

Cerebral Oxygen Extraction and Autoregulation during Extracorporeal Whole Body Hyperthermia in Humans

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Background: **The effects of hyperthermia on the human brain are incompletely understood. This study assessed the effects of whole body hyperthermia on cerebral oxygen extraction and autoregulation in humans.**

Methods: **Nineteen patients with chronic hepatitis C virus infection, not responding to interferon treatment, were subjected to experimental therapy with extracorporeal whole body hyperthermia at 41.8°C for 120 min under propofol anesthesia (23 sessions total). During treatment series A (13 sessions), end-tidal carbon dioxide was allowed to increase during heating. During series B (10 sessions), end-tidal carbon dioxide was maintained approximately constant. Cerebral oxygen extraction (arterial to jugular venous difference of oxygen content) and middle cerebral artery blood flow velocity were continuously measured. Cerebral pressure–flow autoregulation was assessed by static tests using phenylephrine infusion and by assessing the transient hyperemic response to carotid compression and release.**

Results: **For treatment series A, cerebral oxygen extraction decreased 2.2-fold and cerebral blood flow velocity increased 2.0-fold during heating. For series B, oxygen extraction decreased 1.6-fold and flow velocity increased 1.5-fold. Jugular venous oxygen saturation and lactate measurements did not indicate cerebral ischemia at any temperature. Static autoregulation test results indicated loss of cerebrovascular reactivity during hyperthermia for both series A and series B. The transient hyperemic response ratio did not decrease until the temperature reached approximately 40°C. Per degree Celsius temperature increase, the transient hyperemic response ratio decreased 0.07 (95% confidence interval, 0.05–0.09; $P = 0.000$). This association remained after adjustment for variations in arterial partial pressure of carbon dioxide, mean arterial pressure, and propofol blood concentration.**

Conclusion: **Profound hyperthermia during propofol anesthesia is associated with decreased cerebral oxygen extraction, increased cerebral blood flow velocity, and impaired pressure–flow autoregulation, indicating transient partial vasoparalysis.**

WHOLE body hyperthermia has been used since the mid-1960s for the treatment of malignant illnesses, with variable therapeutic effects. Recently, it has also been explored for use in infectious diseases.[1–3] Whole body hyperthermia has been induced clinically with warm contact media (such as water, water-heated suits or mats, hot air), infrared radiation, or extracorporeal methods.[4–8] Recently, a venovenous extracorporeal method of whole body heating was developed that allows homogenous distribution of heat and precise control of temperature gradients.[9,10] Although a number of studies report that whole body hyperthermia is a safe procedure,[4–7] there is still concern about possible neurologic sequelae of cerebral hyperthermia. In heat stroke, loss of thermoregulatory capacity is associated with a disturbed level of consciousness, brain edema, and a high mortality if the temperature exceeds 40°C.[11] However, during therapeutic whole body hyperthermia, central temperatures of 41.8°C are intentionally applied. In this setting, the development of brain edema, intracerebral hemorrhage, intracranial hypertension, and transient central nervous system dysfunction have been reported.[3,7,12–14] Despite these observations, the cerebral pathophysiologic effects of temperature increase have poorly been studied in humans.

In animals, hyperthermia induces various toxic cerebral responses,[15,16] and resting cerebral oxygen and glucose consumption seem to increase, although the magnitude of these metabolic alterations show considerable regional heterogeneity.[17–20] A cerebral blood flow increase has frequently been observed in this setting and is generally believed to be related to increased metabolic demand.[20–22] However, few published studies have formally assessed cerebral metabolic coupling or autoregulation during hyperthermia in both humans and animals, and the results are conflicting.[21,23,24] This issue may be of clinical importance because when metabolism increases and cerebral vasomotor responses become impaired during hyperthermia, it could imply that fever temporarily predisposes patients to neurologic injury if wide perturbations of blood pressure should occur.

The current study aimed to determine the effects of varying temperatures (in a range of approximately 36.6°–41.8°C) on cerebral oxygen extraction and pressure–flow autoregulation. For this, we studied patients with chronic hepatitis C virus infection who were subjected to experimental treatment with whole body hyperthermia, using an extracorporeal heating circuit.

