Effects of prolonged mild hypothermia on cerebral blood flow after cardiac arrest

Laurens L. A. Bisschops, MD; Johannes G. van der Hoeven, MD, PhD; Cornelia W. E. Hoedemaekers, MD, PhD

Objective: The aim of the present study was to assess the cerebral blood flow and cerebral oxygen extraction in adult patients after pulseless electrical activity/asystole or resistant ventricular fibrillation who were treated with mild therapeutic hypothermia for 72 hrs.

Design: Observational study.

Setting: Tertiary care university hospital.

Patients: Ten comatose patients with return of spontaneous circulation after pulseless electrical activity/asystole or prolonged ventricular fibrillation.

Intervention: Treatment with mild therapeutic hypothermia for 72 hrs.

Measurements and Main Results: Mean flow velocity in the middle cerebral artery was low (26.5 (18.7–48.0) cm/sec) at admission and significantly increased to 63.9 (45.6–65.6) cm/sec at 72 hrs (p = .002). Upon rewarming, the mean flow velocity in the middle cerebral artery remained relatively constant with a mean flow velocity in the middle cerebral artery of 71.5 (56.0–78.5) at 108 hrs (p = .381). Jugular bulb oxygenation at the start of the study was 57.0 (51.0–61.3)% and gradually increased to 81.0 (78.5–88.0)% at 72 hrs (p = .003). Upon rewarming, the jugular bulb oxygenation remained constant with a jugular bulb oxygenation of 84.0 (77.3–86.3)% at 108 hrs (p = .919). There were no differences in mean flow velocity in the middle cerebral artery, pulsatility index, and jugular bulb oxygenation between survivors and nonsurvivors.

Conclusions: Temperature by itself is probably not a major determinant in regulation of cerebral blood flow after cardiac arrest. The relatively low mean flow velocity in the middle cerebral artery in combination with normal jugular bulb oxygenation values suggests a reduction in cerebral metabolic activity that may contribute to the neuroprotective effect of (prolonged) mild therapeutic hypothermia in the delayed hypoperfusion phase. (Crit Care Med 2012; 40:2362–2367)

Key Words: brain; cardiac arrest; cerebral blood flow; cerebral metabolic coupling; cerebral oxygenation; hypoxia-ischemia; induced mild hypothermia

Brain damage after cardiac arrest strongly depends on the recovery of the cerebral circulation. Return of spontaneous circulation (ROSC) does not automatically restore normal cerebral blood flow (CBF). A longer duration of global ischemia is associated with increased postischemic perfusion defects, resulting in early microcirculatory reperfusion disorders despite adequate cerebral perfusion pressure in circumscribed areas of the brain (1, 2). Many of the pathophysiological pathways that lead to brain injury occur in the hours and days after ROSC when patients are admitted to the intensive care unit (ICU). Mild therapeutic hypothermia (MTH) improves the neurologic outcome after out-of-hospital cardiac arrest (3–5). MTH mitigates the destructive cascades during ischemia and reperfusion, while at the same time stimulates protective systems promoting cell repair (6). The optimal duration of MTH is unknown. Data from some animal experiments suggest that more severe insults may require longer cooling. In an animal model of forebrain ischemia, longer duration of MTH resulted in increased survival of neurons (7, 8). In addition, neonates with peripartum asphyxia are treated with MTH for 48–72 hrs. This resulted in a highly significant and clinically important reduction in the composite outcome of death or major neurodevelopmental disability in survivors (9). Compared with short-term mild hypothermia, long-term mild hypothermia significantly improved the outcome of severe traumatic brain injured adult patients with cerebral concussion and intracranial hypertension without significant complications (10). In contrast, a shorter duration of mild hypothermia induced rapidly and early after restoration of spontaneous circulation improved postresuscitation microcirculation, myocardial and cerebral functions, and survival as well as, or better than, prolonged duration of hypothermia after resuscitation in a rat model of cardiopulmonary resuscitation (11).

