Resuscitation 86 (2015) 14–18

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical Paper

Microcirculatory perfusion and vascular reactivity are altered in post cardiac arrest patients, irrespective of target temperature management to 33 °C vs 36 °C☆,☆☆

Matty Koopmans[a,*], Michael A. Kuiper[a], Henrik Endeman[b], Gerke Veenstra[a], Namkje A.R. Vellinga[a], Rien de Vos[c], E. Christiaan Boerma[a]

[a] Medical Center Leeuwarden, Department of Intensive Care, Leeuwarden, The Netherlands
[b] Onze Lieve Vrouwe Gasthuis, Department of Intensive Care, Amsterdam, The Netherlands
[c] Academic Medical Center, Department Epidemiologic, Biostatistics and Bioinformatics, Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 1 July 2014
Received in revised form
17 September 2014
Accepted 21 September 2014

Keywords:
Cardiac arrest
Microcirculation
Target temperature management
Vascular reactivity

ABSTRACT

Aim: In previous reports both microcirculatory alterations and impaired vascular reactivity have been described in post cardiac arrest patients treated with mild therapeutic hypothermia. As of now it is unknown whether these alterations are related to the temperature management or to the cardiac arrest itself. Aim of the present study was to investigate the potential difference in microcirculatory alterations and vascular reactivity in comatose patients after out of hospital cardiac arrest treated with target temperature management of 33 °C (TTM33) in comparison to patients treated with 36 °C (TTM36).
Methods: Our study was designed as a predefined substudy of the open label randomized controlled TTM trial in 2 Dutch mixed ICU's. Sublingual microvascular flow index (MFI) was assessed by Side Stream Darkfield imaging and vascular reactivity at the thenar region of the hand by near infrared spectroscopy. Variables, including systemic hemodynamics were recorded at start study (T1), after 12 h (T2) and after 24 h (T3).
Results: 22 patients were included, 13 in TTM33 and 9 in TTM36. At T1 MFI between groups did not differ significantly (1.08 [0.4–1.9] versus 1.67 [0.7–2.4] respectively, $p = 0.59$). The difference between groups remained insignificant over time. At T1 tissue oxygenation (StO_2) was significantly lower in TTM36 in comparison to TTM33: (44.6 ± 15.8 versus 58.9 ± 13.5, $p = 0.03$). Over time this difference between groups disappeared. However, vascular reactivity, expressed as the descending and ascending slope of StO_2 after a standardized ischemic occlusion test was similar between groups.
Conclusions: In this relatively small sample size study microcirculatory blood flow and vascular reactivity did not differ nor change between TTM33 and TTM36.

1. Introduction

After cardiopulmonary resuscitation (CPR), following an out-of-hospital cardiac arrest (OHCA) hemodynamic failure is common, due to a combination of heart failure and ischemia reperfusion (I/R) injury. Comatose post-cardiac arrest patients are treated in the intensive care unit (ICU) with mild therapeutic hypothermia (33°), nowadays referred to as target temperature management (TTM) for an assumed neuroprotective effect.[6] Experimental studies and previous clinical trials suggest an improvement in mortality and neurological function during hypothermia after cardiac arrest, However in the recently published TTM trial that compared a regimen of 33 °C vs 36 °C no difference in outcome was observed.[18] Irrespective of the level of hypothermia well-known clinical signs of shock may be blunted during TTM. Blood pressure, pulse rate, urine production and skin temperature are all influenced by TTM itself. Moreover, therapeutic strategies such as deep sedation, necessary to counteract the physiological response of the human body to hypothermia may obscure the clinical picture. Interpretation of variables, including cardiac output, venous saturation as well as lactate is complicated during TTM.

☆ A Spanish translated version of the abstract of this article appears as Appendix in the final online version at http://dx.doi.org/10.1016/j.resuscitation.2014.09.025.
☆☆ Clinicaltrials.gov nr. NCT01850485.
* Corresponding author.
E-mail address: matty.koopmans@gmail.com (M. Koopmans).

http://dx.doi.org/10.1016/j.resuscitation.2014.09.025

In a recent retrospective observational study in the Medical Center Leeuwarden in 62 patients after cardiac arrest, we observed a rise in cardiac index (CI) and $ScvO_2$ during steady state hypothermia (TTM33) in conjunction with a significant increase of lactate levels.[2,5] Although lactate is a well-known marker of tissue hypoperfusion, increasing concentrations may also result from other reasons, such as metabolic changes. This raised the question whether TTM itself indeed attenuates I/R-injury-induced changes in tissue perfusion.

