after 20 minutes of CPR, a total of 53 animal subjects across three porcine RCTs (19,21,22) were assessed.”

[Results – CerPP]

Page 15, Line 8

“Consistently across six **animal** studies, CerPP was significantly higher with HU-CPR.”

Page 15, Lines 15 to 16

“With regards to the pooled outcome of CerPP after 20 minutes of CPR, a total of 69 **animal** subjects across four **porcine** RCTs(7,19,21,22) were assessed.”

Page 15, Lines 21 to 22

“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.”

Page 15, Lines 24 to 25

The **animal** RCTs assessed in the meta-analyses for ICP and CerPP differed slightly in their methodologies.

[Results - BBF]

Page 16, Lines 11 to 12

“With regards to brain blood flow (BBF), a total of 40 **animal** subjects from 2 RCTs(16,19) were assessed.”

Page 16, Line 16

		<p>“Both porcine RCTs used similar time periods for their interventions.”</p>
<p>10. In the Discussion, reference to the outcomes reported in humans and those reported in animals would be appropriate.</p>	<p>We thank the reviewer for the comment and have since specified the differences in findings based on animal and human studies.</p>	<p>[Discussion]</p> <p>Page 18, Lines 2 to 7</p> <p>“In this systematic review and meta-analysis, several main findings emerged: 1) despite numerous porcine studies on HU-CPR, the only human data came from a single observational study, which reported doubling of ROSC rates, 2) there was overall benefit to neurological outcomes and statistically significant beneficial pooled effect on 24-hour survival in animal subjects, 3) there were statistically significant beneficial pooled effects on ICP, CerPP and BBF in animal subjects.”</p>
<p>11. Table 1 refers to one study that included human cadavers and pigs. However, only the data on humans is reported. Please clarify that the animal data are reported in Table 2.</p>	<p>We thank the reviewer for the comment and apologise for the lack of clarity in the organization of results.</p> <p>Table 1 details the findings from one human observational study and one human cadaver study while Table 2 details the findings from the 12 animal and animal cadaver studies.</p> <p>We have made doubly sure to separate the human and animal findings and have also specified, for Moore 2018, that the human cadaver findings are found in Table 1 while the porcine findings are found in Table 2.</p>	<p>[Table 1]</p> <p>Moore et al 2018 “Findings from the porcine protocols are reported in Table 2.”</p> <p>[Table 2]</p> <p>Moore et al 2018 “Findings from the human cadaver protocol are reported in Table 1.”</p>
<p>12. In addition, when referring to the study by Pepe et al, the description of the bundled intervention is not clear, was the ITD plus LUCAS included in all the bundled interventions? If so, please clarify.</p> <p>Was there any other outcome beyond the resuscitation rate?</p>	<p>We thank the reviewer for the comment and we apologise for the lack in clarity.</p> <p>The pre-intervention period for Pepe et al’s 2019 study saw all crew utilising the LUCAS and the ITD in their resuscitation algorithms.</p> <p>The intervention period included the existing ITD + LUCAS approach, with three additional changes:</p>	<p>[Table 1]</p> <p>Pepe et al 2019 “Additional measures during intervention period:</p>

