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Clinical paper

Elevated jugular venous oxygen saturation after cardiac arrest

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Abstract

Background: We performed a retrospective analysis of our earlier study on cerebral oxygenation monitoring by jugular venous oximetry ($SjvO_2$) in patients of out-of-hospital cardiac arrest (OHCA). The study was focused on high $SjvO_2$ values (≥75%) and their association with neurological outcomes and serum neuron-specific enolase (NSE) concentration.

Method: Forty OHCA patients were divided into (i) high (Group I), (ii) normal (Group II), and (iii) low (Group III) $SjvO_2$, with the mean $SjvO_2 \geq 75\%$, 55–74% and <55% respectively. The neurological outcome was evaluated using the Cerebral Performance Category scale (CPC) on the 90th day after cardiac arrest (post-CA). NSE concentration was determined after ICU admission and then at 24, 48, and 72 hours (h) post-CA.

Results: High mean $SjvO_2$ occurred in 67% of patients, while no patients had low mean $SjvO_2$. The unfavourable outcome was significantly more common in Group I than Group II (74% versus 23%, $p < 0.01$). Group I patients had significantly higher median NSE than Group II at 48 and 72 h post-CA. A positive correlation was found between $SjvO_2$ and $PaCO_2$. Each 1 kPa increase in CO_2 led to an increase of $SjvO_2$ by 2.2 %+/-0.66 ($p < 0.01$) in group I and by 5.7%+/-1.36 ($p < 0.0001$) in group II. There was no correlation between $SjvO_2$ and MAP or $SjvO_2$ and PaO_2.

Conclusion: High mean $SjvO_2$ are often associated with unfavourable outcomes and high NSE at 48 and 72 hours post-CA. Not only low but also high $SjvO_2$ values may require therapeutic intervention.

Keywords: Out-of-hospital cardiac arrest, Cerebral oxygenation monitoring, Jugular venous oximetry, Cerebral oedema, Brain hypoxia, Jugular venous oxygen saturation, Neuron-specific enolase

Introduction

In 2005, the European Resuscitation Council accepted post-resuscitation care as the final link in the chain-of-survival concept. Its usefulness for patients after cardiac arrest has been confirmed by several extensive studies.[1–3] One of the principal tasks of post-resuscitation care during ICU hospitalization is to ensure adequate cerebral oxygenation. Unfortunately, only a handful of studies focused on monitoring cerebral oxygenation after a cardiac arrest, therefore it is impossible to make specific recommendations on the optimal method to monitor cerebral oxygenation and interpret the measured values.

Jugular venous oximetry is one of the bedside methods used to monitor cerebral oxygenation, especially in patients with traumatic brain injury (TBI). It utilizes the concept that almost the entire brain's venous system drains into the internal jugular veins through the jugular bulb. Thus, according to Fick's principle, the oxygen saturation of haemoglobin measured in the jugular bulb ($SjvO_2$) reflects the differ-

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ence between the amount of oxygen entering the brain and the amount of oxygen consumed by brain tissue.[4]

Generally, $SjvO_2$ values within the range of 55-75% are considered normal. $SjvO_2$ values $\geq$ 75% indicate either increased oxygen delivery or decreased metabolic oxygen consumption in the brain ($CMRO_2$). Conversely, $SjvO_2$ values <55% indicate decreased oxygen delivery or increased $CMRO_2$. It has been proven that jugular oxygen desaturation is associated with poor clinical outcomes after TBI.[5] Therefore, the Brain Trauma Foundation's 2016 guidelines recommended that $SjvO_2$ values of <50% be considered a critical threshold (level III recommendation).[6] However, it is unclear whether the same recommendation is appropriate for post-cardiac arrest (post-CA) survivors.

Neuron-specific enolase (NSE) is an enzyme released into the bloodstream after neuronal injury. Its serum concentration directly correlates with the extent of hypoxic-ischemic brain injury and is therefore used to predict the neurological outcome.[7] Unfortunately, due to the variability of techniques used in measuring NSE serum concentrations and the individual NSE kinetics following its initial release, it is difficult to find a consistent threshold for identifying patients with the poor neurological outcome with a high degree of certainty. Current resuscitation guidelines recommend serial NSE measurements. Increasing values between 24 and 48 h or 72 h in combination with high values at 48 and 72 h indicate a poor prognosis.[8]

We recently published results from a prospective, observational study evaluating the incidence of low $SjvO_2$ episodes during the first 72 hours after OHCA in patients admitted to the intensive care unit (ICU) and the impact of low $SjvO_2$ on the neurological outcome.[9] As an incidental finding, we observed high $SjvO_2$ values in the unfavourable outcome group. The aim of this study is a post hoc analysis of our previous results, focusing on high $SjvO_2$ values and their association with neurological outcome and serum NSE concentration.