In the last decade in vivo microscopy of tissue perfusion with Side Stream Darkfield (SDF) imaging has become available at the bedside of critically ill patients.[3] Recent studies indicate that alterations in sublingual microcirculatory blood flow not only can be observed and quantified, but are also associated with patient outcome.[1] During and after cardiac arrest and CPR microcirculatory flow abnormalities indicated by Microvascular Flow Index (MFI) have been observed and appeared to predict outcome.[3]

Changes in muscle tissue oxygenation (StO_2) after an ischemic incident using near-infrared spectroscopy (NIRS) were found in patients with sepsis and in particular in septic shock. Also NIRS may be a useful technique to monitor microcirculatory changes in patients after cardiac arrest.[4]

In this study we tested the hypothesis that, in patients after OHCA, treatment with TTM33 is associated with an increase in microcirculatory flow abnormalities, in comparison to patients treated with TTM36 as measured by SDF (MFI) and tissue oxygenation (NIRS).

2. Patients and methods

2.1. Design and settings

This research study was a sub-study of the target temperature management (TTM) trial.[18] In this TTM study patients were randomized after OHCA for a 24-h management with temperature control at 33 °C versus 36 °C. Our substudy was carried out in two Dutch large teaching hospitals, the Medical Center Leeuwarden and the Onze Lieve Vrouwe Gasthuis. Both Intensive Care Units are 22-bed, mixed medical, surgical and cardiothoracic surgical units and Intensivist directed. This study was carried out between March 2012 and January 2013.

2.2. Ethical approval

The research protocol and consent procedures were approved by the ethics committee, RTPO Leeuwarden. Informed consent was obtained from the legal representative of the patient. Informed consent was also obtained from the patient, as soon the patient was able to judge the situation. The protocol was recorded on clinicaltrials.gov nr. NCT01850485.

2.3. Inclusion and exclusion criteria

All patients above 18 years of age with return of spontaneous circulation (ROSC), but remaining comatose after OHCA were screened. Exclusion criteria were absence of informed consent, recent maxillofacial surgery, and participation in other clinical trials.

2.4. Randomization and blinding

The patients were randomized in a 1:1 ratio via a web-based application using a center-stratified, block-permuted randomization scheme with varying block sizes. Concerning blinding; given the procedure caregivers could not be blinded for TTM. Collection of data was purely based on objective already stored computer data. Analysis of data, including interpretation of SDF images was blinded.

2.5. Sample size

Based on earlier research[13] we anticipated a mean MFI at baseline of 2.5 with a standard deviation of 0.4. We calculated a sample size of 2×11 patients to detect an absolute difference in MFI of 0.5 in a two-sided test with an α of 0.05 and an 80% power.

2.6. Protocol

By protocol (TTM main protocol), after randomization, all patients, both TTM33 and TTM36 experienced guided circulatory resuscitation in order to optimize systemic hemodynamic variables in accordance with the basic principles of early goal-directed therapy.[7] Systemic hemodynamic assessment was achieved through continuous invasive monitoring of arterial blood pressure and right heart catheterization with continuous cardiac output and central venous oxygen saturation (Vigilance®, Edwards Lifesciences, Saint-Prex, Switzerland). Until a pulmonary artery catheter was in place, the use of fluids and vasoactive agents was at the discretion of the attending physician, whose goal was to maintain a minimal mean arterial pressure (MAP) of 75 mm Hg. After calibration, treatment of circulatory failure was performed using the following strict hierarchical order: (1) establishment of fluid-responsiveness by repeated infusions of at least 250 ml crystalloids, colloids or blood products, until the increase in left ventricular stroke volume is less than 10%, or until the pulmonary artery wedge pressure exceeds 18 mm Hg. (2) Treatment of inadequate oxygen delivery, defined as a central venous oxygen saturation <70%, with dopamine administered at up to 10 μg/kg/min and additional enoximone in the event of an inadequate response to dopamine. (3) Reversal of hypotension with norepinephrine in case of MAP < 75 mm Hg despite the afore mentioned steps. The use of hydrocortisone up to a maximum of 100 mg iv 3 times per day was permitted for shock reversal in case of vasopressor dependency; in general the red blood cell transfusion trigger was a haematocrit <25%. Patients in both groups were sedated, endotracheally intubated and mechanically ventilated.

