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Review Article

Regional Cerebral Oxygen Saturation to Predict Favorable Outcome in Extracorporeal Cardiopulmonary Resuscitation: A Systematic Review and Meta-Analysis

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Objective: This systematic review and meta-analysis aimed to investigate the role of regional cerebral oxygen saturation (rSO_2) in predicting survival and neurologic outcomes after extracorporeal cardiopulmonary resuscitation (ECPR).
Design: The study authors performed a systematic review and meta-analysis of all available literature.
Setting: The authors searched relevant databases (Pubmed, Medline, Embase) for studies measuring precannulation rSO_2 in patients undergoing ECPR and reporting mortality and/or neurologic outcomes.
Participants: The authors included both in-hospital and out-of-hospital cardiac arrest patients receiving ECPR. They identified 3 observational studies, including 245 adult patients.
Interventions: The authors compared patients with a low precannulation rSO_2 ($\leq$15% or 16%) versus patients with a high (>15% or 16%) precannulation rSO_2. In addition, the authors carried out subgroup analyses on out-of-hospital cardiac arrest (OHCA) patients.

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Measurements and Main Results: A high precannulation rSO_2 was associated with an overall reduced risk of mortality in ECPR recipients (98 out of 151 patients [64.9%] in the high rSO_2 group, *v* 87 out of 94 patients [92.5%] in the low rSO_2 group, risk differences [RD] -0.30; 95% CI -0.47 to -0.14), and in OHCA (78 out of 121 patients [64.5%] *v* 82 out of 89 patients [92.1%], RD 0.30; 95% CI -0.48 to -0.12). A high precannulation rSO_2 also was associated with a significantly better neurologic outcome in the overall population (42 out of 151 patients [27.8%] *v* 2 out of 94 patients [2.12%], RD 0.22; 95% CI 0.13-0.31), and in OHCA patients (33 out of 121 patients [27.3%] *v* 2 out of 89 patients [2.25%] RD 0.21; 95% CI 0.11-0.30).
Conclusions: A low rSO_2 before starting ECPR could be a predictor of mortality and survival with poor neurologic outcomes.

Key Words: cardiac arrest; resuscitation; regional cerebral oxygen saturation; NIRS; ECPR; intensive care

CARDIAC ARREST is the third leading cause of death in Europe. The annual incidence of out-of-hospital cardiac arrest (OHCA) in Europe is between 67-to-170 per 100,000 inhabitants.[1]

Extracorporeal cardiopulmonary resuscitation (ECPR) has expanded significantly since the first report by Kennedy et al. in 1966.[2] Data from the Extracorporeal Life Support Organization Registry documented an increase in annual ECPR cases from <100 in 2009 to >1,500 in 2019.[3] A recent systematic review, including 2 randomized and 4 propensity score-matched studies, demonstrated higher survival rates with favorable neurologic outcomes in patients with refractory OHCA treated with ECPR than in patients treated with conventional cardiopulmonary resuscitation (cCPR).[4] Nevertheless, there was no improvement in risk-adjusted survival over time, with an average survival at hospital discharge of 29%.[5]

Moreover, the elevated risk of neurologic sequelae is a stimulus to finding useful prognostic markers of favorable outcomes after ECPR. Recently identified markers of good prognosis after ECPR are short low-flow duration, shockable cardiac rhythm, high arterial pH value,[6] low serum lactate concentration, and high hemoglobin concentration on hospital admission.[7]

Regional cerebral oxygen saturation (rSO_2) obtained through near-infrared spectroscopy (NIRS) can be measured noninvasively and without the necessity of arterial pulsation. Regional cerebral oxygen saturation showed promising results in predicting neurologic outcomes and return of spontaneous circulation during cCPR.[8] In 2016, a meta-analysis of 19 nonrandomized observational studies, including 2,436 patients, showed a correlation between higher NIRS values and better resuscitation outcomes, suggesting that failure to obtain an rSO_2 >30% might contribute to the decision to terminate cCPR.[9]

Whether the predictive power of rSO_2 in cCPR could translate into ECPR recipients is unknown. Unfortunately, few studies on rSO_2 in ECPR recipients exist, most of which are case reports or case series without conclusive results.[10,11] Therefore, in the hypothesis that rSO_2 can help to identify refractory cardiac arrest patients who can benefit more from ECPR, the study authors identified all manuscripts dealing with this topic and summarized their findings, trying to identify the best cut-off value.