CBF is low in adult patients treated with MTH after cardiac arrest (12). Rewarming to normothermia after 24 hrs increases CBF to normal values. The low CBF during hypothermia is accompanied by a normal cerebral oxygen extraction rate, strongly suggesting a decrease in cerebral metabolism. This decrease in cerebral metabolism may contribute to the neuroprotective effect of (prolonged) MTH. The aim of the present study was to assess CBF and cerebral oxygen extraction in adult patients after pulseless electrical activity (PEA)/asystole or resistant ventricular fibrillation who were treated with MTH for 72 hrs.
Study Population. We performed a prospective observational study in ten comatose patients successfully resuscitated from an out-of-hospital cardiac arrest. Prolonged MTH (72 hrs) is a standard-of-care in our ICU in comatose patients with ROSC after asystole, PEA, or resistant ventricular fibrillation. The local Institutional Review Board waived the need for informed consent. All patients 18 yrs or older were eligible for the study if they met the following criteria: 1) comatose (Glasgow Coma Scale ≤6) after ROSC; and 2) ROSC after asystole, PEA, or ventricular fibrillation with prolonged (>30 mins) cardiopulmonary resuscitation. Exclusion criteria were: 1) pregnancy; 2) thrombolytic therapy; 3) contraindication to start MTH due to refractory cardiogenic shock despite the use of vasopressor and/or inotropic agents, based on the clinical judgement of the attending physician; 4) life expectancy of <24 hrs; 5) hypoxemia defined as arterial oxygen saturation <90%; 6) chronic renal failure (creatinin >200 µmol/L); 7) chronic liver failure; and 8) known preexisting neurological disease. The last three exclusion criteria were based on potential changes in baseline CBF and/or CBF regulation. Time between collapse and ROSC, start of cooling and start of the experiment were calculated based on data provided by the paramedic team.

Patient Management. All patients were admitted to the ICU of a tertiary care university hospital in Nijmegen, The Netherlands. If necessary, a coronary angiogram and a percutaneous coronary intervention were performed before admission to the ICU. In agreement with our local protocol, all patients were cooled to 32–34°C by rapid infusion of 30 mL/kg bodyweight of cold Ringer’s lactate at 4°C followed by external cooling using two water-circulating blankets (Blanketroll II, Cincinnati Subzero, The Surgical Company, Amersfoort, The Netherlands). Temperature was measured continuously with a rectal temperature probe (YSI Incorporated 401, vd Putte Medical, Nieuwegein, The Netherlands) and maintained at 32–34°C for 72 hrs, followed by passive rewarming to normothermia (defined as ≥36.5°C). All patients were sedated with midazolam and/or propofol and sufentanil during hypothermia. Sedation and analgetics were stopped as soon as the body temperature was ≥36.5°C. In case of shivering, patients received an intravenous bolus injection of rocuronium. All patients were intubated and mechanically ventilated aiming at an arterial oxygen saturation >95% and arterial carbon dioxide pressure between 34 mm Hg and 60 mm Hg. Blood pressure was maintained at ≥60 mm Hg and 60 mm Hg, hemoglobin concentration was kept ≥6.0 mmol/L. Hemodynamic parameters, temperature, and SaO2 were measured continuously. PaO2 and PaCO2, lactate, arterial and central venous oxygen saturation, and jugular bulb oxygenation (SjbO2) were measured every 6 hrs until 114 hrs after admission to the ICU. Mean flow velocity (MFV) in the middle cerebral artery (MCA) (MFV<sub>MCA</sub>) and the PI (pulsatility index) were measured by transcranial Doppler with a 2 MHz probe (Sonosite M-Turbo, Sonoview Nederland BV, Rijswijk, The Netherlands), according to the method developed by Aaslid et al. (14). The PI was calculated as (V<sub>mean</sub> − V<sub>Dias</sub>) / V<sub>mean</sub>. Normal PI in the MCA varies between 0.69 ± 0.10 at 55 mm and 0.71 ± 0.13 at 30 mm (15). MFV<sub>MCA</sub> and PI were measured on admission to the ICU and at 12, 24, 36, 48, 60, 72, 84, 96, and 108 hrs. The MCA was chosen for examination because this vessel perfuses approximately 80% of the cerebral hemisphere and because of its easy and reproducible accessibility for transcranial Doppler. The temporal acoustic window and Doppler depth giving the highest velocities were determined upon admission and used for all measurements. All measurements were performed by two investigators (L.B. and C.H.). Normal mean MCA velocities vary from 41 ± 7 to 94 ± 10 cm/sec (15). Although there is a wide variation in the normal range of MFV, a linear relationship between CBF and MFV<sub>MCA</sub> is present if the diameter of the insonated vessel and the angle of insonation remain constant.

Statistical Analysis. Statistical analysis was performed using GraphPad Prism version 5.0 (GraphPad Software, La Jolla, CA). Data are presented as median with 25th and 75th percentile. In the figures besides median (black lines in boxes), interquartile range 25 and interquartile range 75 (boxes), and minimum and maximum (whiskers) are depicted. Changes over time were analyzed with the repeated measures test for nonparametric data, and the Wilcoxon rank-sum test was used to compare survivors to nonsurvivors. Correlation was tested with the Spearman test (two-tailed). A p value <.05 was considered to indicate statistical significance.