2.7. Measurements of tissue perfusion

In vivo microscopy of sublingual microcirculatory blood flow was performed with a SDF camera (Microscan®, Microvision Medical, Amsterdam, the Netherlands), and subsequent quantification was done in accordance with the guidelines from a round table conference.[12] Microvascular flow was semi-quantitatively graded from 0 (absent), 1 (intermittent), 2 (sluggish) to 3 (normal). The overall MFI was an average of 12 scores (4 quadrants times 3 windows of observation).[8] The measurements were done by a trained research nurse or intensivist.

Tissue saturation (StO_2) and vascular reactivity[4] was assessed with near infrared spectroscopy (NIRS) (Invos 5100C) at the thenar region of the hand, in combination with a standardized occlusion maneuver of the forearm.[11] This test was performed by inflating a pneumatic cuff around the upper arm to 50 mm Hg above the systolic pressure for 3 min to follow the evolution of StO_2. NIRS is a technique that utilizes near-infrared light to measure chromophores in tissues. The analysis of changes in StO_2 during a brief episode of forearm ischemia enables quantification of microvascular dysfunction. This vasoreactivity test evaluates a different aspect of microvascular function than flow; it evaluates microvascular oxygen uptake reserve more than actual microvascular perfusion.

2.8. Data collection

At baseline, the following data were recorded; general characteristics, severity of illness with Acute Physiology and Chronic Health Evaluation (APACHE) IV[9] and Sequential Organ Failure Assessment (SOFA),[10] Glasgow Coma Score (GCS), use of vasopressors and mechanical ventilation. Systemic hemodynamics, SDF and NIRS measurements were recorded at start study (T1), after 12 h (T2) and 24 h (T3). Length of stay in de ICU and survival status of each participant was confirmed. The moment of start study (T1) is as soon as the patient reached the targeted temperature.

The primary endpoint of this study was sublingual microcirculatory blood flow as defined by microcirculatory flow index (MFI) at T1, T2 and T3. Secondary endpoints were StO_2, descending and ascending slope, fluid balance after the first 24 h, use of inotropes and vasopressor dose, cardiac index, lactate, and SvO_2.

2.9. Statistical analyses

In general, all data were tested for normal distribution with the Kolmogorov Smirnov test. Histograms and normal-quantile plots were visually inspected to verify the normality of distribution of continuous variables.

First the demographic characteristics were analyzed. Variables were expressed as mean and standard deviation or medians and interquartile ranges according their distribution.

Secondly, the microcirculation as the primary outcome was compared. To test differences in microcirculatory blood flow using SDF, expressed as MFI, we used the Mann–Whitney *U* test. To analyze differences in time courses StO_2 Anova for repeated measurements followed by paired t-test or non-parametric was used as necessary. A Bonferroni correction was used to correct for multiple comparison.

Finally the hemodynamic and biological data were compared. Variables were expressed as mean and standard deviation or medians and interquartile ranges according to their distribution. Differences between group means were tested by the student *t*-test or Mann–Whitney *U* test.

A *p* value of <0.05 was considered statistically significant.

The Statistical Package for Social Sciences (SPSS 19 for Windows, Chicago, IL, USA) is used for statistical analyses.

3. Results

All adult patients between March 2012 and January 2013, admitted to the ICU after an OHCA, were screened for this study. Out of 36 eligible patients 22 were included. Informed consent could not be obtained in 14 cases (see Fig. 1). All 22 patients were included within 4 h after ROSC. By central computerized randomization 13 patients were allocated to TTM33 and 9 patients at TTM36 for 24 h. One patient died after 5 h in the TTM33 group, the other 21 patients completed the study protocol. Eighty-one percent of the patients were male, with a mean age of 67 (±9.9) with a mean time to ROSC of 24.8 ± 11.4 min. Baseline characteristics are provided in Table 1.

3.1. Microcirculatory variables

MFI was altered in both groups at T1 (Table 2). The MFI in TTM33 was lower in comparison to TTM36, but this was not statistically significantly different (1.08 [0.4–1.9] versus 1.67 [0.7–2.4], $p = 0.55$). In both groups the MFI returned to normal during the 24 follow up period. There was no statistical difference between the two groups on T2, (2.2 [1.6–2.5] versus 1.8 [1.2–2.7], $p = 0.59$) and T3, (2.6 [1.5–2.9] versus 2.8 [1.7–3], $p = 0.55$) on our primary outcome.

