ORIGINAL ARTICLE

Inflammation, edema and poor outcome are associated with hyperthermia in hypertensive intracerebral hemorrhages

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Keywords:
edema, hematoma, hyperthermia, intracerebral hemorrhage

Received 26 October 2017
Accepted 3 May 2018

European Journal of Neurology 2018, **25:** 1161–1168

doi:10.1111/ene.13677

Background and purpose: The deleterious effect of hyperthermia on intracerebral hemorrhage (ICH) has been studied. However, the results are not conclusive and new studies are needed to elucidate clinical factors that influence the poor outcome. The aim of this study was to identify the clinical factors (including ICH etiology) that influence the poor outcome associated with hyperthermia and ICH. We also tried to identify potential mechanisms involved in hyperthermia during ICH.

Methods: We conducted a retrospective study enrolling patients with non-traumatic ICH from a prospective registry. We used logistic regression models to analyze the influence of hyperthermia in relation to different inflammatory and endothelial dysfunction markers, hematoma growth and edema volume in hypertensive and non-hypertensive patients with ICH.

Results: We included 887 patients with ICH (433 hypertensive, 50 amyloid, 117 by anticoagulants and 287 with other causes). Patients with hypertensive ICH showed the highest body temperature (37.5 ± 0.8°C) as well as the maximum increase in temperature (0.9 ± 0.1°C) within the first 24 h. Patients with ICH of hypertensive etiologic origin, who presented hyperthermia, showed a 5.3-fold higher risk of a poor outcome at 3 months. We found a positive relationship ($r = 0.717$, $P < 0.0001$) between edema volume and hyperthermia during the first 24 h but only in patients with ICH of hypertensive etiologic origin. This relationship seems to be mediated by inflammatory markers.

Conclusion: Our data suggest that hyperthermia, together with inflammation and edema, is associated with poor outcome only in ICH of hypertensive etiology.

Introduction

Non-traumatic intracerebral hemorrhage (ICH) accounts for about 15% of all strokes and is one of the most devastating strokes with poor outcome [1]. Therapeutic strategies aimed at minimizing brain injury following ICH are mainly supportive, including airway protection, hemodynamic stabilization and control of intracranial pressure [2]. Hyperthermia has deleterious effects in all types of brain injuries, including ICH. In particular, hyperthermia occurs in up to 30–40% of patients with ICH and is associated with the highest morbidity and mortality rates [3–13]. However, results are not conclusive and there is still a clinical need for new studies and strategies to clarify the temperature-generating effects [13–15]. Understanding the mechanisms by which hyperthermia affects the progression of the lesions may lead to advances in the treatment and care of patients with ICH [16–18]. Previous studies suggested that aspects such as increased intracranial pressure, reduced cerebral blood flow, increase in pro-inflammatory cytokines and axonal death could be involved in the main deleterious consequences of hyperthermia [6,15].

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Primary ICHs include a spectrum of different etiopathogenetic mechanisms and the factors that determine evolution and prognosis are presumably not similar in all of them. Therefore, the application of common therapeutic strategies for every subtype of ICH may affect the different neurological outcomes of these patients [1,16,19]. The objectives of the present study were to: (i) identify the influence of temperature on the clinical evolution of patients with ICH regarding the etiology of bleeding and (ii) evaluate the mechanisms involved in hyperthermia during ICH.

Materials and methods

Study design

From a prospective registry, we conducted a retrospective study enrolling previously functionally independent patients (modified Rankin Scale score of <1) with a spontaneous non-traumatic ICH ($n = 887$), confirmed by neuroimaging, at <24 h from clinical onset. Patients with ICH were admitted to the Neurology Department of the Hospital Clínico Universitario de Santiago de Compostela and were included in a prospective stroke registry (BICHUS). Patients with hemorrhagic transformation from an ischemic stroke subtype or with chronic inflammatory diseases were excluded. The recruitment period was from June 2008 to April 2017. The study was carried out in accordance with the Declaration of Helsinki of the World Medical Association (2008) and approved by the Ethics Committee of Clinical Research of Galicia (CEIC). Written informed consent was obtained from each patient or their relatives after full explanation of the procedures.

Clinical variables

All patients were admitted to an acute stroke unit and treated according to the guidelines of the Cerebrovascular Diseases Study Group of the Spanish Society of Neurology [20,21]. Clinical variables are detailed in Appendix S1.