Materials and Methods

Search Strategy and Study Selection

A systematic search was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines by 2 reviewers.[12] MEDLINE (including PubMed) and Embase databases were searched using the following search string: "ECPR" OR "extracorporeal cardiopulmonary resuscitation" AND "regional cerebral oxygen saturation" OR "tissue oxygenation index" OR "NIRS" OR "near-infrared spectroscopy." References of relevant studies were hand-searched to identify any additional studies with the following inclusion and exclusion criteria. The inclusion criteria were all studies concerning ECPR recipients (both in-hospital and out-of-hospital cardiac arrest, both adult and pediatric cases) and reporting precannulation rSO_2 measurements (static lowest value or, when available, the mean precannulation value). The exclusion criteria were nonhuman experimental studies, case reports, studies involving <20 patients undergoing ECPR, and studies not reporting information on mortality and/or neurologic outcomes. Two investigators independently assessed compliance with selection criteria and selected the studies for the final analyses. The explored outcomes were mortality and neurologic outcomes. Neurologic outcomes were evaluated using cerebral performance categories (CPC); CPC 1 (good performance), and CPC 2 (moderate disability) were defined as "good neurologic outcomes," whereas CPC 3 (severe disability), CPC 4 (vegetative state), and CPC 5 (brain death) were defined as "poor neurologic outcomes," according to recent guidelines.[13] The study authors divided patients into the following 2 groups: patients with a low precannulation rSO_2 versus a high pre-cannulation $rSO2_2$. The ideal precannulation cut-off was 16%. This value to discriminate between high versus low rSO_2 was chosen according to Joo et al.,[14] who carried out a receiver operating characteristic analysis on rSO_2 and identified the optimal cut-off for good neurologic outcomes through the Youden index. Nevertheless, the authors also included studies that used 15% as a cut-off—15% is the lowest value detectable by the INVOS system (Medtronic), and this cut-off has already been used in studies on patients undergoing cCPR.[15] Therefore, in this analysis, low rSO_2 depicted patients with a pre-cannulation rSO_2 of ≤15% or 16%, depending on the studies examined.

The study authors repeated the analyses in the subgroup of OHCA patients. As secondary analyses, they divided patients according to 4 of the following classes of precannulation rSO_2: <16%, between 17% and 40%, between 41% and 60%, and >60%. Then, they analyzed the neurologic outcome in each class. The risk of bias for each study was assessed through the Newcastle-Ottawa quality assessment scale[16] for the nonrandomized trials.

The review protocol was published in the International Prospective Register of Systematic Reviews PROSPERO and is available at www.crd.yorl.ac.uk/PROSPERO under registration number CRD42022347091.

Statistical Analysis

For study analysis, 95% CIs were used to determine the risk differences (RDs). Individual study statistics, as well as combinations of them, were used. The random-effects model was subsequently employed.[17] The analysis also included examining variables, the size of the overall impact, and whether heterogeneity existed. Inconsistency among studies was identified through visual assessment of forest plots, CI, and its minimal or zero overlap.

The study authors did not anticipate a similar impact magnitude because of the diversity of the studies and the demographics, and they forecasted considerable heterogeneity. Due to this, the metafor package for R and R-Studio, version 1.3 (R Foundation for Statistical Computing) were used to employ the random-effects model[18] *a priori*. This strategy decreases the likelihood of Type II mistakes. Effect estimates are displayed for each research as squares, and proportions are shown together with their 95% CIs as horizontal lines. Study heterogeneity was assessed using chi-square and I^2 tests. Low (25%), moderate (50%), and high (75%) heterogeneity levels were used to classify it.[19] Studies that only provided median and IQR were estimated using the method described by Hozo et al.[20] The results were presented as effect estimates and 95% CI. Publication bias was investigated by inspecting the funnel plot's symmetry and Egger's test results.[21]

Results

The search yielded a total of 48 articles, 22 after excluding duplicates. Afterward, 2 reviewers independently screened titles and abstracts to exclude studies not relevant to the authors' purpose. They obtained ten articles for the full-text review. Seven studies did not meet their criteria (Fig 1).