StO_2 as measured by NIRS at T1 (start study) was significantly lower in the TTM36 as compared to TTM33 (59.8 ± 13.7 and 44.6 ± 15.8, $p = 0.03$) (Table 2). This difference between groups disappeared after 12 and 24 h. We found no difference in StO_2 in both groups over time. The descending and ascending slopes of StO_2 after a standardized occlusion maneuver of the forearm were not different between the two temperature groups, nor over time (Table 2).

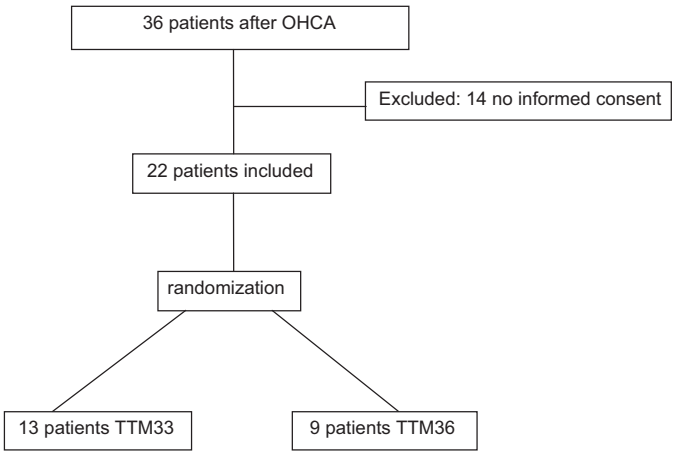

Fig. 1. Flowchart. 36 patients after OHCA

3.2. Hemodynamic and biological data

As shown in Table 3 patients in the TTM33 group had a significantly lower heart rate (64.5 ± 13.8 versus 81.6 ± 19.1, $p = 0.04$), a higher lactate level (2.78 (±1.1) versus 1.71 (±0.5), $p = 0.03$) and hemoglobin level (8.88 (±0.6) versus 8.21 (±0.4), $p = 0.02$) in comparison to the TTM36 group at start study. The TTM33 group was ventilated with significant more PEEP (12 (±2.4) versus 10 (±1.4), $p = 0.04$) and higher FiO_2 (0.48 (±0.16) versus 0.37 (±0.7), $p = 0.03$). We also observed a significant difference in fluid balance, with the TTM33 group receiving more fluids (3.3 L (±1.2) versus 1.8 L (±0.9), $p = 0.02$).

Glucose levels were not significantly different, but the insulin used to reach this levels is significant higher in the TTM33 group at start study (2.6 [0–8] versus 0.8 [0–2], $p = 0.02$) and the total insulin use is significant higher in the TTM33 group (2.0 [1.5–3] versus 1.5 [0.3–2], $p = 0.01$).

The SOFA score as indicator of organ failure was significantly higher after 24 h in the TTM33 group (11 [10–13] versus 9 [7–13], $p = 0.04$).

Table 1
Characteristics at start study.

Variables	TTM33 ($n = 13$)	TTM36 ($n = 9$)	*p*
Gender: male, *n* (%)	12 (92.3%)	6 (66.7%)	0.13
Age, years	68.9 (±9.3)	64.3 (±12.4)	0.42
Temperature in °C (at admission)	35.2 (±0.8)	35.5 (±0.95)	0.55
CPR time to ROSC in minutes	26.3 (±10.7)	22 (±15.2)	0.48
OHCA rhythm VF(*n*)	12	6	0.13
Non-shockable (*n*)	1	3	
APACHE IV	134.4 (±13.6)	94.6 (±24.2)	0.39
Mean arterial pressure, mm Hg	84.9 (±14.0)	79.2 (±18.5)	0.45
Heart rate, beats per minute	78.3 (±14.7)	79.4 (±13.6)	0.85
Cardiac index, l/m^2	2.38 (±0.84)	2.07 (±0.63)	0.35
Lactate, mmol/l	5.55 (±2.2)	4.83 (±3.6)	0.45

GCS, Glasgow Coma Scale; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sepsis-related Organ Failure Assessment. All data are presented as mean (±SD), median (IQR) or as numbers (%).

Table 2
Microcirculatory variables.