Materials and Methods

Patients

This study was approved by the ethics committee of the University Medical Center Utrecht, The Netherlands,

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and written informed consent was obtained. Patients were enrolled in the current protocol ancillary to a pilot study investigating the efficacy and safety of extracorporeal whole body hyperthermia (EWBH) for the treatment of chronic hepatitis C virus infection. This pilot study was designed after encouraging hepatitis C viral load–related observations during the experimental use of systemic hyperthermia for treatment of human immunodeficiency virus infection.[1–3] Patients aged 18–65 yr with chronic hepatitis C virus infection, genotype 1, were eligible for study inclusion. All patients had failed to show a sustained response to interferon alfa therapy and were required to have Child-Pugh classification A (no or minimal cirrhosis).[25] Patients were screened for central nervous system abnormalities, cardiac disease, pulmonary disease, and other major liver or renal disease. Patients were ineligible if abnormalities were present. A history of substance abuse was not an exclusion criterion.

Thirteen patients were treated between August 2001 and April 2002 with a single session of EWBH (series A). Six additional patients and four patients from the first series were (re)treated between December 2002 and February 2003 (series B). Treatment again consisted of a single session of EWBH but was now followed after 6 weeks by the initiation of 12 months of antiviral therapy with interferon alfa and ribavirin.

EWBH Procedure and Anesthesia Management

All EWBH treatments were performed by the same team of anesthesiologists and perfusionists throughout the study period. General anesthesia was induced with propofol–fentanyl–rocuronium and was maintained using a target-controlled propofol infusion pump (Diprifusor; Astra-Zeneca, Ridderkerk, The Netherlands). The trachea was intubated, and the lungs were ventilated with oxygen in air. During a session of EWBH, core temperature was increased in approximately 90 min to a target of 41.8° ± 0.15°C under general anesthesia, using an extracorporeal heater–cooler device with a bifemoral venovenous circuit (TEMET System 1000; First Circle Medical, Minneapolis, MN). Before the start of the extracorporeal bypass, patients were heparinized. After 120 ± 10 min of hyperthermic plateau, patients were cooled to 39°C before the bypass was discontinued. After the procedure, patients were transported to the intensive care unit. Propofol sedation was continued until planned extubation 2–4 h later.

Anesthetic management differed with respect to two important aspects in patients treated during EWBH series A and B. First, during treatment series A, patients were ventilated in a volume-controlled manner to maintain normocapnia at a target end-tidal carbon dioxide of approximately 4.0% during normothermia, and the ventilator settings subsequently remained unchanged throughout the procedure. This resulted in a high end-tidal carbon dioxide but a normocapnic uncorrected arterial partial pressure of carbon dioxide ($Paco_2$), measured at 37°C, during hyperthermia (alpha-stat principle). During treatment series B, patients were also normocapnic during normothermia, but as body temperature was increased, the minute volume of ventilation was gradually increased to maintain an approximately normal end-tidal carbon dioxide, resulting in a hypocapnic uncorrected $Paco_2$ during hyperthermia (pH-stat principle).[26] Second, during EWBH treatment series A, changes in the propofol infusion target were made at the discretion of the attending anesthesiologist. During treatment series B, a routine gradual increase of the propofol infusion target by 1.5 mg/l during warming was implemented in the anesthesia protocol. This routine adjustment of the infusion rate was deemed necessary because blood concentrations of propofol decreased as temperature was increased.

Monitoring

Invasive monitoring of systemic and pulmonary hemodynamics was used. Temperature monitoring sites included the pulmonary artery, the nasopharynx, the esophagus, and the rectum. In addition, a right retrograde jugular bulb catheter (5.5-French Opticath Oximetrix; Abbott Critical Care Systems, Chicago, IL) was used to measure jugular venous temperature, pressure, oxyhemoglobin saturation, and lactate. An arterial to jugular venous difference of lactate less than −0.37 mM was considered abnormal.[27] The position of the catheter tip was verified by a lateral skull x-ray. The blood flow velocity in the middle cerebral artery was measured using transcranial pulsed Doppler ultrasonography (2-MHz probe, Multi-Dop T; DWL, Sipplingen/Bodensee, Germany). The position of the ultrasound transducers was fixed using a metal head frame (series A) or a special headband (series B). Mean peak flow velocities from both hemispheres were averaged. Data were stored at 0.1 Hz and at 250 Hz for off-line analysis using POLY Physiologic Analysis Package (Inspektor Research Systems, Amsterdam, The Netherlands). Laboratory parameters were measured at normothermic baseline, at fixed intervals during warming, and at hyperthermic plateau.

