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Clinical paper

Cerebral regional oxygen saturation during cardiopulmonary resuscitation and return of spontaneous circulation: A systematic review and meta-analysis

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Abstract

Aim: Predicting the return of spontaneous circulation (ROSC) during cardiopulmonary resuscitation in victims of cardiac arrest (CA) remains challenging. Cerebral regional oxygen saturation (rSO2) measured during resuscitation is feasible, and higher initial and overall values seem associated with ROSC. However, these observations were limited to the analysis of few small single-centre studies. There is a growing number of studies evaluating the role of cerebral rSO2 in the prediction of ROSC.

Methods: We conducted an updated meta-analysis aimed at investigating the association of initial and overall values of cerebral rSO2 with ROSC after CA. We performed subgroups analyses according to the location of CA and conducted a secondary analysis according to the country where the study was conducted (resuscitation practice varies greatly for out-of-hospital CA).

Results: We included 17 studies. Higher initial rSO2 values (11 studies, n = 2870, 16.6% achieved ROSC) were associated with ROSC: Mean Difference (MD) -11.54 [95%Confidence Interval (CI)-20.96, -2.12]; p = 0.02 (I^2 = 97%). The secondary analysis confirmed this finding when pooling together European and USA studies, but did not for Japanese studies (p = 0.06). One multi-centre Japanese study was an outlier with large influence on 95%CI. Higher overall rSO2 values during resuscitation (9 studies, n = 894, 33.7% achieving ROSC) were associated with ROSC: MD-10.38; [-13.73, -7.03]; p < 0.00001 (I^2 = 77%). All studies were conducted in Europe/USA.

Conclusions: This updated meta-analysis confirmed the association between higher initial and overall values of cerebral rSO2 and ROSC after CA. However, we found geographical differences, since this association was not present when Japanese studies were analysed separately.

Keywords: near infrared spectrometry; advanced cardiac life support; resuscitation order; cardiopulmonary resuscitation.
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Introduction

Predicting the return of spontaneous circulation (ROSC) during cardiopulmonary resuscitation (CPR) represents a clinical challenge. Despite improvements in CPR and in the post-resuscitation care, mortality in patients suffering from cardiac arrest (CA) remains high. The rate of ROSC is very low, especially among out of hospital (OH) CA; furthermore, less than 50% of patients admitted to hospital after CA are alive at 6-month follow-up.[1–4] To date, there is no formally validated tool to help clinicians in deciding how long to prolong their efforts in CPR, and such decision is often made on clinical grounds only. Importantly, when ROSC is achieved, the principal cause of death is attributable to neurological damage resulting from the ischemia-reperfusion injury.[5,6]

Oximetry is a non-invasive monitoring technology based on near-infrared spectrometry (NIRS), and it has been approved by the Food and Drug Administration. When applied to the patient's forehead, it allows the evaluation of cerebral regional oxygen saturation (rSO_2) from superficial brain cortex regions, which are amongst the most susceptible areas to the ischemic-hypoxic injury.[7] The feasibility of using cerebral rSO_2 monitoring in patients suffering from CA has been repeatedly shown, both by studies investigating NIRS ability in predicting ROSC[8,9] and/or focused on neurological outcome after CA,[10,11]. Moreover, NIRS is under evaluation as tool for the assessment of the CPR quality. [12]

An initial meta-analysis performed in 2015 showed a significant association between the initial (five studies included) or the overall (five studies included) values of cerebral rSO_2 measured during CPR with ROSC in CA patients [13].This meta-analysis included studies performed on both in-hospital (IH)CA, OHCA or mixed CA populations; moreover, at that time, there was a major contribution from two research groups, possibly decreasing the external validity of the mata-analysis findings. Although the introduction of NIRS during CA is still limited in clinical practice, additional research studies have been published after the previous meta-analysis. Therefore, considering the challenges in assessing ROSC probabilities in CA patients, we undertook an updated systematic review and meta-analysis with the aim of confirming the role of rSO_2 values in predicting ROSC. We hypothesized that both initial and overall cerebral rSO2 values are positively associated with ROSC in CA patients undergoing CPR, in both subgroups of patients suffering from IHCA and OHCA.

Methods

We performed this systematic review using an automated literature search performed with the *NHS Library Evidence* tool. A further manual search was conducted independently by four authors (FS, VD, DB, AM), exploring also the list of references of the findings of the systematic search. We followed the approach suggested by the PRISMA statement for reporting systematic reviews and meta--analyses (checklist provided in Supplemental Digital Content – Appendix 1). [14] We registered the protocol of our systematic review and meta-analysis in the PROSPERO database (CRD42020202993).