The study authors included 3 retrospective cohort studies dealing with 245 adult patients.[14,22,23] All studies used the INVOS oximeter for cerebral oxygen saturation monitoring. A total of 151 patients were included in the "high" rSO_2 group, and 94 were included in the "low" rSO_2 group. Characteristics of included studies are presented in Table 1. In addition, Supplementary Table S1 presents the assigned risk of bias for each

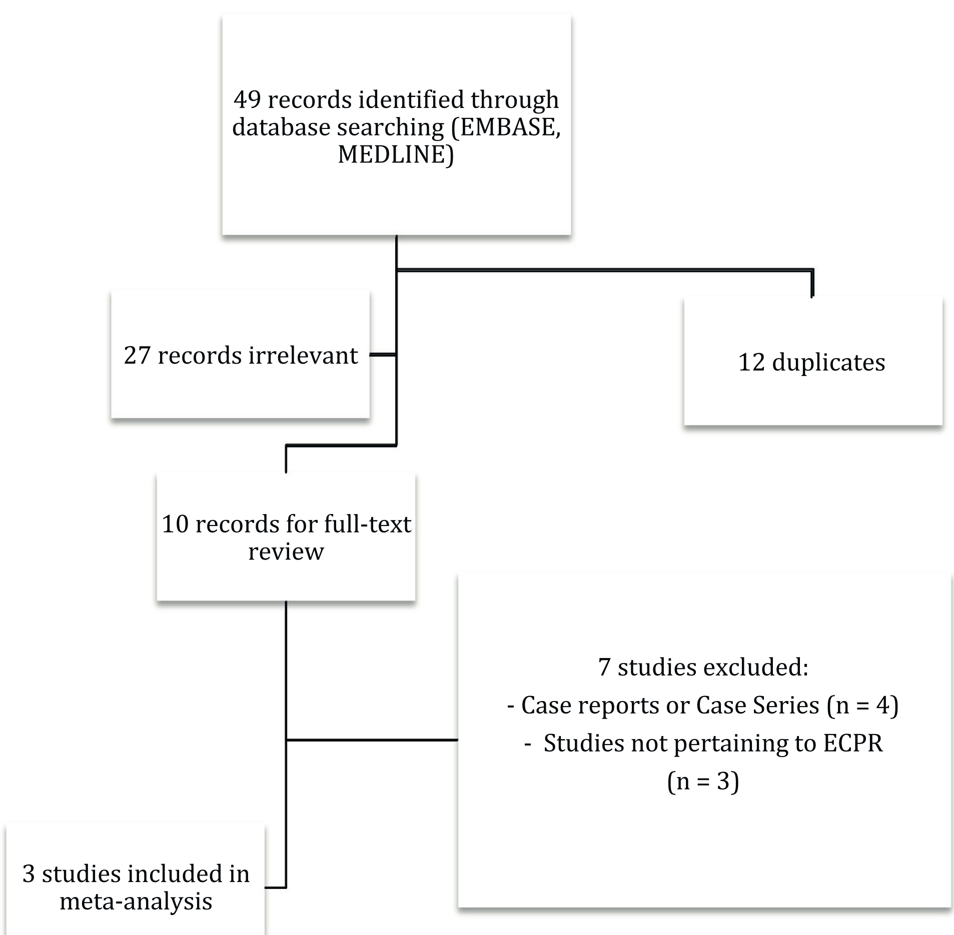

Fig 1. Search strategy. ECPR, extracorporeal cardiopulmonary resuscitation.