Methods

We performed a post hoc analysis of data from our previous study,[9] registered on ClinicalTrials.gov (identifier NCT02806778); the protocol was approved by the Local Medical Ethics Committee (Ethics Committee of University Hospital Ostrava Ref No. 410/2016). The previous study focused on the incidence of low $SjvO_2$ values during the first 72 hours after OHCA and their effect on neurological outcomes.

We consecutively screened adult OHCA patients admitted to the ICU. Patients who met the inclusion criteria were: i) OHCA of presumable cardiac cause, ii) age over 18, iii) Glasgow Coma Scale $\leq$ 8 following successful ROSC. The exclusion criteria were: i) > 6 h of duration between cardiac arrest and first jugular bulb sampling, ii) OHCA secondary to any non-cardiac cause, iii) confirmed acute intracranial bleeding, iv) known terminal disease (cancer, liver disease, etc.) where pre-arrest life expectancy was less than 6 months, v) patients who died within 72 h from CA due to refractory post-CA shock. All eligible patients were included in the final analysis.

The treatment was provided following the European Resuscitation Council guidelines 2015.[10] Targeted temperature management (TTM) was initiated within minutes after ICU admission using an external surface cooling technique. As per institutional protocol, core temperature was measured via a urinary bladder catheter and was maintained between 35–36 °C for 24 hours, followed by passive rewarming.

All patients had a jugular bulb catheter inserted within 6 hours of cardiac arrest. The catheter was inserted retrogradely into the dominant jugular vein determined with ultrasound. The right side was usually preferred when there was no difference in jugular vein diameter between the two sides. Eventually, the correct placement of the catheter tip was confirmed by lateral neck radiography (tip above the lower border of the C1 vertebra).

The first sample of $SjvO_2$ was obtained immediately after the catheter placement (time 0) and subsequently after 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 h or until the patient was extubated. The samples were drawn slowly (<2 ml per min) to avoid mixing with extracranial blood. Simultaneously, blood samples were drawn from the arterial line, and the mean arterial pressure (MAP) values were recorded.

Physicians and ICU staff responsible for the intensive care of patients enrolled in the study were blinded to the $SjvO_2$ results. Therefore, no diagnostic or therapeutic interventions were made based on $SjvO_2$ values.

Blood samples required for NSE analysis were collected immediately after jugular venous catheter insertion and subsequently at 24, 48, and 72 hours after cardiac arrest. Analysis of the samples was started immediately using the COBAS e601 system (Roche Diagnostics, Rotkreuz, Switzerland) in the hospital laboratory.

This post hoc analysis divided the cohort into groups according to mean $SjvO_2$ values calculated from each patient's values. High mean $SjvO_2$ (Group I), normal mean $SjvO_2$ (Group II), and low mean $SjvO_2$ (Group III) were defined as $\geq$ 75%, between 55 and 74%, and < 55%, respectively.

The neurological outcomes were evaluated by the Cerebral Performance Categories scale[11] on the 90th day following cardiac arrest. A CPC of 1–2 was considered favourable, and CPC 3–5 was an unfavourable outcome.

Statistical analyses were performed using the R statistical software version 4.0.3. (R Core Team 2019) with the significance level was set at 0.05. The missing values and outliers were double-checked and removed from the statistical testing process. The categorical variables were represented by the absolute and relative frequency expressed as percentages. The normality of the numeric variables was tested using the Shapiro-Wilk test. Numerical data with normal distribution were expressed by means and standard deviation, and data without normal distribution as medians with a 25–75 % interquartile range. Logarithmic transformation was applied in order to normalize the skewed data when required. Paired t-test or Wilcoxon rank-sum test was utilized to compare numerical variables and the chi-square test or Fisher's exact test to compare categorical variables between patient groups with normal and high mean $SjvO_2$ ($SjvO_2$ 55–74 % vs $SjvO_2$ $\geq$ 75 %). A linear mixed-effects model (patient as a random effect) was used to demonstrate the relationship between $SjvO_2$ and $PaCO_2$, PaO_2, MAP as fixed factors.