We included prospective and retrospective studies conducted in adult patients suffering from CA where NIRS sensors were applied for the evaluation of cerebral rSO_2 values. We included both studies performed on IHCA, OHCA and mixed populations. As primary outcome we evaluated the association between the initial and/or the overall cerebral rSO_2 values and ROSC in the selected population (see PICOS approach, Supplemental Digital Content – Appendix 2). We excluded articles referring to the paediatric population. Language restrictions were applied: only articles published in English were considered. We considered case series if reporting at least 10 patients; series 5–9 patients were included for sensitivity analyses only. Smaller series and case reports were excluded.

Searches, screening and data collection

The computerized search included MEDLINE, from inception until 15.06.2020. We also performed a search on EMBASE limited to the findings from 2017 in order to retrieve the newest conference abstracts not yet published, to allow a reasonable time for peer-review process. In both searches we combined terms from two groups, under the condition that al least one term per group was included in the article title and/or abstract. The first group included the terms "cerebral oximetry", "near infrared", "oxygen consumption", "spectrophotometry" and "spectroscopy"; the second one consisted of the terms "cardiac arrest", "heart arrest", "resuscitation" and "return of spontaneous circulation".

Two authors (VD, DB) independently searched the databases and selected studies for the inclusion in the systematic review. Discordances were resolved by involving two other reviewer (FS, MA). Two authors (VD, DB) extracted data from the included studies in an Excel spreadsheet and two authors (FS, PM) performed a double-check. When needed, we contacted via email the corresponding authors for retrieving more data. Meta-analysis was performed by one experienced authors (FS) and checked by other two authors with experience (AM, MC).

Analyses of outcomes

We planned to analyse the association between cerebral rSO_2 values and ROSC dividing studies in subgroups according to the site of CA (IH, OH, mixed).

We also planned a secondary analysis dividing studies according to the country where these were conducted. In particular, we separated studies conducted in Europe and USA from those performed in Japan. We justify this choice as in the Japanese emergency medical personnel are not allowed to terminate CPR on site, and all OHCAs are brought to the hospital with ongoing CPR.

Three sensitivity analyses were planned: the first one excluding one study at time ("*leave-one-out at time approach*"), the second including case series with less than 10 patients, and the third excluding studies with high risk of bias.

Risk of bias assessment

Five authors (FS, PM, AM, GR, MA) independently assessed the methodological quality of the included studies using the Newcastle-Ottawa Assessment Scale (NOS) which is recommended for the assessment of the quality of non-randomized studies. [15] The scale has three main domains and assigns one point for each of nine items. Studies are then classified as at high (1–3 points), intermediate (4–5 points) or low (6–9 points) risk of bias.

Statistical analysis

Continuous outcome differences were analysed using an inverse variance model with a 95% Confidence Interval (CI). If data were reported only as median and interquartile range or CI, we followed current recommendations to approximate the values of mean and standard deviation (SD) [16–18]. Values are reported as mean difference (MD), p values were two-tailed and considered significant if <0.05. A random model was used. The presence of statistical heterogeneity was assessed using the X^2 (Cochran Q) test. Heterogeneity was likely if $Q > df$ (degrees of freedom) suggested and confirmed if $P \leq 0.10$. Quantification of heterogeneity performed using I^2 statistic. Values of 0−24.9%, 25-49.9%, 50−74.9% and >75% were considered as none, low, moderate and high heterogeneity respectively. [19]

Results

The literature search with the above mentioned criteria produced 894 findings on MEDLINE and 292 findings on EMBASE. The PRISMA flow diagram for screening and selection is shown in Fig. 1. Overall, 1081 were judged not pertinent, and other 81 were excluded with reasons, leaving 24 findings. Of these, after verification of the period of inclusion/publication, we further excluded 3 studies since they included patients subsequently reported in updated versions of the same study by the same group of authors. This avoided to count twice or three times some patients. In particular, Meex et al. 2013[20] and Genbrugge et al. 2015[21] included patients reported subsequently in Genbrugge et al. 2018[22]. Similarly, Singer et al. 2014[9] included patients reported subsequently in Singer et al. 2018[23]. Of the remaining 21 studies, 3 were conference abstract on EMBASE and added for sensitivity analyses. Table 1 shows the characteristics of the remaining 18 studies (published in peer-reviewed journals) included in the primary analysis. Among these, one was considered only for sensitivity analysis as represented a small case series of 9 patients[24]. Studies are divided according to the location of CA and for each study we report the design, the country where it was performed, the baseline data on demographics and confounders, the NIRS device(s) used and the values of cerebral rSO_2 investigated by the authors.

All the studies included in this meta-analysis were non-randomized studied with observational design, and only one was a retrospective study. In particular, five studies included only patients presenting with IHCA[12,25–28], one study included a mixed population of both OHCA (28%) and IHCA (72%)[8] and 11 studies were conducted on OHCA patients[22,23,29–37]. For practicality, we considered in the population of OHCA studies one article where few patients (11%) experienced CA within the Emergency Department (on arrival to hospital) [29]. One case series was included for sensitivity analysis[24]. Among the included studies, one multicentre study was by far larger than the others (data on 1921 patients conducted in 15 hospitals in Japan) [32]. Another study was a multicentre collaboration between USA and United Kingdom[28].

