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Determinants and significance of cerebral oximetry after cardiac arrest: A prospective cohort study

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ABSTRACT

Aim of the study: To study the determinants and the evolution of cerebral oximetry determined by near-infrared spectroscopy after out-of-hospital cardiac arrest of cardiac origin during therapeutic hypothermia and rewarming, and to compare cerebral oximetry values between patients with good and bad prognosis.

Methods: In this prospective, non-interventional, single center study, all consecutive patients between 18 and 80 years admitted for out-of-hospital cardiac arrest (OHCA) with a no flow less than 10 min, a low flow of less than 50 min and a persistent coma after ROSC with Glasgow score equal or less than seven at baseline were included.

Results: Between February 2012 and January 2013, 43 patients were admitted for OHCA in our ICU. Twenty-two patients (51%) were discharged with no or minimal neurologic complications (CPC 1–2). Mortality rate in the ICU was 46.5%. Cerebral oximetry (rSO_2) was correlated with temperature, heart rhythm, PaO_2, hemoglobin, and mean arterial pressure. Mean rSO_2 during the 48 first hours was not different between patients with good and bad neurologic outcomes, respectively, 61.8 (5.9) vs. 58.1 (8.8), $P = 0.13$, as during the period of hypothermia. The minimal value of rSO_2 during the first 48 h was significantly different between patients with good prognosis and those with bad prognosis, respectively, 45.0 (6.8) vs. 31.7 (15.0), $P = 0.0009$.

Conclusions: In this prospective cohort of OHCA patients, main determinants of rSO_2 were systemic variables. Monitoring of rSO_2 does not allow discriminating patients with good or bad outcome, but could be useful for identifying vulnerable periods for the development of neurologic injury.

Introduction

Out-of-hospital cardiac arrest (OHCA) is associated with high morbidity and mortality and is still a major issue for public health. Even when a return of spontaneous circulation (ROSC) is obtained, the vast majority of these patients will die during the post-resuscitation period, mostly because of irreversible hypoxic-ischaemic brain injury.[1] Evaluating the severity of brain damages is very difficult at the very early period and is hindered by therapeutics used at hospital admission, such as hypothermia and sedative drugs. At that time, there is no single predictive factor that can early identify patients with a bad outcome.[2,3] A delayed multimodal prognostication approach is usually recommended in comatose patients but an earlier identification of those with no chance of recovery will help to avoid inappropriate treatment and provide information for relatives.

With the exception of hypothermia, no treatment has demonstrated its ability to reduce the impact of global cerebral ischemia induced by cardiac arrest. This reflects the lack of knowledge on the pathophysiology of the post anoxic encephalopathy, especially in the early phase of resuscitation and during hypothermia. Cerebral oxygen extraction and consumption monitored by jugular venous oxygen saturation ($SVjO_2$) are critical determinants of neurologic

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recovery after cardiac arrest.[4–7] However, these tools are invasive, time-consuming, and laborious in a non-neurosurgical environment. Near-infrared spectroscopy (NIRS) is a non-invasive optical technique based on the transmission and absorption of NIR light as it passes through tissues. NIRS provides real-time information regarding regional cerebral oxygen saturation (rSO_2) in the frontal lobe. Correlation between rSO_2 and $SVjO_2$ is inconstant through studies and clinical situations. Hence this correlation was found to be excellent during cardiac surgery,[8] but insufficient to recommend its clinical use after traumatic brain injury.[9,10] Despite these conflicting results, NIRS was demonstrated to be a useful tool to monitor cerebral oxygenation[11,12] and autoregulation[13] under cardiopulmonary bypass for cardiac surgery. Cerebral oximetry can provide real-time information on oxygen delivery during resuscitation in in-hospital cardiac arrest patients,[14,15] and first rSO_2 measured at hospital arrival was demonstrated to predict neurological outcome after out-of-hospital cardiac arrest.[16] Few studies investigated the feasibility and the utility of NIRS after return of spontaneous circulation. Among them, two studies[17,18] showed a statistically significant difference of rSO_2 between patients with good and neurologic prognosis, but the small numbers of patients included as well as the few available data on other physiological variables limit their interpretability. Cerebral oximetry could be an additional tool in the prediction of neurological prognosis after cardiac arrest, but more data about its interpretability are needed. Hence, we perform a prospective, descriptive study of rSO_2 and its components after ROSC, and during therapeutic hypothermia.