Table 1
Studies Characteristics

Authors	Study Design	Country	Age	NIRS Oximeter	Timing of Pre-cannulation rSO_2 Measurement	Setting	Number of Participants	Examination
Joo et al[14]	Retrospective Cohort	Japan	60 (47-60)	INVOS 5100C (Covidien, Boulder, CO)	Immediately after hospital arrival. Monitoring of rSO_2 for at least 1 minute. The lowest value recorded was used for the study.	OHCA patients who received ECPR	121	Pre-cannulation $rSO_2 \leq 16$ *v* $rSO_2 > 16$ to evaluate neurological outcome and survival
Wiest et al[20]	Retrospective Cohort	Germany	56.2 (45.9-66)	INVOS 7100 (Medtronic, Dublin, Ireland)	Immediately after arrival of ECPR team. Monitoring duration not specified.	OHCA and IHCA patients who received ECPR	97	Pre-cannulation rSO_2 to evaluate neurological outcome and survival
Ito et al[21]	Retrospective Cohort	Japan	64 (48-80)	INVOS, (Somanetics)	Within 3 min of hospital arrival. Monitoring duration not specified.	OHCA patients who received ECPR	27	Pre-cannulation $rSO_2 \leq 15$ *v* $rSO_2 > 15$ to evaluate neurological outcome and survival

Abbreviations: ECPR, extracorporeal cardiopulmonary resuscitation; IHCA: in-hospital cardiac arrest; OHCA: out-of-hospital cardiac arrest; rSO_2: regional cerebral oxygen saturation.

study through the Newcastle-Ottawa quality assessment scale for the nonrandomized trials.[16]

In 2 studies,[14,22] the low precannulation rSO_2 cut-off was set at 16%. In Ito et al.,[15] the low pre-cannulation rSO_2 cut-off was set at 15%.

A high precannulation rSO_2 was associated with an overall reduced risk of mortality in ECPR recipients (98/151 [64.9%] in the high rSO_2 group *v* 87/94 [92.5%] in the low rSO_2 group, RD -0.30; 95% CI -0.47 to -0.14) (Fig 2), a finding that was confirmed in OHCA patients (78/121 [64.5%] *v* 82/89 [92.1%], RD -0.30; 95% CI -0.48 to -0.12) (Supplementary Fig S1).

A high, precannulation rSO_2 was associated with a statistically significant increase in the probability of a good neurologic outcome (42/151 [27.8%] *v* 2/94 [2.12%], RD 0.22; 95% CI 0.13-0.31) (Fig 3), also in the OHCA subpopulation (33/121 [27.3%] *v* 2/89 [2.25%] RD 0.21; 95% CI 0.11-0.30) (Supplementary Fig S2).

The study authors also analyzed shockable and nonshockable presenting rhythm as a secondary outcome—a higher rSO_2 was not associated with the presentation of a shockable rhythm (Supplementary Figs S3 and S4).

The authors conducted their secondary analyses only on data extracted from the studies of Joo et al.[14] and Wiest et al.[22] for 218 patients. They stratified patients into 4 classes of regional cerebral oxygen saturation to evaluate the presence of a linear relationship between precannulation rSO_2