Regarding the primary outcomes, initial cerebral rSO_2 values were reported by 11 studies (1 IHCA[26], 9 OHCA[22,29–33,35–37] and 1 mixed population[8]; 5 of these studies were conducted in Japan[30,32,36–38], 3 in Europe[22,33,35] and 3 in USA[8,26,29]); the values of overall cerebral rSO_2 during CPR were provided by nine studies (5 IHCA[12,25–28] and 4

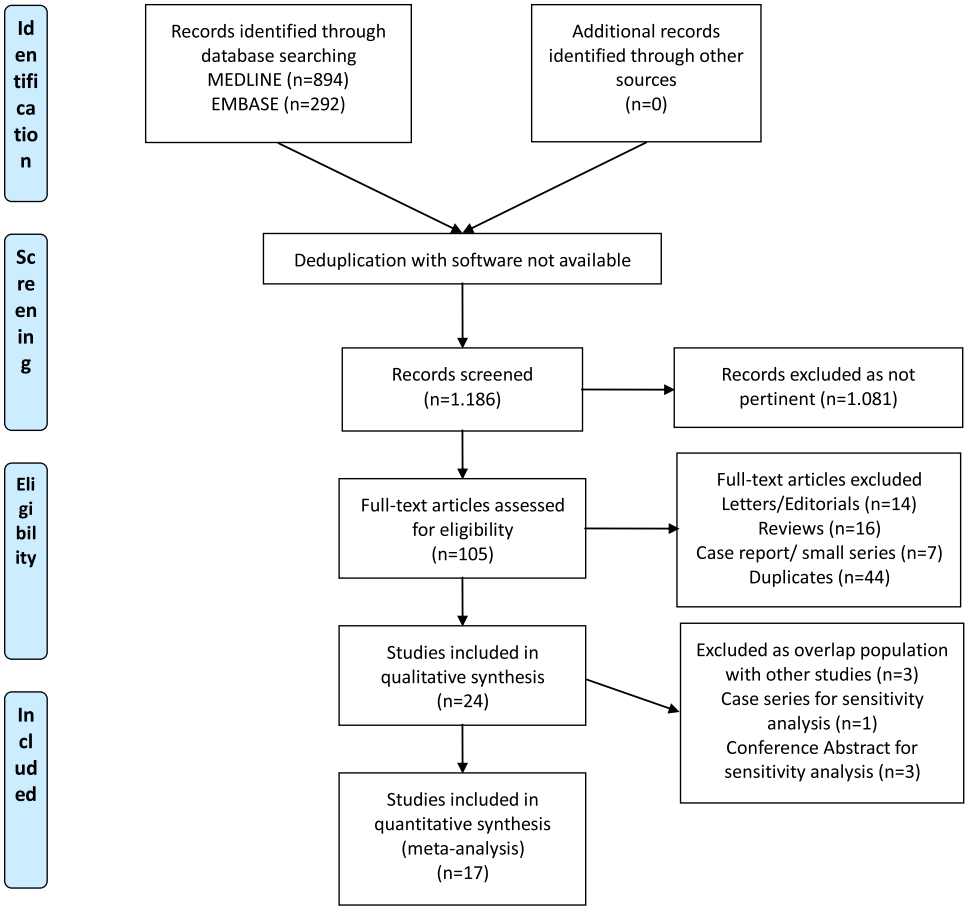

Fig. 1 – PRISMA flow diagram for screening and selection of studies found by the systematic search.

Table 1 – Characteristics of the studies included in the meta-analysis. Studies are divided according to the site of cardiac arrest (IH: in-hospital; OH: out-of-hospital). The summary of characteristics also includes the country where the study was performed and its design, the number of patients with data available with the data on population characteristics, the near-infrared spectroscopy (NIRS) device used for monitoring cerebral oximetry, and the type of data available for outcome analysis. The last column indicates the reference number.