Material and methods

Study setting and patients

This was a prospective, observational, and single center study. Between February 2012 and January 2013, all consecutive patients admitted for OHCA were studied. Patients had to be aged between 18 and 80 years, and cardiac arrest had to meet the following characteristics:

an OHCA of cardiac origin;
a delay from collapse to basic life support less than 10 min ("no flow");
a delay from basic life support to return of spontaneous circulation (ROSC) of less than 50 min ("low flow");
a persistent coma after ROSC with Glasgow score equal or less than seven at baseline;

The exclusion criteria were a non-cardiac OHCA (trauma, sepsis, acute respiratory failure or acute neurologic disorder) and any chronic brain disease. The study protocol was approved by the committee for medical ethics of the French intensive care society (CE SRLF 11–353).

Patient's management

Out-of-hospital resuscitation was performed by an emergency team, including at least one trained physician in emergency medicine, according to international guidelines.[19] Patients in whom the resuscitation process failed were not transported to hospital. According to our previously published procedures,[20,21] patients in whom sustained ROSC was achieved, and without obvious extra-cardiac cause were admitted directly to the catheterization laboratory of our tertiary center, to perform a coronary angiogram, and a left ventricular angiography using standard techniques. A percutaneous coronary intervention was attempted if there was an acute coronary artery occlusion, or if there was an unstable lesion that could be considered as the culprit. After the procedure, patients were admitted to the intensive care unit (ICU) for supportive treatment, which systematically included targeted temperature management between 32 and 34 degrees Celsius. This treatment was instaured for a 24 h period as described in previous works.[22] In cases with obvious extra-cardiac cause, patients were immediately admitted to ICU to promptly benefit of adequate treatment. All patients received a standardized treatment protocol aiming to limit the worsening of brain damages, as previously described.[1,20,23]

Cerebral oximetry

Monitoring of cerebral oximetry (rSO_2) is part of standard care in our ICU for OHCA patients using NIRS. A sensor was used and put on the right temporal area as described by the manufacturer (Somanetics INVOS, Covidien, Boulder, CO, USA). The monitoring was started as soon as possible after ICU admission and was maintained during the first 48 h. Physician and nurses in charge checked the quality of the signal every 3 h to ensure an adequate monitoring. Data were registered in the device and extracted on day three for subsequent analysis.

Data's management

Physiological values were recorded continuously during the whole period of the study. Heart rate (HR), respiratory frequency, mean arterial pressure (MAP), pulse oximetry, body's core temperature, and cerebral oximetry were extracted simultaneously every hour and entered in our database. Values from arterial blood samples (hemoglobin, PaO_2, and $PaCO_2$) were added to the corresponding time. Frequency of this sample was every 6 h and was part of our routine care in post cardiac arrest management. This frequency could be higher if patients were unstable.

Outcome assessment

The primary outcome was defined as the level reached on the cerebral performance categories scale (CPC) at hospital discharge.[24] Favorable outcome included patients with a good cerebral performance (CPC level 1), or a moderate cerebral disability (CPC2). Bad outcome was defined by a severe cerebral disability (CPC3), a coma or a vegetative state (CPC4), or death (CPC5). The CPC level was prospectively assessed by a first physician at hospital discharge and was controlled by a second and independent physician blinded for post-resuscitation treatments. Each case of disagreement was resolved by a consensus. Neurological outcome was daily assessed by ICU physicians until death or ICU discharge. According to guidelines and recent studies[25–28] life-sustaining treatments were withdrawn in case of absence of pupillary responses, absence of corneal reflexes, absent or extensor motor responses, and bilateral absence of the N20 component of the somatosensory evoked potentials with median nerve stimulation. As all patients were treated by therapeutic hypothermia, this neurological assessment was systematically delayed at minimum on day five after OHCA in order to wait for elimination of sedative drugs. Life-sustaining therapies withdrawal was always decided after a collegial decision.[1]