Results

Forty patients were included in the final analysis of the study (Fig. 1). The demographic, laboratory, and clinical data of the patients are presented in Table 1.

The median time from cardiac arrest to the time of first jugular catheter sampling was not statistically different in the normal mean

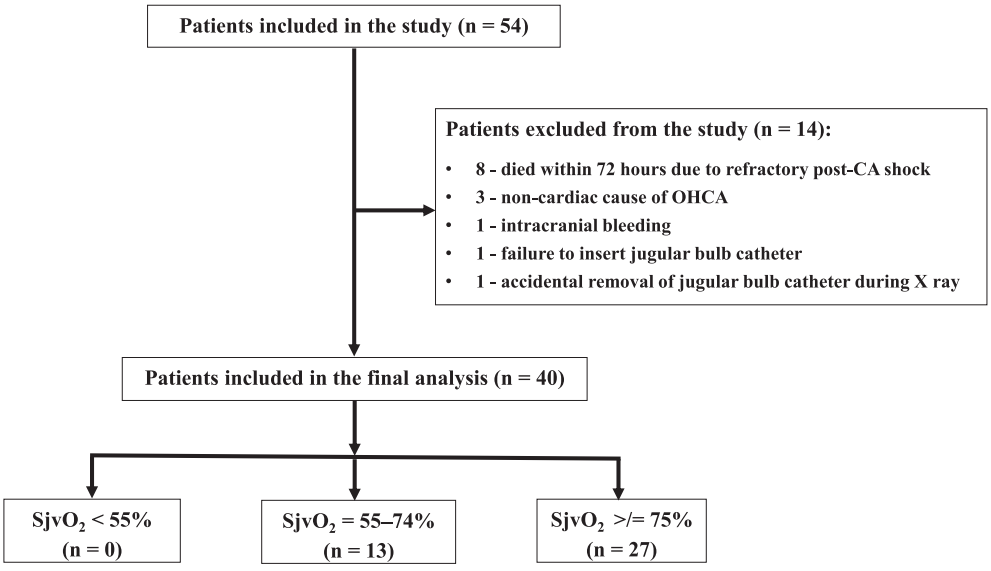

Fig. 1 – Flow diagram of patients included in the study.

$SjvO_2$ (Group II) and the high mean $SjvO_2$ (Group I): 243 min (IQR, 221 to 284) versus 264 min (IQR, 241 to 317), p = 0.31. There were 438 individual measurements of $SjvO_2$ (an average of 11 measurements per patient).

Fig. 2 illustrates the distribution of mean $SjvO_2$ values and the limits dividing the patients into the Groups. Twenty-seven (67%) of 40 patients had high mean $SjvO_2$ values (Group I), 13 patients (33%) had normal mean $SjvO_2$, and no patient had low mean $SjvO_2$. Therefore, only two groups (Group I and II) were included in the final analysis.

Patients with high mean $SjvO_2$ values experienced a significantly higher risk of unfavourable outcomes than patients with normal mean $SjvO_2$ (74% versus 23%, p = 0.0066) (Table 2).

The distribution of individual $SjvO_2$ measurements was similar to the mean $SjvO_2$ (please see the supplementary files). A total of 311 individual $SjvO_2$ measurements (71%) were at 75% or higher, whereas 123 values (28%) were between 55–74% and 4 (1%) were below 55%.

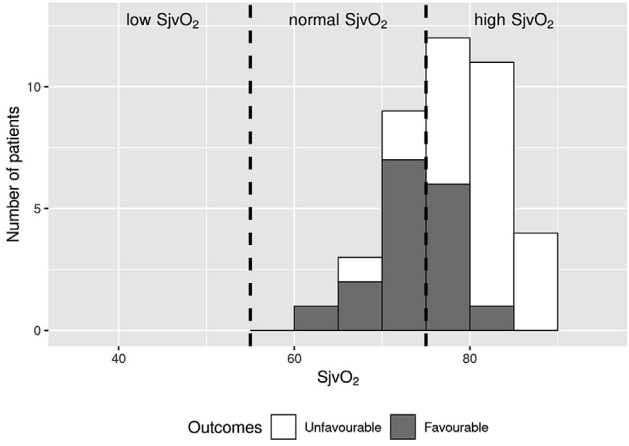

Fig. 2 – Bar diagram showing the distribution of mean $SjvO_2$ values and outcome.

Table 1 – Demographic, clinical and laboratory data of the groups.