Study	Country, Design	N ROSC rate CPR duration	Age -Males Witnessed CA Shockable rhythm	NIRS device used	Oxymetry value	Ref
MIXED POPULATION						
Ahn 2013	USA Prospective	36 IH, 14 OH 52% 34 min	65 y - 72% NR 24%	Equanox 7600,Nonin Medical, Inc, Plymouth, MN,USA	Initial and overall*	8
OUT OF HOSPITAL CARDIAC ARREST						
Engel 2019	USA Prospective	173** 20% NR	62 y - 65% 67% 26%	CerOx INVOS	Initial and overall	29
Takegawa 2019	Japan Retrospective	90 39% NR	75 y - 66% 44% 8%	TOS-OR, Fujita Medical Instruments Co., LTD, Tokyo, Japan	Initial	36
Genbrugge 2018	Belgium Prospective	329 33% 26 min	69 y - 70% 58% 20%	Equanox 7600 or SenSmart Model X-100, Nonin Medical Inc Plymouth, MN,USA	Initial and overall	22
Singer 2018	USA Prospective	100 33% NR	69 y - 73% 67% 14%	Equanox 7600, Nonin Medical, Plymouth, MN, USA	Overall	23
Prosen 2018	Slovenia Prospective	53 42% 37 min	68 y - 85% 91% 28%	Invos Oximeter, Somanetics Corporation, Troy, MI, USA	Initial	33
Tsukuda 2018	Japan Prospective	117 38% NR	70 y - 57% 51% 11%	NIRO-200 NX, Hamamatsu Photonics, Hamamatsu-City, Shizuoka, Japan	Initial	37
Storm 2016	Germany Prospective	23 22% NR	62 y - 78% NR 22%	Invos 5100 C, Covidien, Mansfield, USA	Initial	11
***Tajima 2015*##**	*Japan* *Prospective*	*9* *33%* *NR*	*74 y - 44%* *55%* *11%*	*HAND ai TOS; TOSTEC Co., Ltd, Tokyo, Japan*	*Initial*	*24*
Nishihama 2015 (multicenter=15)	All in Japan Prospective	1921 8% NR	76 y - 61% 50% 11%	INVOS™ 5100C, Covidien, Boulder, CO, USA	Initial***	32
Shewe 2014	Germany Prospective	10 30% NR	73 y - 80% NR 30%	Equanox 7600, Nonin Medical, Plymouth, Minnesota, USA	Overall	34
Fukuda 2014	Japan Prospective	69 23% NR	66 y - 70% 43% 17%	Invos 5100C, Covidien, Boulder, CO, USA	Initial	30
Koyama 2013	Japan Prospective	15 33% 84 min	80 y - 67% NR 7%	NIRO Hamamatsu Photonics, Hamamatsu-shi, Shizuoka, Japan	Initial	31
IN HOSPITAL CARDIAC ARREST						
Yazar 2019	Turkey Prospective	20 40% 24 min	75 y - 40% NR NR	Invos 5100c, Somanetics, Troy, MI, USA	Overall	25
Parnia 2016 (multicenter=5)	1 USA, 4 UK Prospective	183 34% 29 min	69 y - 61% NR 10%	Equanox 7600, Nonin Medical, Plymouth, MN, USA	Overall	28
Ibrahim 2015	USA Prospective	27 70% 20 min	66 y - 96% NR 15%	Invos 5100c, Somanetics, Troy, USA	Initial and overall	26
Parnia 2014	USA Prospective	34 44% 19 min	71 y - 65% NR 15%	Equanox 7600; Nonin, Plymouth, MI, and Invos; Somanetics, Troy, MI	Overall	12
Parnia 2012	USA Prospective	15 33% 16 min	74 y# - NR NR 5%#	Invos Somanetics, Troy, USA	Overall	27

*Ahn et al. 2013: we used only the values of overall rSaO2. Values of initial rSaO2 are presented in subsequent studies from the same group of authors, thus have not been used to avoid duplicates.

** Engle et al 2019 was included amongst OHCA but a small amount of patients suffered from CA in the Emergency Department (n = 19/173, 11%).

***Nishihama 2015: authors provided both values from left and right hemisphere. We arbitrarily used values from left hemisphere (dominant). However, values from right hemisphere were very similar and using these data did not change results.

#Parnia 2012: The data on age and first detected rhythm refers to a population of 19 patients (of these 15 were included in the study on cerebral oximetry).

##Tajima 2015: the study is in italic font as it was used only for sensitivity analysis,. Indeed, the study was an initial experience (case series) on nine patients with OHCA and monitored with a new NIRS portable device.

OHCA[22,23,29,34]; one multicentre study across Europe and USA[28], 3 single center studies conducted in Europe[22,25,34] and 5 in USA[12,23,26,27,29] – none in Japan). No studies clearly reported the exact time between the CA and the first detected cerebral rSO_2 value.

Initial rSO_2 values

A total of 11 studies including 2870 patients reported data on initial cerebral rSO_2 values[8,22,26,29–33,35–37]. Of these, 476 achieved ROSC (16.6%), but excluding the largest study conducted in Japan, ROSC was achieved in 34.6% (n = 328/949). ROSC was associated with significantly higher values of initial rSO_2 compared to the population that did not achieve ROSC (MD -11.54; 95%CI -20.96, -2.12; p = 0.02; Fig. 2), with high heterogeneity (I^2 = 97%) and no subgroup differences (p = 0.52).

We performed a secondary analysis with geographic criteria, differentiating studies conducted in Japan vs Europe-USA. The analysis of five Japanese studies[30–32,36,37] (all of them in OHCA; 2212 patients; ROSC 11.2%) showed a trend towards an association between higher initial cerebral rSO_2 values and ROSC (MD -16.16; 95%CI -32.76, 0.44; p = 0.06; Fig. 3), with high heterogeneity (I^2 = 98%). The analysis conducted on six European-American studies[8,22,26,29,33,35] (1 IHCA, 4 OHCA, 1 mixed population; 658 patients; ROSC 34.7%) showed a significant association between higher initial cerebral rSO_2 values and ROSC (MD -6.68; 95%CI -10.91, -2.45; p = 0.002; Fig. 4), with moderate heterogeneity (I^2 = 64%) and no subgroup differences (p = 0.56).