	Start study (T1)		p	After 12 h (T2)		p	After 24 h (T3)		p
	TTM33	TTM36		TTM33	TTM36		TTM33	TTM36	
MFI	1.1 [0.4–1.9]	1.7 [0.7–2.4]	0.59	2.2 [1.6–2.5]	1.8 [1.2–2.7]	0.59	2.6 [1.5–2.9]	2.8 [1.7–3]	0.55
StO_2	58.9 (±13.5)	44.6 (±15.8)	0.03	65.0 (±12.2)	49.0 (±12.6)	0.07	61.7 (±10.2)	52 (±9.88)	0.09
Dec	−0.15(0.08)	−0.14(0.05)	0.70	−0.15(0.07)	−0.16(0.08)	0.85	−0.14(0.04)	−0.13(0.08)	0.38
Asc	0.97(0.52)	0.92(0.39)	0.81	0.68(0.35)	0.75(0.36)	0.47	0.72(0.40)	0.73(0.35)	0.62

MFI = Microvascular Flow Index; StO_2 = tissue oxygenation; Dec = descending slope in %/s; Asc = ascending slope in %/s. All data expressed as mean (SD) or median (IQR) and analyzed with the Mann–Whitney *U* test.

4. Discussion

The hypothesis tested was that in patients after OHCA, treatment with TTM33 would be associated with an increase in microcirculatory flow abnormalities, in comparison to patients treated with TTM36. However, in our study there was no difference in MFI between TTM33 and TTM36, our primary outcome. Indeed, there was a difference in tissue saturation at T1, with a significant higher StO_2 in TTM33. But this was not accompanied by a difference in vascular reactivity, as expressed by the StO_2 recovery slope. This was associated with a lower heart rate, higher lactate levels, higher use of insulin, higher hemoglobin, higher PEEP and FiO_2, a more positive fluidbalance and a higher SOFA score in comparison to TTM36.

In accordance with previous reports, in our study early post resuscitation phase was characterized by significant abnormalities in microvascular flow.[14] This returns to normal within the next 24 h. Donadello et al. observed in TTM33 a MFI of 2.1 (±0.5) in the first 12 h after ICU admission and an MFI of 2.8 (0.2) after 24–48 h. In our study the TTM36 group seemed to have a slightly higher MFI in comparison to the TTM33 group, but this was not statistically significant. Moreover, in both groups MFI normalized over time. Hypothermia does not seem to have a relation with microvascular alterations.

Van Genderen et al.[15] investigated the microcirculatory perfusion and alterations and concluded that the abnormalities in sublingual microcirculation were independent of systemic hemodynamics and suggested that the observed alterations were probably due to hypothermia-induced vasoconstriction. However, the fact that in our data microcirculatory alterations were not different between two target-temperatures, suggests alternative causes, although a targeted temperature of 36 °C may be considered hypothermia to some extent

In septic patients it is known that presence and persistence of alterations in tissue oxygenation (StO_2) in the first 24 h are associated with worse outcome.[4] Donadello et al.[14] found no changes in StO_2 over time during hypothermia. In our study we observed a significant difference at time point 1 (start study) between groups; StO_2 was significantly lower in TTM36 as compared to TTM33 (59.8 (±13.7) and 44.6 (±15.8), $p = 0.03$). But this difference disappeared after 12 and 24 h. A higher StO_2 in the TTM33 group may be explained by a lower oxygen consumption in response to hypothermia. Alternatively, a higher StO_2 may be present during shunting. Since the catchment area of the StO_2 probe incorporates both capillary and venous blood, this cannot be ruled out, and is in line with the observed higher lactate levels. However, the data on the microcirculation, especially the MFI, which was found to be low in these patients, did not support shunting as an explanation for the increase in StO_2 and lactate. An alternative explanation for the higher lactate levels in TTM33 could be metabolic: the liver might not be able to metabolize sufficient lactate under conditions of hypothermia. It is of note, however that the difference in StO_2 between groups disappeared over time despite maintenance of the target temperature level during this observation period. This may be in line with the concept of oxygen deficit and oxygen debt. An initial greater misbalance between oxygen delivery and consumption in the TTM36 maybe reflected by a prolonged recovery period of the StO_2. Similar observations have been done in patients with reduced oxygen delivery capacity such as heart failure[19] An alternative explanation for this transient disappearance of a significant difference of

Table 3
Hemodynamic, therapeutic and biological data at the start of the study, after 12 and 24 h.