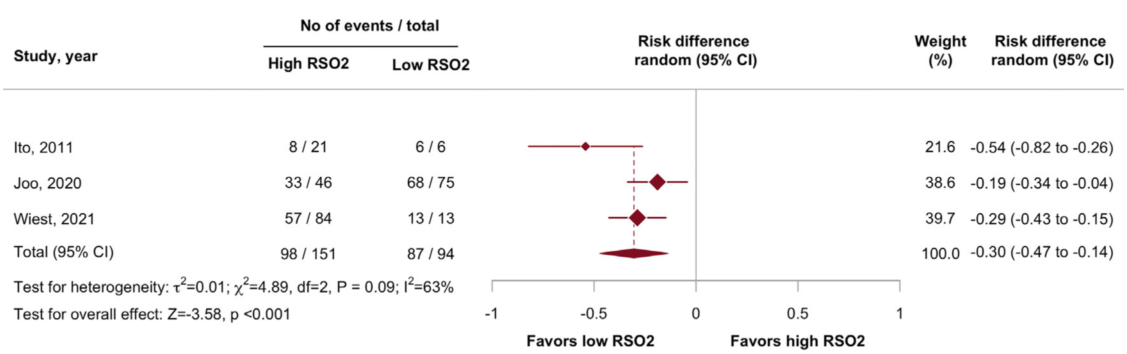

Fig 2. Mortality in extracorporeal cardiopulmonary resuscitation recipients according to regional cerebral oxygen saturation (rSO_2): higher rSO_2 was associated with a reduced risk of mortality in overall extracorporeal cardiopulmonary resuscitation recipients (98 out of 151 patients [64.9%] in the high rSO_2 group *v* 87 out of 94 patients [92.5%] in the low rSO_2 group, risk difference -0.30; 95% CI [-0.47 to -0.14]). ECPR, extracorporeal cardiopulmonary resuscitation.

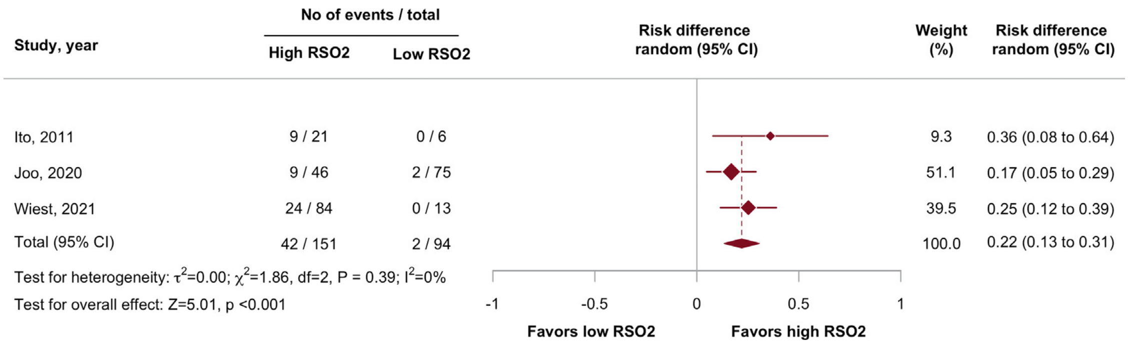

Fig 3. Neurologic outcomes in extracorporeal cardiopulmonary resuscitation recipients according to regional cerebral oxygen saturation: higher regional cerebral oxygen saturation was associated with a statistically significant increase in the probability of a good neurologic outcome (42 out of 151 patients [27.8%] *v* 2 out of 94 patients [2.12%], risk difference 0.22; 95% CI [0.13-0.31]). rSO_2: regional cerebral oxygen saturation.

and neurologic outcome, using additional cut-offs according to the receiver operating characteristic analysis used by Joo et al.[14] They confirmed that a higher rSO_2 revealed an augmented probability of having CPC 1 or CPC 2. However, the group of patients with a precannulation rSO_2 >60% demonstrated a slight reduction of good neurologic outcomes in comparison to the group with an rSO_2 between 41% and 60% (Fig 4).

Discussion

Key Findings

The study authors found that a low rSO_2 before starting ECPR in refractory cardiac arrest was associated with reduced survival and worse neurologic status in survivors in the overall population and OHCA.

Relationship to Previous Studies

To the authors' knowledge, the present investigation was the first systematic review of precannulation rSO_2 to evaluate its predictive power for neurologic outcomes. Preoperative rSO_2 has a positive predictive value in cardiac surgery with cardiopulmonary bypass.[24] Numerous clinical investigations found an association between different NIRS oximetry values and outcomes during cardiac arrest, suggesting that NIRS monitoring can be incorporated into cCPR protocols.[25] Therefore, precannulation rSO_2 can be a predictive marker of return of spontaneous circulation (ROSC) in patients undergoing