Statistical analysis

This report was prepared in compliance with the STROBE checklist for observational studies.[29] Continuous variables were presented as mean ± standard deviation, and categorical variables were presented as percentages. Comparisons between groups (according to neurological outcome, with CPC 1–2 considered as good outcome) were made with Pearson X^2 or Fisher's exact tests

Table 1
Baseline characteristics.

Baseline characteristics	Good outcome, CPC 1–2 *n* = 22 patients	Bad outcome, CPC 3–4–5 *n* = 21 patients	*P*
Age, year (SD)	58.7 (15.9)	61.3 (11.4)	0.54
Male sex, *n* (%)	17 (77)	17 (81)	0.99
Bystander, *n* (%)	22 (100)	19 (90)	0.23
Localization of cardiac arrest			0.56
Home, *n* (%)	8 (36)	11 (52)	
Public places, n (%)	13 (59)	9 (43)	
Other, *n* (%)	1 (5)	1 (5)	
Shockable rhythm, *n* (%)	18 (82)	17 (81)	0.99
No flow, min (SD)	4.5 (4.6)	5.2 (3.3)	0.56
Low flow, min (SD)	15.2 (8.5)	20.8 (14.1)	0.13
Epinephrine, mg (SD)	0.7 (1.1)	2.6 (2.8)	0.005
Lactate level at admission, $mol\,l^{-1}$ (SD)	2.8 (1.6)	4.8 (2.9)	0.008

CPC: cerebral performance category; SD: standard deviation

for categorical variables, and with Student t-tests for continuous variables. Step-by-step analysis of rSO_2 has been performed to determine the threshold associated with the highest sensitivity and specificity in predicting an unfavorable neurological outcome. All tests were two-tailed, and values of $P < 0.05$ were considered significant. Statistical analysis was performed using STATA/SE 11.0 software (College Station, TX).

Results

Cardiac arrest characteristics and outcome

Between February 2012 and January 2013, 43 patients were admitted for OHCA in our ICU. All patients had an OHCA of a cardiac origin, had a ROSC obtained before transportation but were still comatose at time of ICU admission. Baseline characteristics are summarized in Table 1. The median age was 60 years (SD 13.8), and 79% of patients were male. Cardiac arrest occurred at home for 44% of patients and in public place for 51% of patients. Initial rhythm was shockable in 81% of patients. During the study period, mean hemoglobin (13.1 $g\,dL^{-1}$ (SD 1.8) vs. 12.3 $g\,dL^{-1}$ (SD 2.2), $P = 0.0003$), PaO_2 (106 mmHg (SD 57) vs. 95 mmHg (SD 38), $P = 0.047$) and MAP (81.3 mmHg (SD 16) vs. 78.8 mmHg (SD 17), $P = 0.0004$) were significantly different between, respectively, patients with a good neurologic outcome and those with a poor neurologic outcome (Table 2). Mortality rate was 47%. Twenty-two patients (51%) were discharged from the hospital with favorable neurologic outcome (CPC 1–2).

Determinants of rSO_2

As illustrated in Fig. 1, most systemic variables were associated with rSO_2. During the study period, rSO_2 was correlated with temperature ($r = 0.08$, 95%CI [0.03; 0.13], $P = 0.003$), heart rhythm ($r = 0.066$, 95%CI [0.015; 0.12], $P = 0.011$), hemoglobin ($r = 0.29$, 95%CI [0.17; 0.40], $P < 0.0001$), and mean arterial pressure ($r = 0.054$, 95%CI [0.004; 0.10], $P = 0.035$). The correlation between MAP and rSO_2 was only found in the group of patients with a poor neurologic prognosis ($N = 21$, $r = 0.08$, $P = 0.03$), whereas this correlation was not present in the group of patients with a good neurologic prognosis ($N = 22$, $r = -0.06$, $P = 0.08$). Interestingly, rSO_2 was inversely correlated with PaO_2 ($r = -0.24$, 95%CI [−0.36; −0.12], $P = 0.0002$), and no correlation was observed between rSO_2 and $PaCO_2$ ($r = -0.009$, 95%CI [−0.14; 0.11], $P = 0.89$).