Autoregulation Testing

Static autoregulation tests were performed during normothermic flow over the extracorporeal bypass circuit (T1) and during hyperthermic plateau (T2), using a ramped phenylephrine infusion. The static rate of autoregulation was calculated as the ratio of the percent change in cerebrovascular resistance by the percent change in mean arterial pressure, with cerebrovascular resistance estimated as the ratio of mean arterial pressure by cerebral blood flow velocity (CBFV).[28–30] A static rate of autoregulation of 1 indicates perfect adaptation of cerebral resistance vessels to changes in mean

Table 1. Anesthetic Management–related Parameters during Extracorporeal Whole Body Hyperthermia

	Series A (n = 13)			Series B (n = 10)			Series A *vs.* B
	T1	T2	*P* Value	T1	T2	*P* Value	*P* Value
End-tidal CO_2, %	4.1 ± 0.3	5.8 ± 0.5	0.000	4.1 ± 0.4	4.7 ± 0.3	0.020	0.000
Arterial partial pressure of CO_2, mmHg*	38 ± 4	43 ± 6	0.002	39 ± 4	34 ± 4	0.007	0.000
Propofol infusion target, mg/l	4.3 ± 0.7	4.8 ± 0.9	0.040	4.1 ± 0.4	5.5 ± 0.5	0.000	0.006
Propofol blood concentration, mg/l	3.4 ± 1.1	2.8 ± 0.5	0.076	4.7 ± 1.1	4.6 ± 1.0	0.867	0.360
Phenylephrine infusion rate, $ng \cdot kg^{-1} \cdot min^{-1}$	25 ± 37	438 ± 492	0.089	6 ± 16	426 ± 291	0.005	0.975

Values are presented as mean ± SD.

* Arterial partial pressure of carbon dioxide (CO_2) was measured at 37°C (*i.e.,* uncorrected to actual temperature).

T1 = baseline (*i.e.,* normothermic flow over the extracorporeal bypass circuit); T2 = hyperthermic plateau.

arterial pressure, whereas a value close to 0 indicates complete absence of cerebrovascular reactivity. In addition to these formal tests of static pressure–flow autoregulation, transient hyperemic response tests were performed at fixed stages during the EWBH procedure. Transient hyperemic response testing involves measurement of changes in middle cerebral artery flow velocity during and after the release of a 10-s compression of the ipsilateral common carotid artery. If cerebral autoregulation is intact, the decrease in perfusion pressure in the middle cerebral artery at the onset of compression triggers vasodilatation in the distal vascular bed, resulting in a transient increase in the flow velocity after the release of compression. The transient hyperemic response ratio (THRR) was calculated as the ratio of the mean peak flow velocity of the Doppler waveform immediately after the release of compression by that of the waveform immediately preceding the compression. A THRR value close to 1 indicates absence of a vascular response, whereas higher values indicate increasing levels of vasoreactivity. The THRR reflects changes in the static rate of autoregulation and provides a valid measure for assessing graded impairments of cerebral pressure–flow autoregulation.[30,31]

Statistical Analysis

Systemic and cerebral physiologic parameters recorded during normothermia and hyperthermia were compared using paired-samples *t* tests. In addition, changes in these parameters from T1 to T2 were tested for differences between treatment series A and B using independent-samples *t* tests. With respect to cerebrovascular reactivity testing, the THRR was considered the primary measure of pressure–flow autoregulation in this study because transient hyperemic response tests could be repeatedly performed during various stages of the EWBH procedure. Therefore, the THRR was expected to give a more precise estimate of cerebral vasomotor responses than the static rate of autoregulation. Because changes in $Paco_2$, mean arterial pressure, and propofol blood concentration during EWBH treatment might confound the relation between temperature and pressure–flow autoregulation,[29,31] a mixed-effects regression analysis was used to model possible confounding by these parameters, taking into account the nesting of repeated observations within an individual. To allow for differences in vasoreactivity between individual subjects, an intercept was included in the model as a random effect. The crude and adjusted effect estimates of the associa-

Table 2. Systemic Physiologic Parameters during Extracorporeal Whole Body Hyperthermia