RESULTS

Population. We studied ten comatose patients successfully resuscitated from an out-of-hospital cardiac arrest. Individual patient data are shown in Table 1. The primary rhythm was asystole in four patients, ventricular fibrillation in four patients and PEA in two patients. Upon admission to the emergency room, the patients showed signs of prolonged circulatory and respiratory arrest with a median pH of 7.15 (6.93–7.23), a median base excess of −13.4 (−17.1 to −8.1) mmol/L, and a median lactate concentration of 9.6 (5.3–11.8) mmol/L. Six patients died in the ICU: three patients because of circulatory failure and two patients because of severe postanoxic brain damage. One patient, admitted to the ICU after PEA, regained consciousness, but active treatment was withdrawn due to preexisting severe chronic respiratory failure.

Clinical Data. Median temperature at the start of the study was 34.3 (33.4–35.2°C) and was maintained between 32 and 34°C for 72 hrs (Fig. 1). All patients were passively rewarmed after 72 hrs from 33.7 (33.1–33.9°C) at 72 hrs to 38.0 (37.5–38.1°C) at 114 hrs after admission (p < .001). The mean arterial blood pressure at admission was 85.5 (81.0–90.0) mm Hg and was kept at a target of 80 mm Hg according to the local protocol. Upon rewarming the median mean arterial blood pressure gradually increased from 75.5 (73.0–81.0) mm Hg at 72 hrs to 90 (84.5–98.5) mm Hg at 114 hrs (p = .077). Median central venous oxygen saturation gradually increased during admission from 73.5 (70.3–77.3)% at the start of the study to 80.0 (76.5–83.5)% at 72 hrs (p = .038) and remained relatively stable until the end of the study (84.0 [82.5–84.5]%), p = .724).

Norepinephrine was used in all patients. The median dose of norepinephrine significantly increased from 0.00 (0.00–0.02) µg/kg/min to 0.20 (0.07–0.33) µg/kg/min at 72 hrs (p = .003) (Fig. 24). Rewarming resulted in a nonsignificant increased requirement of norepinephrine with a peak of 0.67 (0.16–1.13) µg/kg/min at 84 hrs, gradually decreasing to 0.13 (0.00–0.31) µg/kg/min at the end of the study (p = .727). In four patients a positive correlation between norepinephrine dose and MFV<sub>MCA</sub> was demonstrated, whereas in the remaining six patients no correlation between norepinephrine dose and MFV<sub>MCA</sub> was found.
Table 1. Demographic data and patient characteristics after cardiac arrest

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ED, emergency department; M, male; F, female; PEA, pulseless electrical activity; VF, ventricular fibrillation.

Data are expressed as median values (interquartile range) or percentage.

Dobutamine was added in seven patients. The median dose of dobutamine increased from 0.00 µg/kg/min at admission to 3.16 (0.00–4.17) µg/kg/min at the end of the hypothermia period (p = .801) and was rapidly tapered off to 0.00 µg/kg/min after rewarming (p = .067) (Fig. 2B). In six of seven patients receiving dobutamine no correlation with MFV_{MCA} was found. In one of the seven patients receiving dobutamine, the dose (negatively) correlated with the MFV_{MCA} (p = .0368). Administration of epinephrine was necessary in two patients. In one patient it was started at 6 hrs at a maximal dose of 1.67 µg/kg/min until the patient died at 60 hrs. In this time period MFV_{MCA} increased from 17.8 cm/sec to 63.6 cm/sec while SjbO₂ increased from 72% to 82%. The second patient received epinephrine from 36 hrs until 72 hrs when the patient died. At that moment the patient received a maximal dose of 0.167 µg/kg/min. MFV_{MCA} decreased from 70 cm/sec to 63.9 cm/sec, SjbO₂ increased from 78% to 80%. Both patients showed no correlation between epinephrine dose and MFV_{MCA} (data not shown).

Median PaCO₂ was 40.5 (36.7–45.0) mm Hg upon admission and did not change significantly throughout the study period (p = .980). The median PaO₂ was >75 mm Hg throughout the study.