	<p>1) Delayed positive pressure ventilations after application of oxygen</p> <p>2) Strengthening of the team set-up for fast LUCAS placement</p> <p>3) 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</p> <p>We have since made changes to Table 1, to include these clarifications.</p>	<p>1) Delayed positive pressure ventilations after application of oxygen</p> <p>2) Strengthening of the team set-up for fast LUCAS placement</p> <p>3) 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."</p>
<p>13. In addition, given the weakness of before and after clinical studies, it is very important to determine whether the authors (Pepe et al) applied statistical methods to identify other factors that could have influenced the changing outcome over time.</p> <p>It is understandable that the authors would be biased towards the new intervention and that blinding is impossible, and therefore it is imperative to look for alternatives to isolate the effect. One common tool used is propensity matching. Also, regression analyses could be employed to assess other factors that could have influenced outcome beyond HU-CPR. Because it is the only clinical study (with live subjects) included in this systematic review and meta-analysis, a close scrutiny of the study is paramount.</p>	<p>We thank the reviewer for the comment.</p> <p>Indeed, it is extremely important to examine Pepe et al's study in further detail given its role as the only clinical study with live subjects. As is an observational study, it is important to evaluate the study's statistical methods.</p> <p>Pepe et al's study did not employ tools such as propensity matching to isolate the effect, instead noting the magnitude of sudden improvements upon implementing HUCPR in their well-established EMS system. They hence state their belief that it is unlikely that other factors would be likely in causing these improvements.</p> <p>We acknowledge that in an optimal situation, Pepe et al's study would have conducted further statistical tests. We recognize that this is a potential issue in our meta-analysis and have addressed it in our limitations that our study is limited by the paucity of randomized human data, and that further randomized human trials are required.</p>	NIL
<p>14. Figures 1 through 7 in the copy provided to this reviewer were of poor quality that made it difficult to decipher and adequately review.</p>	<p>We apologise for the unpleasant experience with our figures. We have since saved the figures in files of higher quality.</p>	NIL
Reviewer C		
<p>1. This is a well-written paper. Few improvements are possible before publication.</p>	<p>We express our gratitude to the reviewer for the kind and encouraging comments.</p>	NIL

<p>2. First, the authors need more separation between swine and human. It is something unclear in the paper. When they say subjects, it is hard to know if it is human or swines.</p>	<p>We thank the reviewer for the comment and apologise for the lack of clarity.</p> <p>We have since added the specific description of “animal” or “human” when subjects or studies are mentioned.</p>	<p>[Results – Survival]</p> <p>Page 13, Lines 3 to 4</p> <p>“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-hours post-ROSC.”</p> <p>New paragraph added for Lines 8-10. “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)”</p> <p>Page 13, Lines 15 to 16</p> <p>“In terms of 24-hour survival, a total of 37 animal subjects across two porcine RCTs (6,18) were assessed based on pooled 24-hour survival outcomes.”</p> <p>[Results – ROSC]</p> <p>Page 14, Line 9</p> <p>“With regards to pooled ROSC outcomes, a total of 50 animal subjects across three porcine RCTs (6,7,19) were assessed.”</p> <p>[Results – ICP]</p>
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Page 14, Line 16

“Consistently across seven **animal** studies, HU-CPR significantly lowered ICP.”

Page 14, Lines 20 to 21

“With regards to the pooled outcome of ICP after 20 minutes of CPR, a total of 53 **animal** subjects across three **porcine** RCTs (19,21,22) were assessed.”

[Results – CerPP]

Page 15, Line 8

“Consistently across six **animal** studies, CerPP was significantly higher with HU-CPR.”

Page 15, Lines 15 to 16

“With regards to the pooled outcome of CerPP after 20 minutes of CPR, a total of 69 **animal** subjects across four **porcine** RCTs(7,19,21,22) were assessed.”

Page 15, Lines 21 to 22

“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.”