	Series A (n = 13)			Series B (n = 10)			Series A *vs.* B
	T1	T2	*P* Value	T1	T2	*P* Value	*P* Value
Pulmonary artery blood temperature, °C	36.5 ± 0.7	41.8 ± 0.2	0.000	36.4 ± 0.4	41.8 ± 0.1	0.000	0.651
Heart rate, beats/min	69 ± 10	115 ± 11	0.000	72 ± 16	113 ± 14	0.000	0.188
Mean arterial pressure, mmHg	78 ± 11	69 ± 9	0.001	74 ± 9	70 ± 7	0.073	0.085
Central venous pressure, mmHg	8 ± 3	10 ± 3	0.058	10 ± 4	10 ± 3	0.916	0.355
Pulmonary artery wedge pressure, mmHg	9 ± 5	11 ± 4	0.227	11 ± 3	11 ± 3	0.951	0.420
Cardiac output, l/min	6.8 ± 1.6	13.2 ± 2.2	0.000	6.7 ± 1.6	11.1 ± 3.0	0.001	0.073
Systemic vascular resistance, $dyn \cdot cm \cdot sec^{-5}$	821 ± 242	305 ± 71	0.000	803 ± 253	446 ± 200	0.001	0.131
Arterial oxygen saturation, %	99 ± 1	97 ± 2	0.000	99 ± 1	97 ± 2	0.001	0.458
Hemoglobin, mM*	7.2 ± 1.0	6.9 ± 0.8	0.025	6.9 ± 1.0	7.0 ± 1.1	0.569	0.060
$AVDo_2$, mM	1.2 ± 0.3	0.9 ± 0.2	0.003	1.2 ± 0.2	0.9 ± 0.3	0.004	0.794
$\dot{V}o_2$, $ml \cdot min^{-1} \cdot m^{-2}$	97 ± 24	143 ± 34	0.000	100 ± 24	123 ± 28	0.036	0.110

Values are presented as mean ± SD.

* Hemoglobin was measured after acute hemodilution because of institution of the bypass circuit.

$AVDo_2$ = arterial to mixed venous difference of oxygen content; T1 = baseline (*i.e.,* normothermic flow over the extracorporeal bypass circuit); T2 = hyperthermic plateau; $\dot{V}o_2$ = oxygen consumption, calculated as cardiac output times $AVDo_2$, divided by body surface area.

Table 3. Cerebral Physiologic Parameters during Extracorporeal Whole Body Hyperthermia

	Series A (n = 13)			Series B (n = 10)			Series A *vs.* B
	T1	T2	*P* Value	T1	T2	*P* Value	*P* Value
Jugular bulb blood temperature, °C	36.7 ± 0.6	41.9 ± 0.1	0.000	36.6 ± 0.4	41.8 ± 0.1	0.000	0.647
Jugular bulb venous pressure, mmHg	11 ± 3	14 ± 3	0.000	13 ± 2	15 ± 3	0.018	0.052
Cerebral blood flow velocity, cm/s	28 ± 4	56 ± 9	0.000	26 ± 7	38 ± 11	0.001	0.000
$AjVDo_2$, mM	2.9 ± 0.6	1.3 ± 0.3	0.000	2.4 ± 0.8	1.5 ± 0.7	0.000	0.024
AjVDL, mM	0.07 ± 0.57	−0.07 ± 0.26	0.506	0.05 ± 0.27	−0.24 ± 0.36	0.054	0.560

Values are presented as mean ± SD.

AjVDL = arterial to jugular venous difference of lactate; $AjVDo_2$ = arterial to jugular venous difference of oxygen content; T1 = baseline (*i.e.,* normothermic flow over the extracorporeal bypass circuit); T2 = hyperthermic plateau.

tion of temperature with the THRR are presented with 95% confidence intervals. Data in the text are presented as mean ± SD.

Results

Thirteen sessions of EWBH treatment were performed during series A, and 10 sessions were performed during series B, in a total of 19 patients (age 44 ± 9 yr, 14 [74%] male). Table 1 shows various anesthetic management–related parameters at T1 (normothermia) and T2 (hyperthermia). End-tidal carbon dioxide and uncorrected $Paco_2$ values show the effect of the changes in ventilation management that were introduced between treatment series A and B. Likewise, the differences in propofol infusion targets show the effect of protocol changes between series A and B. The calculated target blood concentration of propofol grossly overestimated the true blood concentration at T2.

Table 2 shows systemic parameters. During hyperthermia, systemic vascular resistance decreased considerably, despite the use of increased infusion rates of phenylephrine. As a consequence, cardiac output and heart rate increased, and mean arterial pressure decreased. Simultaneously, systemic oxygen consumption increased by 47% and 23% for treatment series A and B, respectively. The hemodynamic and metabolic changes were more outspoken during treatment series A (high–carbon dioxide group) than during series B (low–carbon dioxide group), although these differences did not reach statistical significance.