Overall rSO_2 values

Nine studies including 894 patients reported data on overall rSO_2 values during CPR, and 301 of them achieved ROSC (33.7%) [12,22,23,25–29,34]. ROSC was associated with significantly higher values of overall cerebral rSO_2 compared to the population that did not achieve ROSC (MD -10.38; 95%CI -13.73, -7.03; p < 0.00001; Fig. 5) with high heterogeneity (I^2 = 77%) and subgroup differences (p = 0.03). All the studies reporting the overall cerebral rSO_2 values during CPR and ROSC were conducted in Europe or USA, thus the secondary analysis with geographical criteria was not meaningful.

Sensitivity analyses

An initially unplanned sensitivity analysis was performed excluding the study of Nishihama et al. [32] from the analysis of initial cerebral rSO_2 values as this large multicentre study represented a clear outlier. Its exclusion did not change the results of the primary analysis (MD -8.30; 95%CI -12.07, -4.54; p = 0.008; high heterogeneity I^2 = 80%; no subgroup differences p = 0.58). However, its exclusion from the secondary analysis of initial rSO_2 values in the Japanese studies changed the trend (p = 0.06) towards a significant association between higher initial cerebral rSO_2 values and ROSC (MD -10.51; 95%CI -20.52, -0.50; p = 0.04; high heterogeneity I^2 = 91%). Readers should keep in mind that exclusions of outliers are not associated with worse study design or quality and indeed in this case the outlier was a high-quality multicentre study. [32]

The first group of planned sensitivity analyses was conducted with *leave-one-ot at time* approach; none of these changed the results of the primary analyses regarding the initial or the overall values of cerebral rSO_2 and ROSC.

The sensitivity analyses performed including the feasibility study (case series of 9 patients) conducted by Tajima et al. [24] did not change any of the results. Similarly, the inclusion of the data from the 3 conference abstracts (Supplemental Digital Content – Appendix 3) did not change the results. Regarding the risk of bias assessment, the criteria for assigning (or not) the points are reported; as all the included studies were at low risk of bias scoring between 7 and 9 points of the NOS (Supplemental Digital Content – Appendix 4); therefore, no sensitivity analyses were conducted in this regard.

We conducted a post-hoc calculation on the mean initial and overall values of rSO_2, calculating it from the values of each study

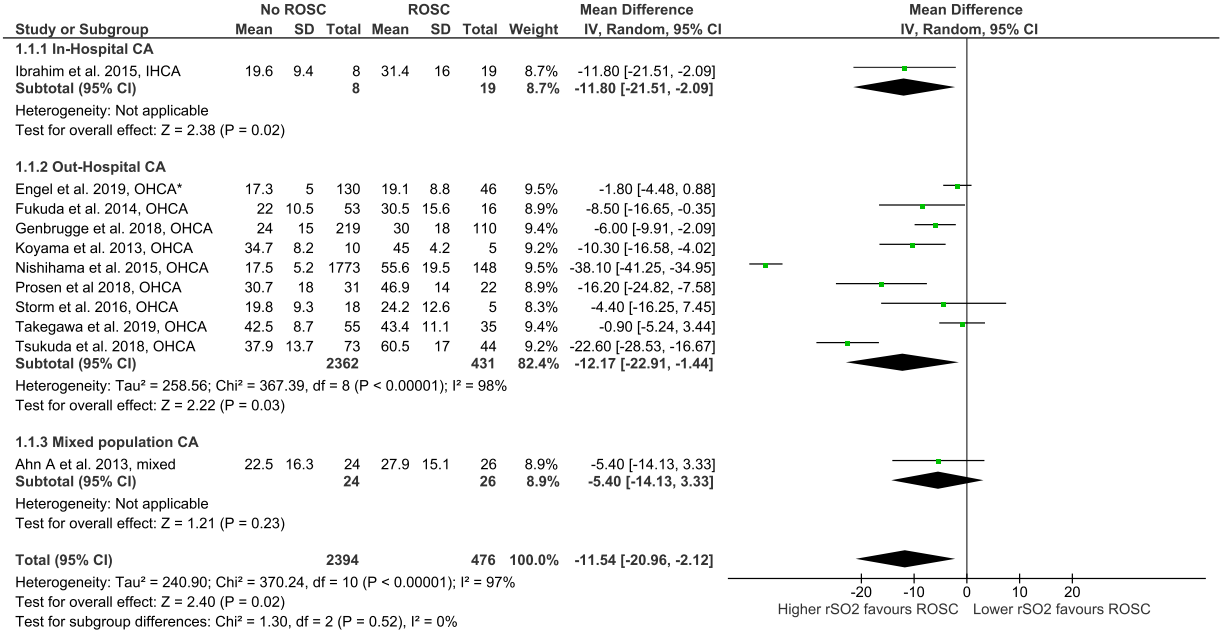

Fig. 2 – Forest plot investigating the association between initial values of cerebral regional oxygen saturation (rSO_2) and return of spontaneous circulation (ROSC). Subgroup analysis is conducted according to location of cardiac arrest (CA). CI: Confidence interval; IV = inverse variance; IH: In Hospital; OH: Out of Hospital; SD: standard deviation.