Table 2
Cerebral oximetry according to neurologic outcome.

NIRS value	CPC 1–2 *N* = 22	CPC 3–4–5 *N* = 21	*P*
H12 (mean, SD)	56.5 (7.6)	56.2 (10.9)	0.91
H24 (mean, SD)	64.2 (6.5)	59 (10.8)	0.09
H36 (mean, SD)	67.5 (11.0)	60.3 (15.1)	0.17
H48 (mean, SD)	71.2 (9.7)	63.2 (16.0)	0.14
Mean rSO_2 during hypothermia	58.3 (6.1)	57.2 (8.4)	0.64
Mean rsO_2 during normothermia	62.3 (8.8)	60.0 (8.8)	0.44
Mean rSO_2 value (SD)	61.8 (5.9)	58.1 (8.8)	0.13
Minimal value (mean, SD)	45.0 (6.8)	31.7 (15.0)	0.0009
Maximal value (mean, SD)	82.1 (8.9)	77.1 (10.2)	0.10
Time with NIRS < 30, s (mean, SD)	0	1412 (2428)	0.02
At least one measure < 40, *n* (%)	3 (15.8)	12 (60)	0.008
At least one measure < 30, *n* (%)	0 (0)	9 (45)	0.003
Hb (mean, SD)	13.1 (1.8)	12.3 (2.2)	0.0003
MAP (mean, SD)	81.3 (15.7)	78.8 (17.4)	0.0004
PaO_2 (mean, SD)	105.5 (57)	95.5 (38.3)	0.048

NIRS: near infrared spectroscopy; rSO_2: regional cerebral oxygen saturation; Hb: hemoglobin; MAP: mean arterial pressure.

Association of cerebral oximetry with outcome

Mean rSO_2 at baseline, H12, H24, H36, and H48 does not allow discriminating patients with good and bad neurologic prognosis (Table 2). In our cohort, mean rSO_2 was not different between patients with good or poor prognosis during hypothermia, during normothermia, and during the whole periods, respectively (58.3 (6.1) vs. 57.2 (8.4), $P = 0.64$), (62.3 (8.8) vs. 60.0 (8.8), $P = 0.44$), and (61.8 (5.9) vs. 58.1 (8.8), $P = 0.13$). If the maximal value of rSO_2 reached during the study period was not different in patients with a good prognosis and those with poor prognosis (82.1 (8.9) vs. 77.1 (10.2), $P = 0.1$), the lowest value of rSO_2 measured during the first 48 h was significantly lower among patients with unfavorable neurologic outcome (31.7 (15.0) vs. 45.0 (6.8), $P = 0.0009$). The threshold value of 30 for rSO_2 was the best to discriminate neurologic outcome: as illustrated in Fig. 2, all patients with a good neurologic outcome had a minimal value of rSO_2 above 30. When considering a threshold of rSO_2 of 30 (Table 3), sensitivity for unfavorable neurological outcome was 45%, and specificity was 100%. Negative predictive value was 65%, and positive predictive value was 100%.

Discussion

In a well-characterized cohort of OHCA patients, we demonstrate that 1/rSO_2 after cardiac arrest is correlated with systemic variables as MAP, Hb, PaO_2, HR, and temperature; 2/the correlation between MAP and rSO_2 varies according to the neurologic prognosis; 3/mean rSO_2 is not different in patients with good or poor neurologic prognosis; 4/reaching a low cerebral oximetry during the first 48 h could be associated with a poor prognosis in patients resuscitated from an OHCA.