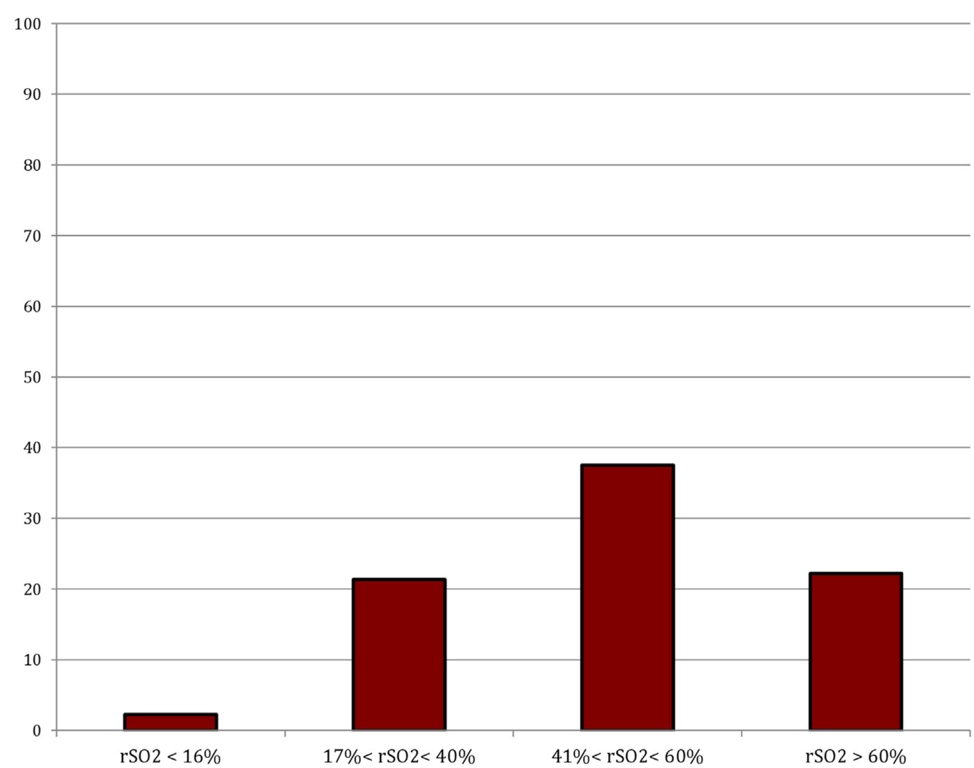

Fig 4. Percentage of patients with cerebral performance categories 1 or cerebral performance categories 2 according to 4 different regional cerebral oxygen saturation classes. rSO_2: regional cerebral oxygen saturation.

cCPR.[9] Parnia et al. demonstrated that in their population with in-hospital cardiac arrests, an $rSO_2 \geq 25\%$ provided 100% sensitivity and 100% negative predictive value for the prediction of ROSC. However, an rSO2 ≥65% provided 99% specificity but low sensitivity for the prediction of ROSC. They also demonstrated that every 5% increase over time with $rSO_2 > 50\%$ during cCPR provided a 15% higher probability of achieving a CPC 1 or CPC 2.[26] Ito et al. also illustrated that a value of $rSO_2 < 15\%$ (the lowest detectable value for the INVOS instrument [Medtronic, Ireland]) was a strong predictor of poor outcomes in patients with OHCA subjected to cCPR—no patient with an arrival $rSO_2 < 15\%$ survived at hospital discharge.[15]

Significance of Study Findings

The authors' meta-analysis demonstrated that an rSO_2 threshold ≤16% was associated with a mortality increase and an unfavorable neurologic outcome.

Age and rSO_2 in these patients did not appear to be correlated in the analyzed studies. Interesting data came from the work of Ehara et al. in their analysis of 16 cases of ECPR.[10] They found that a significant increase in rSO_2 values with ECPR initiation was linked to poor neurologic outcomes. They assumed that in the group of patients with a good neurologic outcome, minor changes in rSO_2 were due to performing brain tissue starting to consume oxygen with the initiation of extracorporeal support. It seems clear that rSO_2 may play a role even in the ongoing extracorporeal support, giving an insight into what is happening to brain tissue at the start of reperfusion.