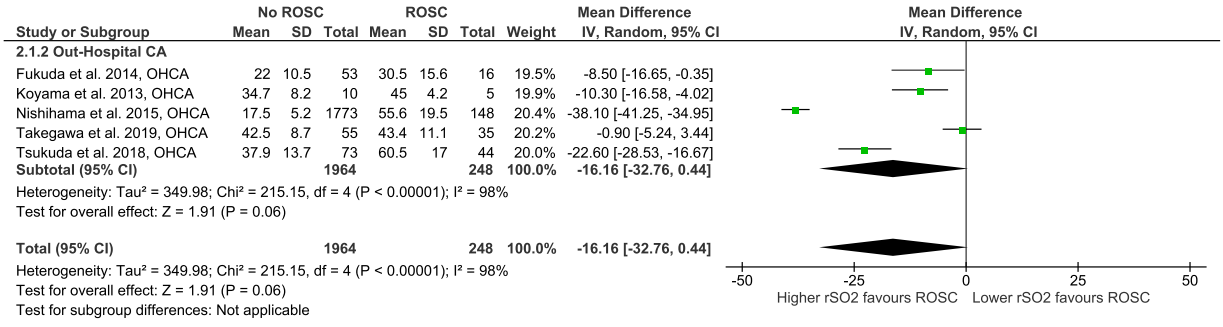

Fig. 3 – Forest plot investigating the association between initial values of cerebral regional oxygen saturation (rSO_2) and return of spontaneous circulation (ROSC), with analysis conducted including Japanese studies only. CA: cardiac arrest; CI: Confidence interval; IV = inverse variance; IH: In Hospital; OH: Out of Hospital; SD: standard deviation.

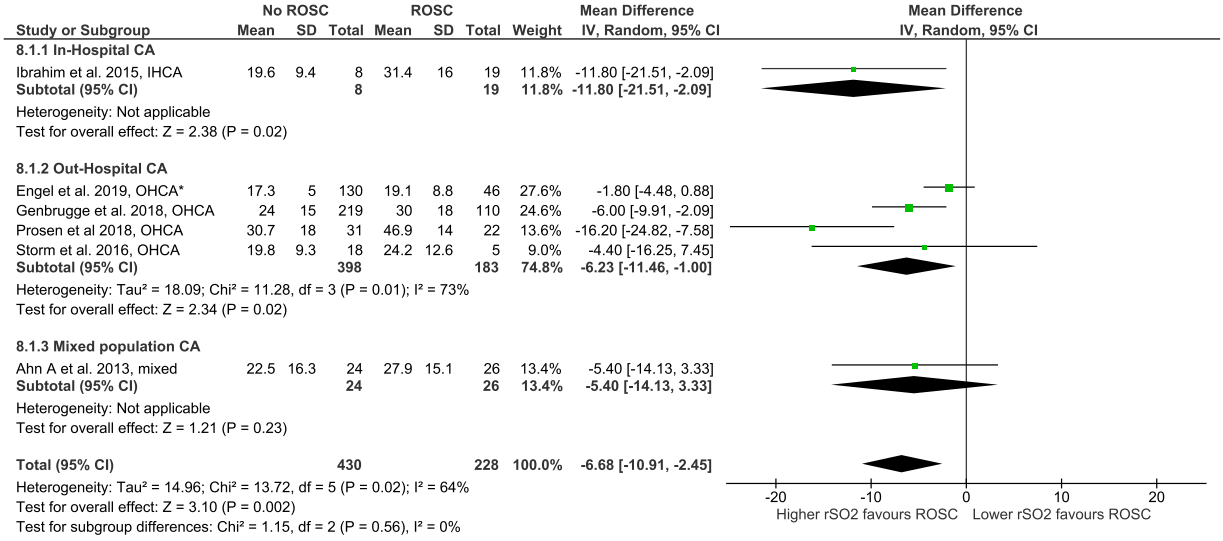

Fig. 4 – Forest plot investigating the association between initial values of cerebral regional oxygen saturation (rSO_2) and return of spontaneous circulation (ROSC), with analysis conducted including studies from Europe and USA only (excluding Japanese studies). CA: cardiac arrest; CI: Confidence interval; IV = inverse variance; IH: In Hospital; OH: Out of Hospital; SD: standard deviation.