Clinical outcomes

According to the definition used in previous studies [22,23], axillary temperature ≥37.5°C was considered as hyperthermia. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) score at admission, 24, 48 and 72 h. Early neurological deterioration was defined as an increase of ≥4 points in NIHSS score within the first 48 h with respect to baseline NIHSS score. The study's main variable was the poor neurologic outcome at 3 months (defined as modified Rankin Scale score of >2). Both NIHSS and modified Rankin Scale scores were evaluated by internationally certified neurologists (M.R.-Y., S.A., M.S., E.R.-C. and I.L.-D.).

Neuroimaging studies

The computed tomography study was performed at admission and between days 4 and 7, except for patients with a neurological complication or a decrease of four points in the NIHSS score. ICH and perihematomal edema volumes were calculated by using the ABC/2 method [24]. ICH topography was classified as lobar when it predominantly affected the cortical/subcortical white matter of the cerebral lobes or as deep when it was limited to the internal capsule, basal ganglia or thalamus. All infratentorial ICH cases were excluded (despite our knowledge that ICHs in the pons, deep cerebellar, etc. are probably hypertensive related and were also regarded as deep). Neuroimaging evaluations were made by the same neuroradiologist blinded to the clinical data.

Statistical analyses

Statistical analysis is detailed in Appendix S1.

Results

Patients

We included 887 patients. ICH etiology was related to hypertension in 433 patients (48.8%), amyloid angiopathy in 50 patients (5.6%), anticoagulants in 117 patients (13.2%) and other causes in 287 patients (32.4%) (49 arteriovenous malformations, 34 hematological diseases, 21 secondary to drugs, 19 brain tumors, 13 vasculitis and 151 without known cause). A total of 57.8% of the total patients included were males. The mean age was 72.9 ± 13.1 years.

Longitudinal studies of groups

Table 1 details the baseline clinical characteristics by neurologic outcome at 3 months. Maximum temperature in the first 24 h [odds ratio (OR), 1.31; 95% confidence intervals (CI), 1.13–1.64], fibrinogen (OR, 1.01; 95% CI, 1.00–1.01), edema volume at day 4–7 (OR, 1.05; 95% CI, 1.00–1.10), NIHSS score at admission (OR, 1.21; 95% CI, 1.01–1.1.34) and early neurological deterioration (OR, 2.77; 95% CI, 1.12–6.88) were independently associated with poor

Table 1 Baseline clinical characteristics, vascular risk factors, stroke subtype, biochemical parameters and neuroimaging findings in patients with good or poor outcome at 3 months

	Good outcome (n = 374)	Poor outcome (n = 513)	P-value
Age (years)	67.5 ± 14.4	72.1 ± 12.1	<0.0001
Male	60.2	56.1	0.242
Time from stroke onset (min)	227.2 ± 268.5	187.5 ± 207.8	0.611
History of hypertension	55.3	61.8	0.062
History of diabetes	18.7	21.6	0.312
Smoking habit	13.1	9.7	0.131
Alcohol consumption	14.2	15.6	0.569
History of hyperlipidemia	35.8	34.7	0.776
History of atrial fibrillation	12.8	19.3	0.011
History of ischemic heart disease	8.4	7.8	0.804
Previous stroke	15.0	19.5	0.193
Body temperature at admission (°C)	36.4 ± 0.6	36.5 ± 0.7	<0.0001
Maximum temperature during the first 24 h (°C)	36.9 ± 0.7	37.1 ± 0.9	<0.0001
Temperature increase during the first 24 h (°C)	0.5 ± 0.4	0.5 ± 0.5	0.581
Glucose level (mg/dL)	128.3 ± 50.9	133.8 ± 0.5	<0.0001
Leukocytes ($\times 10^3$/mL)	8.3 ± 2.6	8.6 ± 3.3	0.008
Fibrinogen (mg/dL)	415.1 ± 99.8	438.6 ± 103.9	0.004
Microalbuminuria (mg/24 h)	17.2 ± 40.0	20.8 ± 31.2	0.117
C-reactive protein (mg/L)	3.4 ± 3.6	5.7 ± 5.4	<0.0001
Glycosylated hemoglobin	5.6 ± 0.6	5.7 ± 0.9	0.008
Sedimentation rate (mm)	19.9 ± 18.7	24.6 ± 22.8	<0.0001
LDL cholesterol (mg/dL)	112.0 ± 37.3	111.9 ± 35.9	0.403
HDL cholesterol (mg/dL)	41.2 ± 21.8	35.0 ± 18.7	0.575
Triglycerides (mg/dL)	96.2 ± 48.2	101.6 ± 43.8	0.230
Hematoma volume at admission (mL)	22.8 ± 18.7	50.8 ± 38.2	<0.0001
Hematoma volume at day 4–7 (mL)	28.4 ± 20.3	59.6 ± 43.4	<0.0001
Hematoma growth (mL)	6.0 ± 9.2	8.8 ± 15.8	0.001
Edema volume day 4–7 (mL)	8.3 ± 10.3	23.1 ± 25.5	<0.0001
Topographic diagnosis of ICH			
Deep hemisphere	53.2	50.5	0.362
Lobar	36.9	37.0	
Cerebellar	6.4	4.3	
Brainstem	3.5	4.1	
Primary intraventricular	2.7	19.3	
Ventricular contamination	12.3	19.3	0.006
NIHSS score at admission	6 [3, 12]	15 [12, 18]	<0.0001
NIHSS score at 48 h	8 [4, 14]	20 [15, 25]	<0.0001
Early neurological deterioration	35.6	62.6	<0.0001
ICH etiology			
Hypertensive	46.5	50.5	<0.0001
Amyloid	2.7	7.8	
By anticoagulants	10.7	15.0	
Other/unknown cause	40.1	26.7	