At the onset of cardiac arrest, ischemia acts as the main damaging factor; it leads to the depletion of adenosine triphosphate and consequent dysfunctional Na^+/K^+ pump. This generates a massive influx of Na^+, creating cytotoxic edema. At the same time, it generates efflux of K^+, which depolarizes the cell membrane, opening voltage-sensitive Ca^{2+} channels. Reperfusion, either spontaneous with the return of circulation or mediated by extracorporeal support, causes the second insult to the brain tissue. Reperfusion powers glutamate excitotoxicity, creating oxygen free radicals and activating the immune system and macrophages, leading to inflammation.[27] Animal studies showed that ECPR holds the ability to reduce the inflammation burden compared to cCPR.[28] Nevertheless, the authors know little about the adequate blood flow requirement, oxygenation, and CO_2 levels during the reperfusion phase.

Optimization of cerebral perfusion is a cornerstone in the reperfusion phase. However, there is also a lack of evidence about the proper mean arterial pressure (MAP) to maintain after a cardiac arrest. Retrospective studies in postcardiac arrest patients treated with cCPR demonstrated that a higher MAP was associated with better outcomes.[29,30] In addition, about one-third of comatose survivors' autoregulation of cerebral blood flow (CBF) is lost after cardiac arrest. In the others, it is narrowed and right-shifted; hence, a higher MAP is necessary to guarantee an adequate CBF.[31]

Taccone et al. demonstrated the linear correlation between the rSO_2 and the estimated cerebral perfusion pressure (calculated through the Doppler imaging of the medium cerebral artery) in postcardiac arrest survivors.[32] This evidence enhanced the results of different studies demonstrating a good sensitivity of the COX index in highlighting the correct MAP in postcardiac arrest patients treated with cCPR.[33,34] The COX index is the correlation coefficient between rSO_2 and MAP; the optimal MAP is associated with minimal COX. Conversely, there is no firm evidence of COX index reliability in the ECPR population. The partial pressure of CO_2 also plays a central role in manipulating cerebral blood flow. In postcardiac arrest patients, cerebrovascular reactivity to CO_2 is generally preserved. Therefore, optimizing and adapting CO_2 levels may be used to modify CBF. The Carbon dioxide, Oxygen and Mean arterial pressure After Cardiac Arrest and Resuscitation (COMACARE)[35] and the CCC[36] trials demonstrate a probable protective effect of mild hypercapnia in post-cardiac arrest patients; these data could be clarified by the ongoing trial Targeted Therapeutic Mild Hypercapnia After Resuscitated Cardiac Arrest (TAME) (NCT03114033).

Nevertheless, in patients undergoing ECPR, cerebrovascular reactivity to CO_2 is probably abnormal due to the loss of a pulsatile flow.[37] In addition, a study in patients undergoing cardiopulmonary bypass for cardiac surgery demonstrates an anomalous cerebrovascular CO_2 reactivity.[38] These data could jeopardize the reliability of rSO_2 variation as an accurate instrument to tailor therapies to correct cerebral blood flow in ECPR recipients.

Another cornerstone of the resuscitation phase is oxygenation. The damage induced by hypoxia is remarkable. Contrary to the promotion of reactive oxygen species release, there is uncertainty about the damage of hyperoxia.

Although according to the authors' analysis, there was a decline in positive neurologic outcomes in the patient group with a rSO2 >60%, and this evidence should be used with caution, as only 9 patients belong to this category. Additionally, the 4 patients from the Wiest et al. study[22] arrived at the hospital with a mean temperature that was much lower (31.25°C) than the average of the other classes. This severe hypothermia may have affected NIRS monitoring results. Furthermore, an extremely high rSO_2 could be a sign of persistent cellular damage, as if the cerebral tissue was unable to use the metabolite. Ehara et al.,[10] also reporting that a significant increase in rSO_2 values with ECPR initiation is linked to poor neurologic outcomes, assumed that in the group of patients with a worse neurologic impact, a mismatch between O_2 delivery and consumption occurs; hence, a higher rSO_2 could be associated with graver outcomes.