Page 15, Lines 24 to 25

		<p>The animal RCTs assessed in the meta-analyses for ICP and CerPP differed slightly in their methodologies.</p> <p>[Results - BBF]</p> <p>Page 16, Lines 11 to 12</p> <p>“With regards to brain blood flow (BBF), a total of 40 animal subjects from 2 RCTs(16,19) were assessed.”</p> <p>Page 16, Line 16</p> <p>“Both porcine RCTs used similar time periods for their interventions.”</p>
<p>3. Their review of literature is almost complete. However, they missed a second Paper by Moore in 2020. (Controlled sequential elevation of the head and thorax combined with active compression decompression cardiopulmonary resuscitation, and an impedance threshold device improves neurological survival in a porcine model of cardiac arrest. DOI: 10.1016/j.resuscitation.2020.09.030)</p>	<p>We thank the reviewer for the comment.</p> <p>The paper quoted by the reviewer has already been included and analysed in this review as Moore et al 2021.</p> <p>The full reference in the bibliography is as follows: Moore JC, Salverda B, Rojas-Salvador C, Lick M, Debaty G, G Lurie K. Controlled sequential elevation of the head and thorax combined with active compression decompression cardiopulmonary resuscitation and an impedance threshold device improves neurological survival in a porcine model of cardiac arrest. Resuscitation. 2021;158:220–7.</p>	<p>NIL</p>
<p>4. I would recommend to the team to insist on the necessity of having very high-quality CPR. They already start doing this with their references 9, 39.</p>	<p>We thank the reviewer for the comment.</p> <p>We absolutely agree with the reviewer on the importance of high-quality CPR. Even if there were head and thorax elevation, there would be no clinical benefit if the rudimentary criteria of effective chest compressions are not met.</p> <p>We have added a sentence in the discussion to highlight this point.</p>	<p>[Discussion]</p> <p>Page 22, Lines 20 to 21</p> <p>“The value of the novel intervention of HU-CPR is present only if the rudimentary criteria of high-quality chest compressions are met. (10,12,39)”</p>

<p>5. Replace conventional CPR (S-CPR) by standard CPR (S-CPR)</p> <p>“The pooled effect on ROSC 19 in three studies was OR=3.63” Please add the word swine if those three studies are done in swine. That also needed the added swine as above.</p>	<p>We thank the reviewer for the comment and apologise for the lack of clarity.</p> <p>We have since made the changes in the Abstract.</p>	<p>[Abstract – Background]</p> <p>Page 4, Lines 5 to 6</p> <p>“We evaluated whether HU-CPR improved survival and surrogate outcomes as compared to standard CPR (S-CPR).”</p> <p>Page 4, Lines 18 to 19</p> <p>“The pooled effect on ROSC in three porcine studies was OR=3.63 (95%CI 0.72-18.39).”</p>
<p>6. “Head-up CPR (HU-CPR) is an experimental technique which involves performing CPR with the patient’s torso and head in an inclined position.”</p> <p>I would recommend the authors to add that the HU-CPR also included a high-quality CPR component to create enough forward flow and that by the HU-CPR studies used mechanical ACD-ITD CPR.</p>	<p>We thank the reviewer for the comment.</p> <p>We agree with the reviewer’s recommendation and have specified the CPR to be of high-quality.</p>	<p>[Introduction]</p> <p>Page 6, Lines 11 to 12</p> <p>“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.”</p>
<p>7. “The primary hypothesis was that HU-CPR improves survival in cardiac arrest compared to S-CPR.”</p> <p>How do the authors know that they have enough power to demonstrate that endpoint if the studies were not designed for this? The global number of swine and human remain low. And there is only one human study.</p>	<p>We thank the reviewer for this comment.</p> <p>Indeed, the total number of studies evaluating the effect of HUCPR remains low, with human studies on this matter scarce as well.</p> <p>However, given the backdrop of multiple EMS centers already implementing HUCPR with impressive preliminary results, we believe it is still important to conduct a review to clarify the current literature on HUCPR’s clinical effects.</p> <p>We do acknowledge that the low number of studies is an inevitable limitation of our study and have stated as such in our limitations.</p> <p>We have also stated the importance of conducting further randomized human trials in our conclusion as follows:</p>	<p>NIL</p>