Table 3
Neurologic outcome according to occurrence of $rSO_2 < 30$.

NIRS value	CPC 1–2	CPC 3–5	*P*
Minimal value ≤ 30	0	9	9
Minimal value > 30	20	11	31
	20	20	40

Sensibility of NIRS = 30 for predicting unfavorable outcome = 9/20 = 45%; specificity = 100%; positive predictive value = 100%; negative predictive value = 65%.

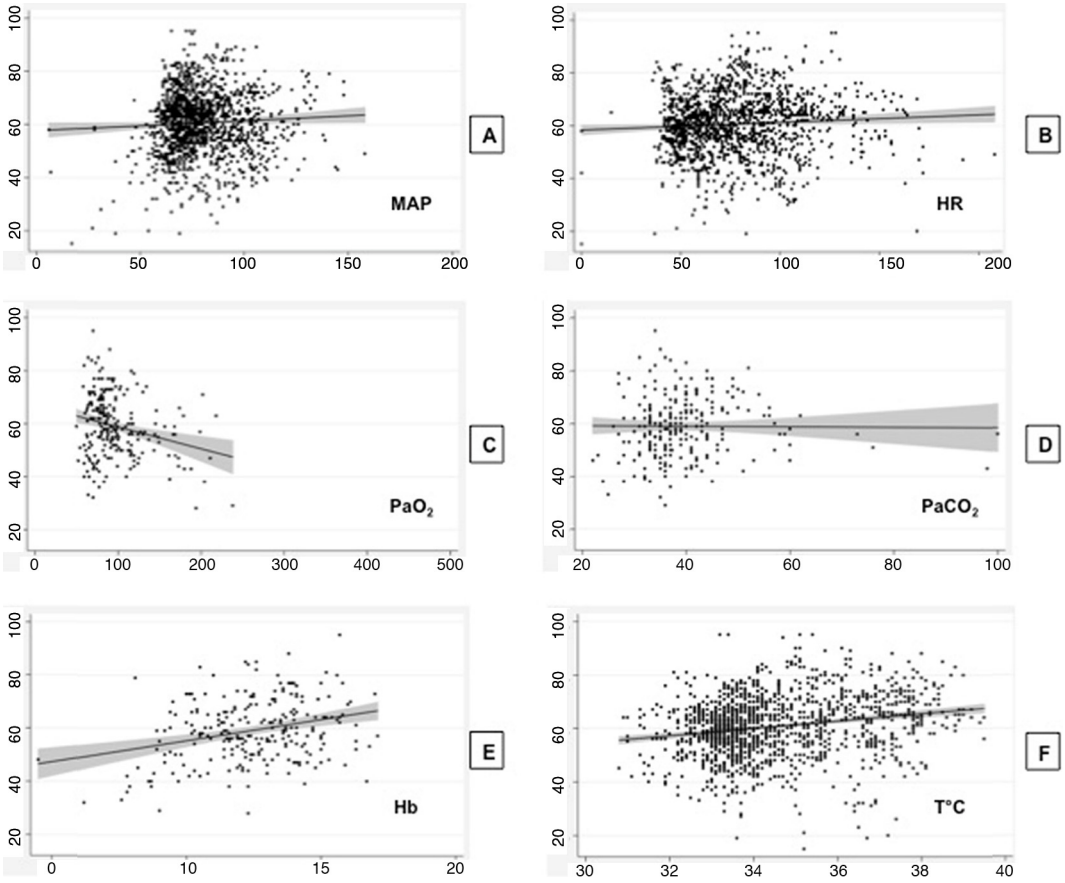

Fig. 1. Linear regression analysis of mean rSO_2 according to systemic hemodynamic parameters. rSO_2 is regional cerebral oxygen saturation. Linear regression analysis of rSO_2 demonstrates a correlation between lower values of rSO_2 and lower MAP (A), lower heart rate (B), lower hemoglobin (E) and lower temperature (F), and between lower values of rSO_2 and higher values of PaO_2 (C).