	Start study (T1)		p	After 12 h (T2)		p	After 24 h (T3)		p
	TTM33	TTM36		TTM33	TTM36		TTM33	TTM36	
Mean arterial pressure, mm Hg	79.1 (12.7)	70.4 (12.1)	0.13	73 (8.86)	66.5 (7.3)	0.16	70.6 (13.2)	93.6 (17.3)	0.17
Heart rate, beats per minute	64.5 (13.8)	81.6 (19.1)	0.04	60.2 (9.7)	79.6 (12.5)	0.00	71.9 (6.9)	78.3 (9.7)	0.01
Cardiac Index, l/m^2	1.9 (0.73)	2.1 (0.64)	0.42	2.1 (0.74)	2.1 (0.74)	0.08	2.3 (0.49)	3.0 (0.67)	0.02
Lactate, mmol/l	2.78 (1.05)	1.71 (0.48)	0.03	3.48 (2.2)	1.6 (0.84)	0.01	2.73 (1.51)	2.17 (1.73)	0.46
pH	7.32 (0.08)	7.38 (0.11)	0.24	7.3 (0.087)	7.34 (0.014)	0.14	7.34 (0.07)	7.34 (0.05)	0.83
PaO_2, kPa	14.4 (4.6)	17.1 (4.1)	0.08	13.4 (2.7)	11.9 (2.0)	0.33	14.0 (3.27)	14.0 (3.15)	0.94
SvO_2, %	69.4 (10.27)	61.2 (13.56)	0.20	71.8 (8.9)	75.8 (4.95)	0.40	74.2 (7.8)	73.4 (6.2)	0.72
Glucose, mmol/l	10.6 (3.69)	8.7 (2.72)	0.22	7.1 (2.9)	5.8 (1.1)	0.43	6.18 (1.81)	6.97 (1.85)	0.20
Actrapid, ml/h	2.6 (0–6)	0.83 (0–2)	0.02	2.5 (1–8)	1.69 (0–4.5)	0.33	2.58 (0.5–12)	1.62 (0–4)	0.46
Platelets, g/l	242.3 (60.3)	204.7 (38.6)	0.12						
Hemoglobin, mmol/l	8.88 (0.63)	8.21 (0.44)	0.02	8.9 (0.85)	8.2 (0.66)	0.10	8.68 (1.25)	8.13 (0.80)	0.18
Noradrenaline, mcg/kg/min	0.087 (0.081)	0.090 (0.089)	0.89	0.093 (0.013)	0.097 (0.011)	0.94	0.12 (0.12)	0.07 (0.09)	0.29
Dopamine, mcg/kg/min	0.00 (0.00–4.89)	0.00 (0.0–1.9)	0.55	0.00 (0.00–1.9)	0.05 (0.0–0.32)	0.53	0.50 (0.92)	0.22 (0.63)	0.36
Peep, cm H_2O	11.96 (2.4)	9.75 (1.39)	0.04	10.8 (2.49)	10.1 (1.46)	0.53	10.9 (1.57)	9.5 (1.41)	0.06
$FiO_{2,\%}$	0.48 (0.16)	0.37 (0.7)	0.03	0.40 (0.11)	0.33 (0.4)	0.11	0.37 (0.6)	0.33 (0.3)	0.07
Fluidbalance, L							3.33 (1.18)	1.79 (0.92)	0.02
SOFA, points							11 (10–13)	9 (7–13)	0.04

All data expressed as mean (SD), median (IQR) and analyzed with the *T*-test or Mann–Whitney *U* test according their distribution.

StO_2 between groups over time may be a difference in the speed of reduction of oxygen consumption between groups.

Microvascular reactivity as expressed in the descending and ascending slope of the StO_2 was unpredictable and gave a large inter-individual variability. There was no significant difference in reactivity between TTM33 and TTM36. This variability was also described by Donadello et al.[14] in a group of hypothermic patients.

Limitations of the study were related to the small sample size. In our sample size calculation, we anticipated a MFI of 2.5 with a SD of 0.4, but this is not in agreement with the actual observations. With regard to the reliability, the observed differences between the groups are well beyond the described coefficients of variation of both SDF and NIRS.[16,17] Secondly, there was a large inter-individual variability in the microvascular reactivity. Therefore, a small difference between groups may have been undetected in this study.