Table 3 shows cerebral parameters. For series A, cerebral oxygen extraction (arterial to jugular venous difference of oxygen content) decreased 2.2-fold, compared with a simultaneous 2.0-fold increase in CBFV. For series B, cerebral oxygen extraction decreased 1.6-fold, and CBFV increased 1.5-fold. For all 23 treatment sessions of series A and B combined, jugular venous oxygen saturations below 50% were observed in two instances at T1 and never at T2. Signs of cerebral lactate production (arterial to jugular venous difference of lactate < -0.37 mM) were observed in three instances at T1 and in five instances at T2. The simultaneous occurrence of jugular venous oxygen desaturation and abnormally low arterial to jugular venous difference of lactate was not observed. Figure 1 shows the cerebral and systemic arterial to venous oxygen extraction at different temperatures during the EWBH procedures. For both treatment series A and B, the systemic oxygen extraction decreased linearly with increasing temperature. In contrast, cerebral oxygen extraction decreased in a nonlinear manner, with the greatest decrease occurring at temperatures above approximately 40°C.

Table 4 shows measures of cerebrovascular reactivity.

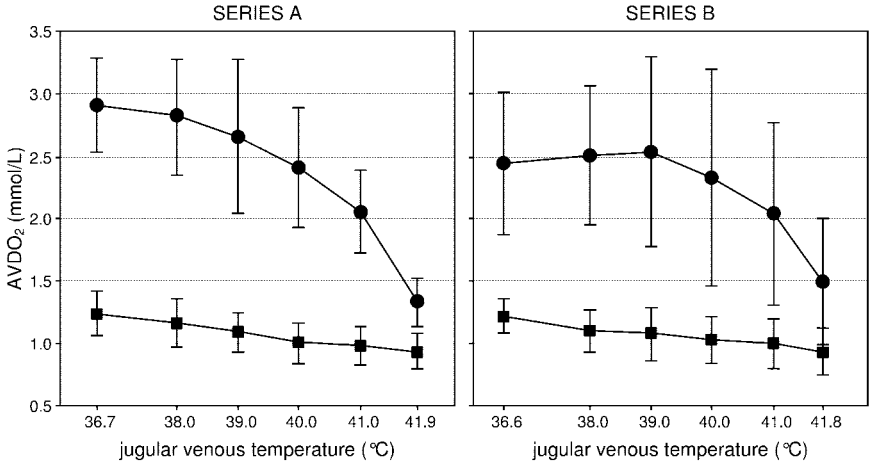

Fig. 1. Cerebral and systemic oxygen extraction during extracorporeal whole body hyperthermia. *Closed circles* = arterial to jugular venous difference of oxygen content; *squares* = arterial to mixed venous difference of oxygen content ($AVDo_2$). Values are presented as mean ± 95% confidence interval.

Table 4. Cerebral Vasomotor Responses during Extracorporeal Whole Body Hyperthermia

	Series A			Series B			Series A *vs.* B
	T1	T2	*P* Value	T1	T2	*P* Value	*P* Value
Static rate of autoregulation*	0.60 ± 0.15	0.12 ± 0.24	0.001	0.85 ± 0.24	0.25 ± 0.35	0.001	0.429
Transient hyperemic response ratio†	1.5 ± 0.2	1.2 ± 0.2	0.004	1.9 ± 0.2	1.3 ± 0.1	0.001	0.019

Values are presented as mean ± SD.

* n = 8 and n = 9 for series A and B, respectively. † n = 7 and n = 7 for series A and B, respectively.

T1 = baseline (*i.e.,* normothermic flow over the extracorporeal bypass circuit); T2 = hyperthermic plateau.

Cerebral pressure–flow autoregulation was assessed by 37 static autoregulation tests during 17 EWBH procedures and by 220 transient hyperemic response tests during 14 procedures. The static rate of autoregulation and the THRR significantly decreased from T1 to T2 in both series A and B. Figure 2 shows the THRR at fixed temperatures during the EWBH procedures (series A and B combined). The THRR did not decrease until the jugular venous blood temperature reached approximately 40°C. Subsequently, the crude mixed-effects regression model (table 5) showed a decrease in the THRR of 0.07 (95% confidence interval, 0.05–0.09) per degree temperature increase ($P = 0.000$). After adjustment of the crude association for variations in $Paco_2$, mean arterial pressure, and propofol blood concentration during the EWBH procedure, the association remained ($P = 0.000$).