Sedation and Anesthetics. Administered doses of midazolam and sufentanil over time are shown in Fig. 3. At 0 hrs median dose of midazolam was 5.0 (0–10.0) mg/hr and significantly increased to 20.0 (13.8–25.0) mg/hr at 72 hrs (p < .0001). Midazolam dose significantly decreased from 20.0 (13.8–25.0) to 0.5 (0–10.0) mg/hr at 144 hrs (p < .0001). In six of seven patients receiving midazolam an increase in median dose was found over time. The median dose of sufentanil increased from 0.00 (0–0.02) mg/hr at 0 hrs to 0.02 (0.00–0.05) mg/hr at 144 hrs. In six of seven patients receiving sufentanil an increase in median dose was found over time.
mg/hr at 72 hrs to 0 (0–0) mg/hr at 108 hrs (p = .02). Median sufentanil dose at 0 hrs was 2.5 (0–10.0) µg/hr and significantly increased to 15.0 (13.8–16.3) µg/hr at 72 hrs (p < .0001) and subsequently significantly decreased to 0 (0–10) µg/hr at 108 hrs (p = .01). Propofol doses were omitted from the graph because propofol was used only in a minority of patients in a low dose for only a few hours.

**DISCUSSION**

To the best of our knowledge, this study is the first study in adult patients describing the effects of 3-day hypothermia treatment on the CBF after cardiac arrest. CBF was low after cardiac arrest, and gradually increased during the 3-day cooling period toward normal values. The SjbO₂ was normal in the majority of patients throughout the study. Normal SjbO₂, together with the low MFV₉₉₉₉, strongly suggests a decreased cerebral metabolism during MTH in the first 24–48 hrs. CBF and the cerebral oxygen extraction rate did not change during rewarming to normothermia after 72 hrs.

In the first hours after cardiac arrest CBF was low. This low flow state is a typical feature of the delayed hypoperfusion phase of the post-cardiac arrest syndrome and is partly explained by an increase in cerebrovascular resistance due to a disbalance in the local production of endothelin and cyclic guanosine monophosphate (16, 17). During hypothermia, MFV₉₉₉₉ gradually increased toward normal physiological values and continued to increase until 96 hrs after admission, simultaneously with rewarming. The restoration of normal CBF is congruent with the fourth phase of the post-cardiac arrest syndrome, starting at approximately 20 hrs after ROSC in which normal blood flow is restored, remains low, or is hyperemic (18). Cardiac output can change CBF, independently of changes in mean arterial blood pressure (19). Postresuscitation myocardial dysfunction results in low cardiac output in the first hours after ROSC (20). Recovery of myocardial function, together with progressive vasoplegia, gradually increases cardiac output in the course of days. The initial low cardiac output, reflected by low central venous oxygen saturation in our patients, may to some extent contribute to the relatively low MFV₉₉₉₉ in the first hours of the study.

The results from this study indicate that temperature by itself is not a major determinant in restoration of CBF towards normal values. When comparing our data with those from normothermic cardiac arrest survivors, MTH seemed to delay the restoration of CBF towards normal values, possibly by decreasing the metabolic demand of the brain (16). The prolonged treatment with hypothermia may have further decelerated the restoration of the MFV₉₉₉₉ to normal values, since MFV₉₉₉₉ at 24 and 48 hrs after admission in the present cohort was lower compared to our previous study in patients that

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**Figure 2.** A. Pulsatility index (PI), mean flow velocity of the middle cerebral artery (MFV₉₉₉₉), and norepinephrine dose changes over time. Values (median [black lines in boxes], interquartile range 25 and interquartile range 75 [boxes], and minimum and maximum [whiskers]) are depicted for PI (white bars), MFV₉₉₉₉ (light gray bars), and norepinephrine dose (dark gray bars). #, significant difference MFV₉₉₉₉ (p = .002); *, significant difference norepinephrine dose (p = .003). B, PI, MFV₉₉₉₉, and dobutamine dose changes over time. Values (median [black lines in boxes], interquartile range 25 and interquartile range 75 [boxes], and minimum and maximum [whiskers]) are depicted for PI (white bars), MFV₉₉₉₉ (light gray bars), and dobutamine dose (dark gray bars). #, significant difference MFV₉₉₉₉ (p = .002); *, significant difference dobutamine dose (p = .067).
were treated with hypothermia for 24 hrs (12). The relatively low MFV<sub>MCA</sub> in combination with (generally) normal SjbO<sub>2</sub> values suggests a reduction in cerebral metabolic activity that may contribute to the neuroprotective effect of (prolonged) MTH in the delayed hypoperfusion phase. Although a reduction in brain metabolism is the most likely explanation for the normal SjbO<sub>2</sub> values, mitochondrial dysfunction, arteriovenous shunting, or impaired tissue oxygen delivery through maldistribution of capillary flow may also contribute to the relatively high SjbO<sub>2</sub> values (21).