HDL, high-density lipoprotein; ICH, intracerebral hemorrhage; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale. Data are shown as mean ± SD or intervals, [ ].

outcome in the logistic regression model (Table 2). Similar results were obtained when a multivariable model was performed only in patients with hypertensive ICH, i.e. maximum temperature in the first 24 h (OR, 1.48; 95% CI, 1.03–2.36), fibrinogen (OR, 1.12; 95% CI, 1.00–1.23), edema volume at day 4–7 (OR, 1.29; 95% CI, 1.01–1.38), NIHSS score at admission (OR, 1.55; 95% CI, 1.20–2.00) and early neurological deterioration (OR, 1.55; 95% CI, 2.80–16.31).

Figure 1 shows the axillary temperature determined at admission, maximum temperature in the first 24 h and their increase in relation to the bleeding etiology. Hypertensive patients showed the maximum temperature (37.5 ± 0.8°C) and the maximum increase in temperature (0.9 ± 0.1°C) in the first 24 h. When analyzing patients according to the etiology of bleeding, it was verified that hyperthermia was a factor in poor outcome at 3 months in hypertensive ICH, but not in ICH of non-hypertensive etiology (Table 3).

Temperature and biomarkers

A higher correlation was obtained in patients with hypertensive versus non-hypertensive ICH between the maximum temperature in the first 24 h and different inflammation and endothelial dysfunction markers, i.e. leucocytes ($r = 0.359$, $P < 0.0001$ and $r = 0.260$, $P = 0.035$), fibrinogen ($r = 0.251$, $P < 0.0001$ and $r = 0.103$, $P = 0.054$), C-reactive protein ($r = 0.701$, $P < 0.0001$ and $r = 0.186$, $P = 0.062$), sedimentation rate ($r = 0.546$, $P < 0.0001$ and $r = 0.358$, $P < 0.0001$) and microalbuminuria ($r = 0.280$, $P < 0.001$ and $r = -0.049$, $P = 0.502$) (Fig. 2). When molecular markers were included in the logistic regression models, we observed that the main variables were independently associated with poor outcome in hypertensive ICH (Table S1). We found no association between the growth of the hematoma during the first week and the increase in body temperature in the first 24 h in all patients (hypertensive, $r = 0.047$, $P = 0.412$; non-hypertensive, $r = 0.036$, $P = 0.695$). However, a positive relationship between the edema volume and body temperature in the first 24 h was demonstrated only in hypertensive patients (Fig. 3). This relationship seems to be mediated by inflammation markers (leucocytes, $r = 0.438$, $P < 0.0001$; fibrinogen, $r = 0.229$, $P < 0.001$; C-reactive protein, $r = 0.672$, $P < 0.0001$)