A retrospective analysis of over 10,000 patients on venous-arterial ECMO demonstrated that higher partial pressure of O_2 (pO_2) on the first day of extracorporeal support was associated independently with ischemic stroke.[39] Cashen et al., in their analysis of 484 pediatric patients on ECMO, 69 undergoing ECPR, demonstrated that a high pO_2 in the first 48 hours of ECMO was associated independently with increased mortality.[40] This could contribute to the explanation of why, in the authors' secondary analysis, patients with pre-cannulation rSO_2 above 60% might have experienced a reduction in good neurologic outcomes.

However, rSO_2 has a poor predictive power on cerebral hyperoxia due to the variability induced by cerebral perfusion and the influence of extra-cranial tissues.

Cerebral oxygen saturation also could be an early marker of neurologic complications during extracorporeal support. Acute cerebral complications proved to be more frequent in patients with cerebral desaturation or significant right-left differences in rSO_2.[41] Nevertheless, complications occurring outside the frontal areas (ie, the posterior circulation) were not detectable.[41] Cerebral oximeters only can measure local cerebral oxygen saturation, primarily in the frontal lobe, and this is probably their most prominent limit. The rSO_2 findings must be evaluated carefully because the examined region is small and other parts of the brain are not examined.[42]

Strengths of the Study

The authors can identify 3 strengths in their study. First, they found a low heterogeneity in the study population. Secondly, they also were able to analyze the subgroup population of OHCA. Lastly, all the studies examined used the INVOS oximeter system, although with different models.

Limitations of the Study

The authors' analysis has limitations. First, the small number of considered studies and the absence of randomized controlled trials. The authors' meta-analysis included only 245 patients from in-hospital cardiac arrest and OHCA, which could have increased variability. Second, they identified only data from studies conducted in high-income countries, obtaining data that may not be generalizable to all sites worldwide. Third, several data were not obtainable for the analysis: there was no information provided regarding follow-up after intensive care unit or hospital discharge, nor about organ dysfunction or cognitive function different from CPC status. Also, the impact of skin pigmentation, potentially leading to erroneous readings, was not addressed in the studies analyzed. Additionally, the interval between OCHA and the beginning of ECPR was not known, but because tertiary emergency care facilities were included, it was presumed that ECPR was introduced quickly, minimizing the discrepancies between OCHA and ICHA. Fourth, the authors considered only the pre-cannulation rSO_2 static value, not taking into account variation of rSO_2 at the start and during extracorporeal support, because they could not find data on the variation of rSO_2 from baseline to ECPR initiation or recorded timeframes. A serial evaluation of the rSO_2 trend could have allowed us to understand why the patients with a $rSO_2 > 60\%$ showed a trend toward a decline in neurologic outcome. Fifth, different cerebral oximeters have vastly different readings and use different wavelengths of light. Although all the included studies used INVOS, these numbers will not necessarily be translatable to other devices.[43] Also, there has been a movement away from the INVOS device over time because it is not an "absolute" value but more of a trend monitor. Finally, the authors also acknowledge that it is unclear whether mean, initial, maximum, or serial changes from the baseline rSO_2 readings should be used prior to ECPR initiation.

Future Studies and Prospects

The proven use of NIRS as a marker during cCPR and the authors' highly predictive data in ECPR should trigger the initiation of other studies with the aim of modifying future guidelines. Also, before assuming that patients with a low precannulation rSO_2 would not benefit from ECPR and taking that as a conclusion that would help to decide whose patients are eligible for ECPR or not, larger sample sizes, more studies, and future investigations are needed. On the other hand, if future studies confirm these results, rSO_2 may become an independent predictive criterion for a good outcome in ECPR recipients; the authors may have found a simple instrument to prevent futile cannulations and avoid unnecessary costs.

Conclusions

In the authors' analysis, rSO_2 was a predictive marker of positive neurologic outcomes and survival in patients undergoing ECPR. Further studies are required to determine if such findings might have relevant clinical practice implications.

Conflict of Interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1053/j.jvca.2023.01.007.

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