Discussion

Experimental treatment using EWBH in patients with chronic hepatitis C virus infection under propofol anesthesia resulted in a decreased cerebral oxygen extraction that was accompanied by an increase in CBFV of a similar magnitude. These effects were more pronounced when end-tidal carbon dioxide was allowed to increase during warming (series A), compared with when end-tidal carbon dioxide was more rigidly maintained (series B). Second, heating resulted in impaired cerebrovascular responses to both a vasoconstrictor stimulus (static autoregulation testing) and a vasodilator stimulus (transient hyperemic response testing), indicating impaired pressure–flow autoregulation. This effect remained after adjustment for changes in $Paco_2$, mean arterial pressure, and propofol blood concentration. Together with systemic findings, these data indicate that a transient partial vasoparalysis develops during profound hyperthermia.

There are several methodologic issues that must be discussed. First, we measured arterial to jugular venous difference of oxygen content and found an apparent decrease in cerebral oxygen extraction. However, this could be a spurious finding if cerebrovenous blood would be grossly contaminated with extracerebral venous blood, known to have a higher oxygen saturation, during hyperthermia. In the current study, of 164 fiberoptic jugular venous oxygen saturation readings, 106 were verified by cooximetry using a laboratory-based blood gas analyzer. Cooximetry values were on average 3.5 ± 7.4% higher than fiberoptic values, and these differences were independent of temperature. These slightly higher values may indeed be explained by admixture of extracerebral blood when a sample is actively drawn from the jugular bulb catheter.[32] Because this effect was still apparent and independent of temperature, we consider it unlikely that gross contamination occurred during hyperthermia. Second, the reduction of cerebral oxygen extraction was accompanied by an increase in CBFV by a factor of almost equal magnitude. One interpretation of these observations is that cerebral oxygen consumption did not change appreciably during hyperthermia. However, the increase in peak flow velocity may have underestimated the true increase in erythrocyte flux during hyperthermia. This could have occurred if the insonated segment of the middle cerebral artery had increased in diameter over time. Studies that have specifically looked at the cross-sectional area of the

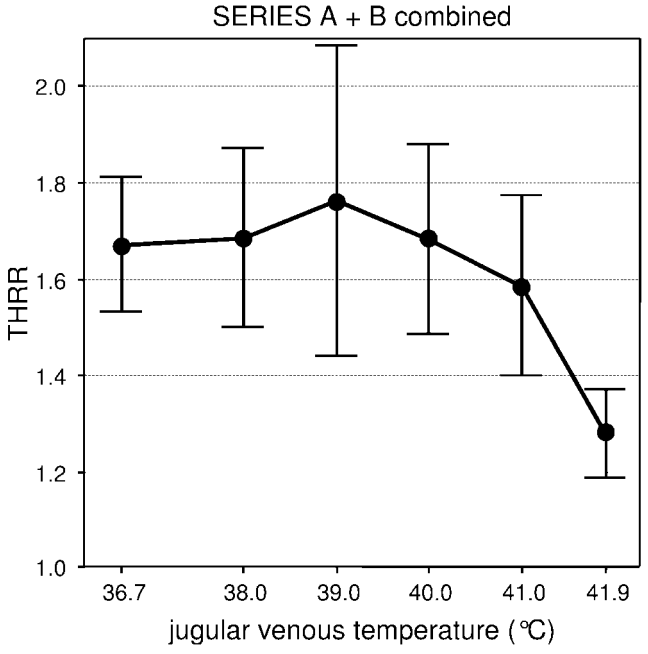

Fig. 2. Transient hyperemic response ratio (THRR) during extracorporeal whole body hyperthermia. Values are presented as mean ± 95% confidence interval.