SjbO<sub>2</sub> was low at the start of the study, and gradually increased to reach a plateau after 24–30 hrs. Although in four patients the ischemic threshold (SjbO<sub>2</sub> < 55%) was exceeded at the start of the study, the SjbO<sub>2</sub> generally was normal during the first phase of MTH. In combination with the relatively low MFV<sub>MCA</sub> this finding strongly suggests a decrease in cerebral metabolism in these patients. The SjbO<sub>2</sub> reached a plateau after 24–30 hrs after admission, indicating a relatively low cerebral oxygen extraction, while CBF was still increasing. PET studies that measured cerebral metabolic activity in normothermic patients after cardiac arrest indicated that metabolic activity is decreased after cardiac arrest, most markedly in the gray matter and to a lesser extent in the white matter (22, 23). This metabolic decrease is most profound in the cerebral cortex and basal ganglia and less in the pons and cerebellum. Several pathophysiological mechanisms may underlie this relative decrease in cerebral oxygen extraction. First, cerebral metabolic coupling may be (temporarily) lost during hypothermia and subsequent rewarming, resulting in a steeper increase in flow velocities compared to cerebral oxygen extraction. This loss of metabolic coupling would increase the risk of hyperemia with subsequent brain edema and elevated intracranial pressure, contributing to secondary brain damage. Secondly, cerebral metabolism may not recover immediately after ROSC. This disturbed cerebral metabolism may be related to the mitochondrial dysfunction that is observed after global brain ischemia (1). The mitochondrial damage is the result of intracellular calcium accumulation and results in transient swelling, disappearance of polyribosomes, and abnormal Golgi complexes. Plasma from patients after cardiac arrest can induce major endothelial cell toxicity with an impairment of the mitochondrial chain activity (complexes II, III, and IV) in endothelial cell cultures (24). We speculate that as a result of mitochondrial dysfunction, oxygen uptake by the brain may be diminished after cardiac arrest, resulting in relatively high SjbO<sub>2</sub> values. Alternatively, the amount of ischemic brain tissue may increase over time, reducing the capacity of the brain to extract oxygen. As no differences in SjbO<sub>2</sub> and MFV<sub>MCA</sub> values and patterns were found between survivors and nonsurvivors this seems highly unlikely.

This study has a number of limitations. We performed an observational study in a limited cohort of patients after cardiac arrest. Because MTH is an essential part of standard care, a normothermic control group was considered unethical. The results of this study may be biased in several ways. We used transcranial Doppler as a measure of CBF because this is the most widely used noninvasive and bedside technique; it is, however, a measure of CBF velocity and may be inaccurate as the diameter of the median cerebral artery changes. Treatment with MTH requires adequate levels of sedation and analgesia. Sedation is well-known to reduce the metabolic demands of the brain and to decrease CBF. However, MFV<sub>MCA</sub> increased during constant hypothermia while sedation increased in the first 12 hrs and remained unchanged until a temperature of 36.5°C was reached. No significant changes in MFV<sub>MCA</sub> or SjbO<sub>2</sub> occurred after cessation of sedation. This strongly suggests a minor role for sedation in influencing the CBF during MTH. All patients required norepinephrine infusion to ensure adequate cerebral perfusion pressures. The effects of norepinephrine on CBF in patients after cardiac arrest are unknown and probably depend on the metabolic activity of the brain, the integrity of the blood-brain barrier, and the level of autoregulation (25). Cerebral autoregulation is either absent or shifted to the right in the majority of patients in the acute phase after cardiac arrest (26). The effects of hypothermia on autoregulation in patients after cardiac arrest are unknown. Studies in patients after traumatic brain injury suggest that hypothermia and subsequent rewarming do not change cerebrovascular reactivity, unless the body temperature exceeds 37°C (27).

CONCLUSIONS

Temperature by itself is probably not a major determinant in regulation of CBF after cardiac arrest. The relatively low MFV<sub>MCA</sub>, in combination with normal SjbO<sub>2</sub> values suggests a reduction in cerebral metabolic activity that may contribute to the neuroprotective effect of (prolonged) MTH in the delayed hypoperfusion phase. A randomized controlled trial is necessary to evaluate the optimal duration of cooling in patients after cardiac arrest.

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