Variables	$SjvO_2$ = 55–74	$SjvO_2$ =/>75	All
n	13	27	40
Sex [M (%)]	11 (85 %)	25 (93 %)	36 (90 %)
Age [years]	56 (52–70)	60 (53,5 – 67)	60 (52–68)
Clinical data			
APACHE II	26 (23–28)	29 (25–33)	28 (25–30)
Primary rhythm [n (%)]:			
• Non-shockable	1 (8 %)	6 (22 %)	7 (18 %)
• Shockable	12 (92 %)	21 (78 %)	33 (82 %)
Resuscitation [min]	18 (10–27)	21 (15.5–30)	20.5 (14–29.25)
Coronary angiography [yes (%)]	12 (92 %)	26 (96 %)	38 (95 %)
PCI [yes (%)]	7 (54 %)	16 (59 %)	23 (58 %)
Laboratory values			
Haemoglobin	148 (141–152)	143 (132–151)	146 (134–152)
pH	7.32 (7.25–7.37)	7.25 (7.16–7.35)	7.27 (7.18–7.36)
Lactate [mmol/l]	1.9 (1.3–6.1)	2.2 (1.5–5.55)	2.1 (1.3–5.72)

Categorical variables are described by absolute (relative) frequency. Numeric variables are characterized by median (interquartile range).

Table 2 – Outcomes according to mean $SjvO_2$.

	Unfavourable	Favourable
$SjvO_2$ = 55–74	3	10
$SjvO_2$ =/> 75	20	7

The table shows the incidence of favourable and unfavourable outcomes according to mean $SjvO_2$. A p-value = 0.0066 of the Fisher's exact test shows a strong association between high mean $SjvO_2$ and unfavourable and between normal mean $SjvO_2$ and favourable outcome.

NSE determinations were available in 38 patients at the time of admission (17 patients from normal mean $SjvO_2$ Group versus 21 patients from high mean SjvO2 Group), 40 at 24 hours post-CA (17 versus 23), 40 at 48 hours post-CA (17 versus 23) and 35 at 72 hours post-CA (12 versus 23). Normal mean $SjvO_2$ Group demonstrated similar median NSE values after admission and 24 hours post-CA compared to high mean $SjvO_2$ Group. However, 48 hours and 72 hours post-CA, median NSE values in the normal mean $SjvO_2$ group were already significantly lower; 10 (IQR, 9 to 16) vs 32 ng/ml (IQR, 13 to 54, $p < 0.01$) and 9 (IQR, 7 to 13) vs 46 ng/ml (IQR, 14 to 65, $p < 0.01$) respectively (Fig. 3).

A linear mixed model was used to assess the correlation between $SjvO_2$ and MAP, $SjvO_2$ and CO_2, as well as $SjvO_2$ and PaO_2, respectively. Closer observation revealed a correlation between $SjvO_2$ and CO_2 in Group I: an increase by 1 kPa in CO_2 led to an increase by 2.2 % +/- 0.66 ($p < 0.01$) in $SjvO_2$. No similar associations were identified between $SjvO_2$ and MAP or between $SjvO_2$ and PaO_2 values. A further stronger correlation was found between $SjvO_2$ and CO_2 in Group II: each 1 kPa increase in CO_2 led to an increase by 5.7% +/- 1.36 ($p < 0.0001$) in $SjvO_2$. No similar associations were identified between $SjvO_2$ and MAP or $SjvO_2$ and PaO_2.

We also divided patients according to the mean $SjvO_2$ values on each individual day to determine whether the number of patients with high daily mean $SjvO_2$ values differed between the first, second, and third days after cardiac arrest. These changes are shown in Fig. 4. The number of patients with a high daily mean $SjvO_2$ value was lowest on day 1 (23 patients), and an increase occurred on day 2 (28 patients). On the contrary, the highest number of patients with a normal daily mean $SjvO_2$ value was found on day 1 (17 patients), and a decrease occurred on day 2 (12 patients).