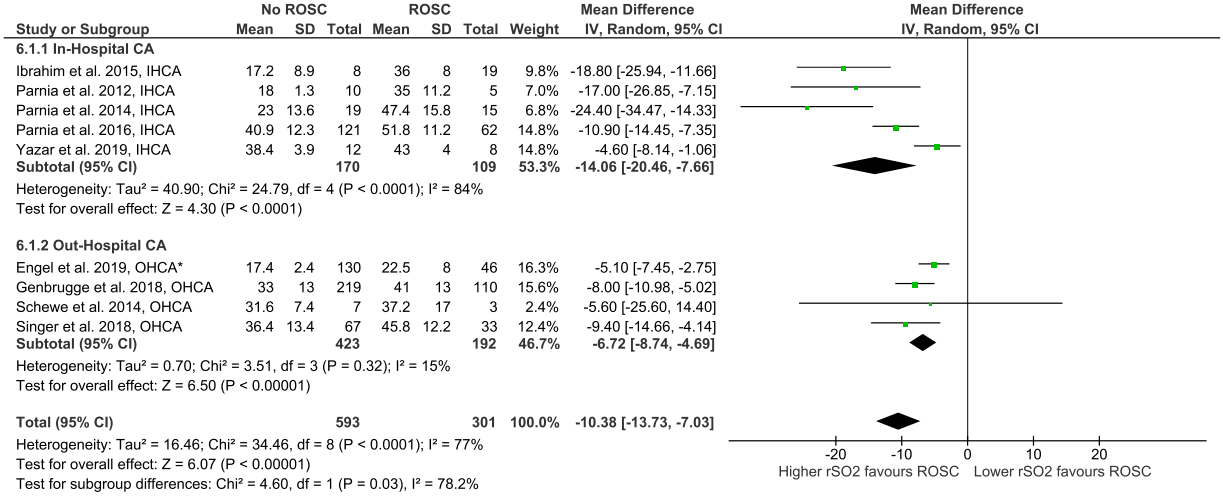

Fig. 5 – Forest plot investigating the association between overall values of cerebral regional oxygen saturation (rSO_2) during resuscitation and return of spontaneous circulation (ROSC). Subgroup analysis is conducted according to location of cardiac arrest (CA). CI: Confidence interval; IV = inverse variance; IH: In Hospital; OH: Out of Hospital; SD: standard deviation.

weighted for their sample size. For the mean initial rSO_2 value, we found that patients achieving ROSC had a mean of 43.8% vs 19% in those not achieving ROSC (absolute difference 24.8%). Similarly, for the mean overall value during resuscitation, we calculated that patients who achieved ROSC had a mean cerebral rSO_2 value of 40.8% vs 30.9% in those not achieving ROSC (absolute difference 9.9%).

Discussion

This updated meta-analysis confirmed a significant association between both higher initial and overall values of cerebral rSO_2 and ROSC in CA patients undergoing CPR. This finding is reinforcing the results of the precedent meta-analysis[13], with the advantage of a much larger sample size. Moreover, the previous meta-analysis included 9 studies but 4 of them were conducted by one research group, and 2 by another group, thus limiting the external validity of previous findings. In the present study, the inclusion of 17 studies and the removal of studies from the same research group with overlaps in the recruitment period (and thus included patients) increases the external validity of our findings.

Importantly, we also conducted analyses based on "geographical" criteria, separating the studies reporting initial rSO_2 values conducted in Europe-USA from those performed in Japan. Our idea was based on the significant difference in the management of OHCA in Japan, where the emergency medical personnel is not allowed to terminate CPR in the OH setting (unless rare occasions), and consequently all OHCA patients are brought to ED. These analyses confirmed the results of the primary analysis, though the association between the initial cerebral rSO_2 values and ROSC was less clear when analysing Japanese studies only ($p = 0.06$, though become significant excluding one large multicentre study behaving as outlier[32]).

The association of rSO_2 values with ROSC is expected for several reasons. Values of cerebral rSO_2 are correlated with oxygenation measured at the jugular venous bulb[39,40] and, more importantly, with coronary and cerebral perfusion pressure.[41–43] Thus, higher values of cerebral oxygenation may theoretically indicate better coronary perfusion pressure and a greater efficacy of CPR. Indeed, a coronary perfusion pressure above 15 mmHg should be maintained during CPR in order to obtain a successful resuscitation.[44] As there is no available tool for measuring coronary perfusion pressure during CPR, cerebral oxygenation may represent a reasonable surrogate, considering also that application of NIRS sensors on the forehead is easy and feasible without causing dealys in CPR. However, one study on quality controlled manual chest compression found that high quality CPR was not significantly reflected in the cerebral rSO_2 quantified by NIRS.[45] Studies evaluating the value of rSO_2 according to the CPR quality are needed. Nonetheless, it is important to consider that cerebral monitoring has been consistently used in patients undergoing cardiac surgery during the non-pulsatile perfusion with cardiopulmonary bypass.[46]

Considering the mean values of each study and accounting for each study's size we calculated the weighted mean for the initial and the overall values of cerebral rSO_2. We found that the difference between weighted means for ROSC and no-ROSC group were larger for the intial NIRS values (almost 25% greater in successfully resuscitated patients) as compared to overall NIRS values (almost 10% higher in those achieving ROSC). Whether the initial value may be of greater help in prognostication remains to be established.