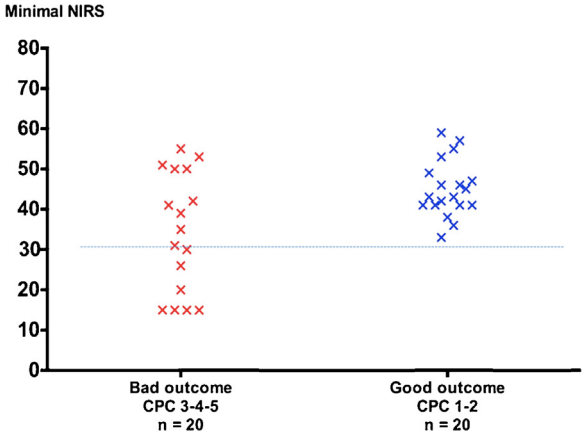

Fig. 2. NIRS minimal according to neurological outcome. Each cross represents a patient according to the minimal rSO_2 value during the 48 first hours: red crosses are for patients with bad outcome (CPC 3–5), and blue crosses for patients with good outcome (CPC 1–2). All patients with a good neurologic outcome had a minimal value of rSO_2 above 30.

In our study, systemic variables as MAP, HR, and PaO_2 are the main determinants of rSO_2. While we expected an association between rSO_2 and PaO_2, we highlighted an inverse correlation between these two variables. We do not know the significance of this association, and we cannot rule out an artifact. This relationship may reflect an attempt by the physician in charge of the patient to correct the low rSO_2, increasing FiO_2, and therefore PaO_2. Actually, there are doubts about the real significance of rSO_2, including its ability to reflect global cerebral oxygenation, or at least a surrogate marker as jugular bulb venous oxygen saturation ($SvjO_2$). Tateishi et al. showed that the direction and magnitude of changes induced by CO_2 variation in cerebral oximetry measured by NIRS were similar to those changes in $SvjO_2$ in patients with acute brain injury.[30] Similarly, in 40 children undergoing cardiac procedure, the correlation between rSO_2 and $SvjO_2$ was high, although this association was found especially for high values of $SvjO_2$.[8] However, in a study about 10 patients with traumatic brain injury, the correlation between rSO_2 and $SvjO_2$ was poor.[9] As our aim was to perform a non-invasive and observational study, we did not measure $SvjO_2$ or oxygen tissue partial pressure ($PtiO_2$), so we cannot assume that the measured rSO_2 effectively reflects global cerebral oxygenation. However, as the ischemia-reperfusion injury secondary to cardiac arrest is a global insult, and since main determinants of $SvjO_2$ are shown to be associated with rSO_2, we can hypothesize that rSO_2 after cardiac arrest may reflects cerebral tissue oxygenation. Our study does not allow concluding to a correlation between measured rSO_2 and cerebral oxygenation, but we believe that in case of a low rSO_2 value, particular attention should be brought to correction of a low MAP, PaO_2, or HR.

In patients with traumatic brain injury, static cerebral autoregulation is significantly correlated with cerebral tissue oxygen reactivity,[31] and patients with impaired autoregulation are at increased risk for secondary cerebral hypoxia.[32] Hence, during cardiopulmonary bypass, a cerebral oximetry index calculated as a moving Pearson's correlation coefficient between MAP and rSO_2 was used to determine the lower limit of cerebral autoregulation.[33] This cerebral oximetry index was used to determine an optimal MAP according to vasoreactivity (MAP_{OPT}) in 36 cardiac arrest

children. In this study, the time spent with MAP below MAP_{OPT} was associated with neurologic prognosis,[34] suggesting that monitoring of cerebral autoregulation could help individualize hemodynamic management goals after OHCA. In our observational study, we did not perform an invasive measurement of brain tissue partial pressure of oxygen, nor than an invasive measurement of ICP, so we cannot conclude that autoregulation was maintained or not in our cohort. However, as the correlation observed between MAP and rSO_2 was only found in the group of patients with a poor neurologic prognosis, it could suggest that cerebral autoregulation was impaired in this group. Taken together, these data suggest that autoregulation may play a role in the pathophysiology of post anoxic encephalopathy, and that a hemodynamic management according to cerebral autoregulation should be a way of research in future for OHCA patients.