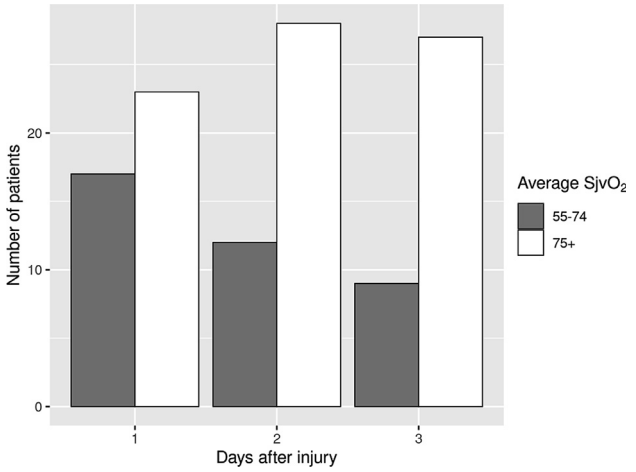

Fig. 4 – Distribution of daily mean $SjvO_2$ values during the first three days post-CA. The total number of patients on Day 3 was lower than Day 2 because some patients were already extubated.

Discussion

In the present post hoc analysis, OHCA patients were observed from a different perspective: patients were divided and evaluated according to the mean $SjvO_2$ values measured during the first 72 hours after cardiac arrest. Our analysis showed that high mean $SjvO_2$ values are

	$SjvO_2$=55-74	SjvO2>/=75
Admission	17	20
24h	14	17
48h	10	32
72h	9	46

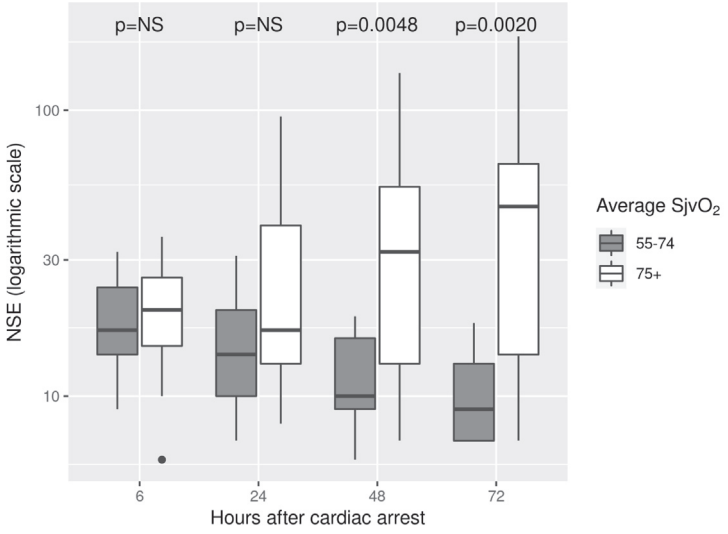

Fig. 3 – Time course of NSE according to average $SjvO_2$. Data presented as the median and interquartile range.

primarily associated with unfavourable neurological outcomes and high NSE values at 48 and 72 h after cardiac arrest.

There is a consensus that low $SjvO_2$ values indicate cerebral hypoxia requiring immediate therapeutic intervention and that such low values are associated with poor neurological outcomes. On the other hand, the importance of high $SjvO_2$ values in OHCA patients is yet to be explored. Although it could be concluded from high $SjvO_2$ values that the brain does not suffer from lack of oxygen, our analysis highlights that unfavourable outcome was associated in three-quarters of patients with high mean $SjvO_2$ values.

Comparable results were shown in the only similar study carried out by Cormio et al., published in the late 20th century, which, unlike our study, included patients with traumatic brain injury.[12] They showed high mean $SjvO_2$ values in 19% of 450 TBI patients, and similar to our analysis, three-quarters of those patients had an unfavourable outcome.

Our study showed an increased number of patients with high mean $SjvO_2$ between the first and second days after cardiac arrest. However, there was no further increase between days 2 and 3. This interesting finding may imply that the "breaking point" is between days 1 and 2. Such a conclusion agrees with other studies that divided patients in terms of good versus poor outcome: Van den Hoeven et al. did not identify any differences in $SjvO_2$ values during the first few hours after cardiac arrest in both groups.[13] However, in patients with poor outcomes, Buunk et al.'s study[14] and our previous study[9] demonstrated a significant increase in mean $SjvO_2$ values approximately at 24 h and the Lemiale study at 36 h after cardiac arrest.[15] In addition, Hoedemaekers et al. demonstrated a continuous increase in $SjvO_2$ in patients with poor outcomes from admission to 72 h post-CA.[16]

The $SjvO_2$ value reflects the difference between cerebral oxygen delivery (CDO_2) and cerebral oxygen consumption ($CMRO_2$). Therefore, in their studies, Lemiale et al. and Hoedemaster et al.[15,16] assessed, during the first 72 h after OHCA, in addition to $SjvO_2$ values, cerebral oxygen delivery by measuring cerebral blood flow (CBF) using a transcranial Doppler (CBF is the most critical determinant of CDO_2, because the second determinant, the oxygen content in arterial blood, is stable under most circumstances). Initial CDO_2 values were low but gradually increased into the standard range, with no difference between the survivor and the non-survivor groups. Initial $SjvO_2$ values also showed no difference between the two groups, but subsequently, there was a significant increase in $SjvO_2$ values in the non-survivor group. These results suggest that the leading cause of high $SjvO_2$ values in patients with poor clinical outcomes is reduced cerebral oxygen consumption, not increased oxygen delivery.