5. Conclusion

Although this is a small sample size study, our data suggest that after OHCA, the microvascular flow index is altered, independent of TTM33 or TTM36. Since there was found no statistical difference between groups, we reject our hypothesis that a difference in temperature management under TTM is associated with alterations in microvascular blood flow. Since tissue oxygenation at the start of the study appears to be higher in the TTM33 group, without a rise in shunt fraction, reduction of oxygen consumption, or attenuation of oxygen debt seems to be the most logical explanation for this outcome. This suggests that in clinical practice elevation of lactate levels during hypothermia may not only reflect impaired organ perfusion and other causes should be considered.

Conflict of interest statement

All authors declare no conflicts of interest.

Acknowledgment

We express our gratitude to all intensivists and nurses of both intensive care units for their efforts to include patients and collect data.

References

1. Sakr Y, Dubois MJ, De Backer D, et al. Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. Crit Care Med 2004;32:1825–31.
2. Fries M, Tang W, Chang YT, et al. Microvascular blood flow during cardiopulmonary resuscitation is predictive of outcome. Resuscitation 2006;71:248.
3. Goedhart P, Khalilzada M, Bezemer R, et al. Sidestream dark field (SDF) imaging: a novel stroboscopic LED ring-based imaging modality for clinical assessment of the microcirculation. Opt Express 2007;15:15101.
4. Creteur J, Carollo T, Soldati G, et al. The prognostic value of muscle StO_2 in septic patients. Intensive Care Med 2007;33 (9):1549–56.
5. Kaptein S, Boerma EC, Kuiper MA. Evolution of hyper dynamic hyperlacataemia during therapeutic mild hypothermia. In: ESICM Barcelona abstract 0841 ICM. 2010. p. S296.
6. Bergman R, Braber A, Adriaanse MA, et al. Haemodynamic consequences of mild therapeutic hypothermia after cardiac arrest. Eur J Anaesthesiol 2010;27:383–7.
7. Rivers E, Ngyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe and septic shock. N Engl J Med 2001;345:1368–70.
8. Boerma EC, Mathura KR, van der Voort PHJ, et al. Quantifying bedside-derived imaging of microcirculatory abnormalities in septic patients: a prospective validation study. Crit Care 2005;9:R601.
9. Zimmerman JE, Kramer AA, McNair DS. APACHE. IV Hospital mortality assessment for today's critically ill patients. Crit Care Med 2006;34:1297–300.
10. Vincent JL, de Mendonca A, Cantraine F. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. In: Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med, vol. 26. 1998. p. 1793–800.
11. Thooft A, Favory R, Ribeiro S, et al. Effects of changes in arterial pressure on organ perfusion during septic shock. Crit Care 2011;15:R222.
12. De Backer D, Hollenberg S, Boerma EC, et al. How to evaluate the microcirculation: report of a round table conference. Crit Care 2007;11:R101.
13. Boerma EC, Koopmans M, Konijn A, et al. Effects of nitroglycerin on sublingual microcirculatory blood flow in patients with severe sepsis/septic shock after a strict resuscitation protocol: a double-blind randomized controlled trial. Crit Care Med 2010;38:93–100.
14. Donadello K, Favory R, Sagado-Riberio D, et al. Sulbingual and muscular microcirculatory alterations after cardiac arrest: a pilot study. Resuscitation 2011;82:690–5.
15. Genderen van ME, Lima A, Akkerhuis M, et al. Persistent peripheral and microcirculatory perfusion alterations after out-of-hospital cardiac arrest are associated with poor survival. Crit Care Med 2012;40:2287–90.
16. Boerma EC, van der Voort PH, Spronk PE, et al. Relationship between sublingual and intestinal microcirculory perfusion in patients with abdominal sepsis. Crit Care Med 2007;35:1055–60.
17. Lima A, Bakker J. Near-infrared spectroscopy for monitoring peripheral tissue perfusion in critically ill patients. Rev Bras Ter Intensiva 2011;23:341–51.
18. Nielsen N, Wetterslev J, Cronberg T, et al. TTM trial investigators targeted temperature management at 33 °C versus 36 °C after cardiac arrest. N Engl J Med 2013;369:2197–206.
19. Picozzi NM, Clark AL, Lindsay KA, et al. Responses to constant work exercise in patients with chronic heart failure. Heart 1999;82:482–5.