	<p>Page 23, Lines 2 to 5</p> <p>“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.”</p>	
<p>8. “In terms of 24-hour survival, a total of 55 subjects a” The authors should say if the subjects are swine or human or both.</p>	<p>We apologise for the lack of clarity and we thank the reviewer for the comment.</p> <p>We have since made the change to specify 37 animal subjects.</p>	<p>[Results – Survival]</p> <p>Page 13, Lines 15 to 16</p> <p>“In terms of 24-hour survival, a total of 37 animal subjects across two porcine RCTs (6,18) were assessed based on pooled 24-hour survival outcomes.”</p>
<p>The authors are reporting 55 subjects across two RCTs with 24h survival. However, figure 2 shows only 37 swines.</p>	<p>We apologise for the error and we thank the reviewer for pointing this out.</p> <p>We have made the change to 37 animal subjects.</p>	<p>[Results – Survival]</p> <p>Page 13, Lines 15 to 16</p> <p>“In terms of 24-hour survival, a total of 37 animal subjects across two porcine RCTs (6,18) were assessed based on pooled 24-hour survival outcomes.”</p>
<p>9. Furthermore, I would recommend to show a trend to improve 24h survival compare to a negative result in few of their figure. In particular, because the control group are different.</p> <p>In the 2016 study, the control group is ACD + ITD flat, while in the 2020 it is standard CPR. The presence of an ICD ITD group in the control group is going to help a lot for ROSC and less for the neuro CPC.</p>	<p>We thank the reviewer for this comment.</p> <p>We have made the change to comment on the trend for 24hr survival under the Results section and commented on the different control groups in our Discussion.</p>	<p>[Results – 24 hr survival]</p> <p>Page 13, Lines 19 to 20</p> <p>“However, it is worth noting that meta-analytic estimates in Figure 2 showed a trend favouring HU-CPR.”</p> <p>[Discussion]</p> <p>Page 18, Lines 17 to 19</p> <p>However the moderate heterogeneity (I²=71%) limited inference on the true magnitude of</p>

		effect, and is possibly related to variations in HU-CPR protocol, such as differences between the types of study control used.
<p>10. In the text and figure 3, the authors report only three studies with ROSC. However, they do not report several other studies with ROSC, for example Moore 2016 (to have 24h survival you need ROSC);</p> <p>Moore 2020 gave ROSC number (only for head up group, no flat group).</p>	<p>We thank the reviewer for this comment.</p> <p>We understand that Moore et al 2016 reported 24hr survival rates, and all animals that survived to 24hrs achieved ROSC. However, given that Moore et al 2016 did not specifically report ROSC, we believe it might be disingenuous to use their 24hr survival numbers as ROSC numbers, given that more animals could have achieved ROSC but did not survive to 24 hours.</p> <p>Moore et al 2020 did report ROSC number for the head up group. However as they lacked a supine group to compare a ROSC number against, we are unable to include it in the meta-analysis in Figure 3.</p>	
<p>11. Park does not do the same high-quality CPR, and result might not be comparable to the others' studies. Furthermore, Park did not do the prime the pump described by the other authors before doing HU.</p>	<p>We thank the reviewer for this comment.</p> <p>Indeed, we noted that Park et al was the only study that reported a significantly worse rate of ROSC and 24-hour survival, and suggested the anomaly could be due to Park et al's longer period of untreated VF at 15 minutes compared to other studies.</p> <p>We agree that Park has the limitations of not priming the pump, and have made the changes to the discussion section.</p>	<p>[Discussion]</p> <p>Page 19, Lines 17 to 20</p> <p>"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, which could have also affected the rate of ROSC and survival rate."</p>
<p>12. There is a discrepancy between those two phrases on in the result section and on in the discussion: "Meta-analytic estimates for 24-hour survival showed no 14 statistically significant benefit for animals where HU-CPR was conducted in comparison to 15 animals that underwent S-CPR, as shown in Figure 2" "There was an overall benefit to neurological outcomes and statistically significant beneficial pooled effect on 24-hour survival"</p>	<p>We thank the reviewer for the comment and we apologise for the discrepancy.</p> <p>We have since made the changes to the discussion section.</p>	<p>[Discussion]</p> <p>Page 18, Lines 4 to 6</p> <p>"2) there was overall benefit to neurological outcomes and 24-hour survival in animal subjects, although statistically insignificant,"</p>
<p>13. "mCPR" the authors should define at least one mechanical CPR.</p>	<p>We thank the reviewer for the comment.</p>	<p>NIL</p>