Several mechanisms may contribute to reduced cerebral oxygen consumption. We can presume that this is a consequence of irreversible neuronal damage[14–16] or mitochondrial dysfunction.[17] Another mechanism, but potentially reversible, may be cerebral oedema.[18–20] Increased diffusion distance limits oxygen diffusion from capillaries to neurons, leads to brain hypoxia and disruption of cellular metabolism. The oxygen remains in the bloodstream, and the $SjvO_2$ values become "arterialized." This undoubtedly underestimated problem has been known in nature for billions of years: the size of the first oxygen-using life forms was limited by the ability of oxygen to diffuse passively into the organism from the surrounding ocean. It took billions of years to develop the circulatory system and the red blood cells that carry oxygen from outside the organism to the capillaries near the cells of each tissue. It is only this fact that has allowed organisms to reach much larger sizes.[21] Currently, a similar problem is well known in the context of pulmonary oedema. In this case, oedema limits oxygen diffusion from the pulmonary alveoli to the pulmonary capillaries, leading to respiratory failure.[22]

Cerebral oedema is the main finding on brain computed tomography in patients after cardiac arrest.[10] It can be detected as early as one h after resuscitation[23] and its magnitude, measured as the ratio between grey and white matter density (GWR), increases during the first 24 hours.[24] At the same time, there is a decrease in cerebral compliance and an increase in intracranial pressure (ICP). However, these values rarely reach values of intracranial hypertension defined as ICP > 20 mmHg.[25,26] The severity of cerebral oedema has even become part of the decision-making algorithm for predicting neurological outcomes in patients after cardiac arrest, according to the 2015 ERC guidelines.[8,10] The improvement in cerebral oxygenation after administration of anti-oedema therapy to post-CA patients suggests that this mechanism might be potentially modifiable.[20]

The ascending trend and high median serum concentration of NSE at 48 and 72 h post-CA, identified in the high $SjvO_2$ Group (Fig. 5), supports the idea that there is a connection between high $SjvO_2$ and unfavourable neurological outcomes. The most extensive literature study to date focused on NSE in patients with OHCA documented the highest median NSE values at 48 hours after cardiac arrest.[27] However, our post hoc analysis and other large studies have found that the highest median NSE is 72 h after cardiac arrest.[28,29] Given that the estimated half-life of NSE is approximately 24 hours, the observed highest median NSE value 72 h after cardiac arrest may be explained by ongoing hypoxic brain damage, theoretically offering scope for therapeutic intervention.

Our post hoc analysis has several limitations. First of all, this is a single-centre study with a small sample of patients. Secondly, the monitoring of $SjvO_2$ values was intermittent, not continuous, which could have biased the results by failing to detect some values outside the norm. Thirdly, the design of this analysis was conceived post hoc and not included in the original study protocol. Finally, no other brain monitoring tools, such as transcranial Doppler ultrasound or brain tissue oxygen tension monitoring, were used simultaneously, which could contribute to detecting the causes of high $SjvO_2$ values.

Conclusion

Our study suggested an association between high mean $SjvO_2$ values on the one hand and unfavourable outcomes with high NSE values on the other hand. Further studies should confirm not only this association, but also the assumption that high $SjvO_2$ values in patients with unfavourable outcome are caused by reduced oxygen consumption in the brain and not by its over-delivery to the brain. Further, future studies should focus on identifying the mechanisms responsible for reduced oxygen consumption in the brain. Revealing possible reversible mechanisms might enable targeted treatment and better neurological outcomes for patients after cardiac arrest.

CRediT authorship contribution statement

Jaromir Richter: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Peter Sklienka:** Conceptualization, Investigation, Funding acquisition. **Nilay Chatterjee:** Writing – review & editing. **Jan Maca:** Methodology, Writing – review & editing.

Roman Zahorec: Methodology, Supervision. **Michal Burda:** Data curation, Formal analysis.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2021.10.011.

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