Table 5. Mixed-effects Regression Models for 220 Transient Hyperemic Response Tests in 14 Patients

Model	Estimate ± SE	95% CI	*P* Value
Crude model for THRR			
Temperature, per °C	−0.07 ± 0.01	−0.09 to −0.05	0.000
Intercept (random effect)	4.51 ± 0.40	3.73 to 5.30	0.000
Random-effect variance	0.03 ± 0.02		0.013
Residual variance	0.08 ± 0.01		0.000
Adjusted model for THRR			
Temperature, per °C	−0.08 ± 0.01	−0.10 to −0.05	0.000
Uncorrected $Paco_2$, per mmHg	−0.01 ± 0.01	−0.02 to 0.00	0.085
Mean arterial pressure, per 10 mmHg	0.05 ± 0.03	−0.01 to 0.11	0.060
Propofol blood concentration, per mg/l	−0.03 ± 0.03	−0.09 to 0.03	0.299
Intercept (random effect)	4.69 ± 0.70	3.32 to 6.06	0.000
Random-effect variance	0.03 ± 0.02		0.013
Residual variance	0.08 ± 0.01		0.000

$Paco_2$ = arterial partial pressure of carbon dioxide;
CI = confidence interval; THRR = transient hyperemic response ratio.

middle cerebral artery have concluded that the diameter of this large vessel is grossly unaffected by changes in temperature, $Paco_2$, and blood pressure.[33–37] Also, changes in hematocrit and blood viscosity in theory may confound the relation between peak flow velocity and erythrocyte flux. An *in vitro* study examining the effect of varying temperature (in a range of 19°–37°C) and hematocrit (in a range of 0.05–0.54) showed that the linear relation between flow and velocity was not affected.[38] Another study in anesthetized patients reported on the effect of a sudden decrease in hematocrit from 0.38 to 0.30 and concluded that CBFV well reflects true cerebral blood flow changes after hemodilution.[39] In the current study, the effect of hemodilution by the circuit priming had stabilized before the first (normothermic) measurements. Nonetheless, we cannot rule out that small increases in middle cerebral artery diameter occurred during either EWBH series A or EWBH series B, which would result in a significant underestimation of true erythrocyte flux.

The current data indicate that the cerebrovascular bed during hyperthermia is still responsive to a dilatory stimulus, such as a brief carotid compression, at temperatures up to approximately 40°C (fig. 2). At higher temperatures, however, we found that cerebral pressure–flow autoregulation becomes progressively impaired. There are few studies assessing cerebral vasomotor responses during whole body hyperthermia, and the ones that are available have shown conflicting results. A study in dogs concluded that the main cerebral autoregulation system is paralyzed during whole body hyperthermia at 41.5°C.[21] Similarly, a recent study in humans has shown an increased pressure–flow dependency during an inflow of hyperthermic blood into the brain during rewarming from hypothermic cardiopulmonary bypass.[24] These reports of hyperthermia-induced cerebral vasoparalysis contrast with an animal experiment that indicated that the dilated cerebrovascular bed during hyperthermia is still responsive to indomethacin as a constrictor stimulus.[20] This finding, as well as the results of the current study, suggests that hyperthermia-induced vasoparalysis is partial rather than complete. Furthermore, the association between temperature and loss of cerebrovascular reactivity may be nonlinear, as suggested by figure 2 and by a report of improved dynamic autoregulation during a 0.4°C temperature increase in awake human volunteers submersed in hyperthermic baths.[23] The results of the adjusted mixed-effects regression analysis suggest that the THRR becomes also increasingly depressed as $Paco_2$ increases, mean arterial pressure decreases, and propofol blood concentration increases, although none of these effects reached statistical significance (table 5). The current findings may have clinical implications, as transient cerebral vasoparalysis during periods of induced hyperthermia or fever could potentially predispose to neurologic injury. Although the blood–brain barrier is most likely grossly preserved at temperatures below 42–43°C,[21,22] it has been suggested that brain edema may occur easily when arterial blood pressure fluctuates excessively and cerebral autoregulation is absent.

In conclusion, whole body hyperthermia is associated with decreased cerebral oxygen extraction and increased cerebral blood flow velocities in patients under propofol anesthesia. These findings are more marked when end-tidal carbon dioxide is allowed to increase compared with when it is more rigidly controlled. In addition, hyperthermia is associated with impaired cerebrovascular responses to both blood pressure increase and carotid occlusion, indicating that transient partial cerebral vasoparalysis develops when temperature exceeds approximately 40°C.

Special Note: The research presented in this article was performed as an ancillary protocol to pilot trials on the safety and efficacy of extracorporeal whole body hyperthermia for treatment of chronic hepatitis C virus infection. This project has been halted by the Utrecht

University Medical Center after an internal investigation concluded that the principal investigator of the therapeutic trials had failed to report serious side effects, in particular peripheral neuropathy, to the hospital's medical ethics committee and that funds had not been properly declared from personal agreements with the commercial study sponsor. The authors related to this manuscript have not been implicated with respect to these issues.

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