	mCPR has been defined as mechanical CPR in the Results section, on page 11, Line 18.	
<p>14. "Of note, Park et al was the only study that ..." Park's study did not used prime the pump. Overall different quality of CPR which can change the perfusion pressure.</p> <p>The Putzer paper also had a different CPR as it did not use ITD.</p> <p>For both this paper, this difference in CPR might be an important confounder as shown in the figure 7 of this document.</p>	<p>We thank the reviewer for this comment.</p> <p>We agree with the reviewer's point on Park et al's study and have made changes in response to the reviewer's comment in point 11 above.</p> <p>We recognize that Putzer et al had a different CPR protocol and thank the reviewer for pointing it out. Upon reviewing the meta-analysis we have conducted, the exclusion of Putzer et al would not have an impact on the overall significance level of our outcomes as all studies showed a significant effect favouring HU-CPR for the analysis of the clinical outcomes that Putzer et al was included in.</p> <p>In addition, given Putzer et al poorer overall effects, the removal of Putzer et al from our meta analysis would actually lead to an improvement in clinical outcomes.</p> <p>We have thus decided to comment on the difference in study protocol in the discussion.</p>	<p>[Discussion]</p> <p>Page 20, Lines 8 to 12</p> <p>"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. (Figure 4-5)"</p>
<p>15. "It was posited that" The authors should replace this by "It was assumed" as posited in not a word frequently used.</p>	<p>We thank the reviewer for the comment and accept the suggestion to replace the word "posited" with "assumed".</p>	<p>[Discussion]</p> <p>Page 21, Lines 2 to 3</p> <p>"It was assumed that CSE augmented right to left pulmonary flow and improved autoregulation of systemic vasculature."</p>
<p>16. Even if I usually do not like to speak of a brand in review of science. I found it hard in this case not to cite anywhere in the document the "EleGARD™" (https://www.elevatedcpr.com/) that was created by part of the research team that did some of the swine studies. The device could allow a normalization of the HUT with a CSE.</p>	<p>We thank the reviewer for the comment.</p> <p>While we agree that the EleGARD holds great promise in the normalisation of HU-CPR, we have yet to find a peer-reviewed journal article examining the efficacy of the EleGARD in relation to the measurement of neurological parameters in human or human-cadaver models.</p> <p>Most of the animal studies in this review were headed by the team that developed the EleGARD, which could raise</p>	<p>[Discussion]</p> <p>Page 23, Lines 5 to 7</p> <p>"A possible solution is the EleGARD™ device which has been mentioned in some literature (23,42), although further research into its specific use in human models of cardiac arrest is needed."</p>

	<p>concerns of bias. Moreover, the device used to induce CSE and HUT in those animal studies was not the EleGARD per se, but another Customised Elevation Device (CED) that was modelled to resemble the EleGARD. (see Moore et al 2020, Moore et al 2021 and Rojas-Salvador et al 2020).</p> <p>The closest study available that reported on the EleGARD is Holley et al 2020 (Holley J, Moore JC, Jacobs M, Rojas-Salvador C, Lick C, Salverda BJ, Lick MC, Frascone RJ, Youngquist ST, Lurie KG. Supraglottic airway devices variably develop negative intrathoracic pressures: A prospective cross-over study of cardiopulmonary resuscitation in human cadavers. Resuscitation. 2020 Mar 1;148:32-8.) The study however did not report on the benefit of the EleGARD in specific relation to neurological parameters in sudden cardiac arrest.</p> <p>We accept the reviewer's suggestion to make a mention of the EleGARD, but specify that no current research has reported any clinical benefit.</p>	
<p>17. "Figure 7" this figure is taken as is from one of the cited papers. The editor should check if the authors have consent to use this figure from the editor of the figure.</p>	<p>We thank the reviewer for raising this concern.</p> <p>Figure 7 of our paper was reproduced from Ryu et al 2016 with permission from Elsevier.</p>	<p>NIL</p>