In our study, if mean rSO_2 was not different between patients with favorable and unfavorable neurologic outcome, either during hypothermia or during normothermia, the lowest value of rSO_2 measured during the first 48 h was significantly lower among patients with poor neurologic outcome. On the same way, Meex et al. showed in a prospective observational study in 28 OHCA patients that the lowest value of cerebral oximetry was significantly lower in non-survivors than in survivors, respectively, 58% (55–59) vs. 62% (59–66), $P = 0.02$.[17] Ahn et al. showed a significant difference for median rSO_2 during the first 24 h in survivors compared to those who did not survive, respectively, 68.2% (66.0–71.0) vs. 62.9% (56.5–66.0), $P = 0.01$.[18] More recently, in a cohort of 60 OHCA patients, median rSO_2 was significantly higher in patients with a good neurologic outcome ($N = 23$, median $rSO_2 = 68\%$) than in patients with a poor neurologic outcome ($N = 37$, median $rSO_2 = 58\%$), $P < 0.01$.[35] Data available does not suggest that rSO_2 during therapeutic hypothermia or rewarming could be a useful tool helping clinician at bedside to predict neurologic outcome using a threshold value, and not even distinguishing patients to the neurologic outcome.

To reach a low value of cerebral oxygenation is associated with poor outcome during cardiopulmonary bypass. Slater et al. failed to demonstrate a benefit of a rSO_2-targeted management during cardiac surgery, but patients with rSO_2 desaturation had a significantly higher risk of postoperative cognitive decline and a significantly increased risk of prolonged hospital stay.[12] In our cohort, to reach an rSO_2 below 30 was strongly associated with poor outcome. These observations suggest that rSO_2 could be a useful marker of brain hypoxia in this setting, even if its use as a treatment target is not yet established. By analogy with interventional studies conducted in cardiac surgery,[11,12] a goal-directed strategy based on PaO_2, $PaCO_2$, MAP, and hematocrit, aiming at maintaining rSO_2 above a predefined threshold could be beneficial for OHCA patients. At least, continuous monitoring of cerebral oxygenation could help to alert physicians, highlighting vulnerable periods for the brain.

Several limitations of this study must be considered. First, as illustrated by the high rate of shockable rhythm, the relatively short "no-flow" and "low-flow", and the high incidence of CPC 1–2 at ICU discharge, our population appears selected, and these results are obviously not extendable to an overall population of cardiac arrests.

Second, because of the design of our study, we did not monitor $SvjO_2$, $PtiO_2$ nor than ICP. We cannot affirm that rSO_2 effectively reflects cerebral oxygenation, and that autoregulation is maintained or not. By analogy with data obtained during CPB, a study with a continuous calculation of the correlation between rSO_2 and MAP should be of particular interest in cardiac arrest patients.

Finally, we did not compare the prognostic value of cerebral oximetry with known predictors of poor neurologic outcome including clinical examination, absent N20 responses of somatosensory evoked potentials (SSEPs) or elevated neuron specific enolase (NSE). These are preliminary data as our aim was only to describe determinants and significance of this new tool to monitor cerebral oxygenation after cardiac arrest.

Conclusion

In this prospective observational study, main determinants of cerebral oximetry after OHCA were PaO_2, $PaCO_2$, MAP, hematocrit, and temperature. We observed no difference for main rSO_2 according to neurologic prognosis during the study period. However, to reach a low cerebral oximetry during the first 48 h was strongly associated with a poor prognosis in patients resuscitated from an OHCA. Monitoring of cerebral oxygenation may be a useful technique for identifying vulnerable periods for the development of neurologic injury after OHCA.

Conflict of interest statement

Authors have no conflict of interest.

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