The end-tidal CO_2 ($etCO_2$) is the most extensively studied indicator of CPR quality and predictor of ROSC.[47] It is interesting that Engel et al.[29] showed that both rSO_2 and $etCO_2$ are good predictors of ROSC, but rSO_2 performed better than $etCO_2$. This may be partially explained by the dependency of $etCO_2$ on both effective minute ventilation and administration of vasoactive drugs.[48–50] The $etCO_2$ has been investigated and it is recommended as a tool indicating the efficacy of chest compressions;[51] also rSO_2 is currently investigated for this scope but more studies are needed before drawing conclusions. The rSO_2 has the advantage of being theoretically applicable to all patients, whilst the use of $etCO_2$ requires advanced airway management.

Values of cerebral rSO_2 have been also considered for prognostication of neurological outcome after CA. Two studies[10,11] found significantly higher rSO_2 values measured at hospital arrival in patients with favourable neurological outcome (56% and 68%, respectively) as compared with values in patients with poor outcome (20% and 58%, respectively). However, Bougle et al. reported no difference in the mean values rSO_2 during the first 48 h after CA between favourable (62%) and poor neurological outcome (58%)[52]. Of note, all these data should be interpreted considering that several variables may influence cerebral oximetry, starting from hemodynamic and respiratory management, but taking into account also the influence of target temperature management.[53]

Limitations

This meta-analysis has several limitations. First, our meta-analysis investigates only the associations between NIRS values and ROSC, but the lack of individual patient data does not allow to correct for confounders performing analysis accounting for age, cause and location of CA, first detected rhythm, witnessed CA and presence of bystander CPR, etc. This should not be confused with the risk of bias assigned to each study according to the quality in its design. Indeed, the risk of bias in individual studies is subjective and open to interpretation, and the low risk of bias in the included studies does not mean low risk of bias in the meta-analysis findings. In practice, our meta-analysis investigated the associtation between NIRS values and ROSC, but it cannot comment on correlation and causation. Secondly, the delay between CA and first application of the cerebral oximetry sensors was not clearly specified by the included studies and it greatly influences the first recorded cerebral oximetry value. For this reason we conducted a "geographical" analysing separately the studies conducted in Japan where OHCA patients are transported to the nearest hospital (not permitted to terminate resuscitation on the scene) and the application of the NIRS sensors in these patients may happen long time after the CA. Third, study size varied greatly from small single center to large multicentre (international) studies. In this context, it should be kept in mind that the largest muticenter study conducted in Japan[32] did not have a great influence on the results but it significantly skewed the 95%CI. Fourth, as shown in Table 1, different devices have been used to measure rSO_2. The multiple NIRS devices commercially available use different algorithms to adjust for confounding factors such as the interference of extra-cerebral tissue and spatial resolution between and superficial brain tissue,[54] the differences in the cerebral arterial/venous blood partitioning[54] (commonly considered as a ratio of 30%/70%),[55] the effect of blood- and tissue- derived chromophores (i.e. melanin, haemoglobin, myoglobin, conjugated bilirubin).[56] Myoglobin absorbency signal overlaps with hemoglobin. Chromophore concentration cannot be

calculated by the Beer-Lambert law equations which is a limitation of tissue NIRS. Thus, the use of different devices potentially introduces a monitoring bias due to differences in calibration and algorithms of each device.[57] Moreover, there is a significant risk of contamination of the NIRS signal by extracerebral sources as strict probe placement on frontal lobe skin avoiding hair follicles and attachment of the probes may be difficult if the skin is wet. Probes may also be influenced by ambient light.[58]

Finally, the value of cerebral oxygen saturation for the prognostication on neurological outcome after CA is at early stage of research, and it could not be properly analysed. More studies are warranted to understand the relationship between initial and overall values of cerebral oxygen saturation with neurological outcome after CA.

Conclusions

Greater initial and overall values of cerebral oxygen saturation monitored with near infrared spectrometry are both associated with more possibilities of achieving return of spontaneous circulation in patients with cardiac arrest. This finding seems consistent for both in-hospital and out-hospital cardiac arrest settings. Moreover, we showed consistency with a geographical analysis conducted differentiating Japan from other countries.

Conflict of interest statement

The authors declare no conflict of interest in regards of this work.

On behalf of all co-authors,

F Sanfilippo

Conflict of interest statement

All the authors declare no conflict of interest with regards of this topic.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2020.12.002.

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