Table 2 Adjusted odds ratio (OR) of poor outcome at 3 months for baseline associated variables in the univariable analysis

Independent variable	OR	95% CI	*P*-value
Age	1.02	0.98–1.05	0.167
History of atrial fibrillation[a]	0.80	0.30–2.15	0.342
Maximum temperature during the first 24 h	1.31	1.13–1.64	0.003
Glucose levels	0.99	0.98–1.01	0.225
Fibrinogen	1.01	1.00–1.01	0.042
C-reactive protein	1.12	0.95–1.32	0.322
Glycosylated hemoglobin	1.31	0.82–2.10	0.653
Hematoma volume at admission	1.02	0.99–1.04	0.114
Hematoma growth	1.00	0.97–1.03	0.239
Edema volume at day 4–7	1.05	1.00–1.10	0.008
NIHSS score at admission	1.21	1.01–1.34	0.002
Early neurological deterioration[a]	2.77	1.12–6.88	<0.0001

[a]Categorical variables. CI, confidence intervals; NIHSS, National Institutes of Health Stroke Scale.

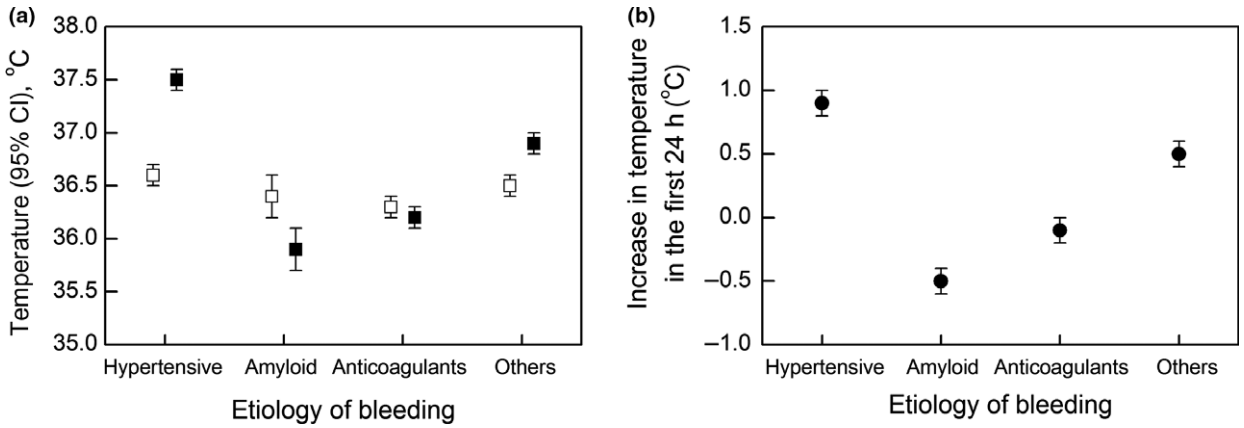

Figure 1 Body temperature and intracerebral hemorrhage etiologic groups. (a) Axillary temperature at admission (□); maximum temperature during the first 24 h (■). (b) Temperature increase during the first 24 h. CI, confidence intervals.

Table 3 Crude odds ratio (OR) of poor outcome at 3 months for temperature variables by intracerebral hemorrhage (ICH) etiologic groups

	Subtypes of ICH			
Crude OR	Hypertensive	Amyloid	Anticoagulants	Others
Temperature at admission	3.1 (2.2–4.3)	2.5 (0.6–10.1)	2.2 (0.9–5.0)	1.0 (0.7–1.3)
	<0.0001	0.674	0.551	0.392
Maximum temperature during the first 24 h	3.3 (2.4–4.5)	2.2 (0.5–9.3)	2.1 (0.9–4.4)	1.0 (0.7–1.4)
	<0.0001	0.469	0.388	0.691
Increase in temperature during the first 24 h	19.1 (13.1–133.6)	0.6 (0–52.1)	0.1 (0–2.5)	12.1 (1.2–119.7)
	<0.0001	0.780	0.532	0.003
Maximum temperature during the first 24 h ≥ 37.5°C (categorized)	5.3 (3.4–8.4)	–	0.5 (0.3–8.4)	1.0 (0.6–1.8)
	<0.0001	–	0.483	0.622

Data are given as OR, 95% confidence intervals, *P*-value.

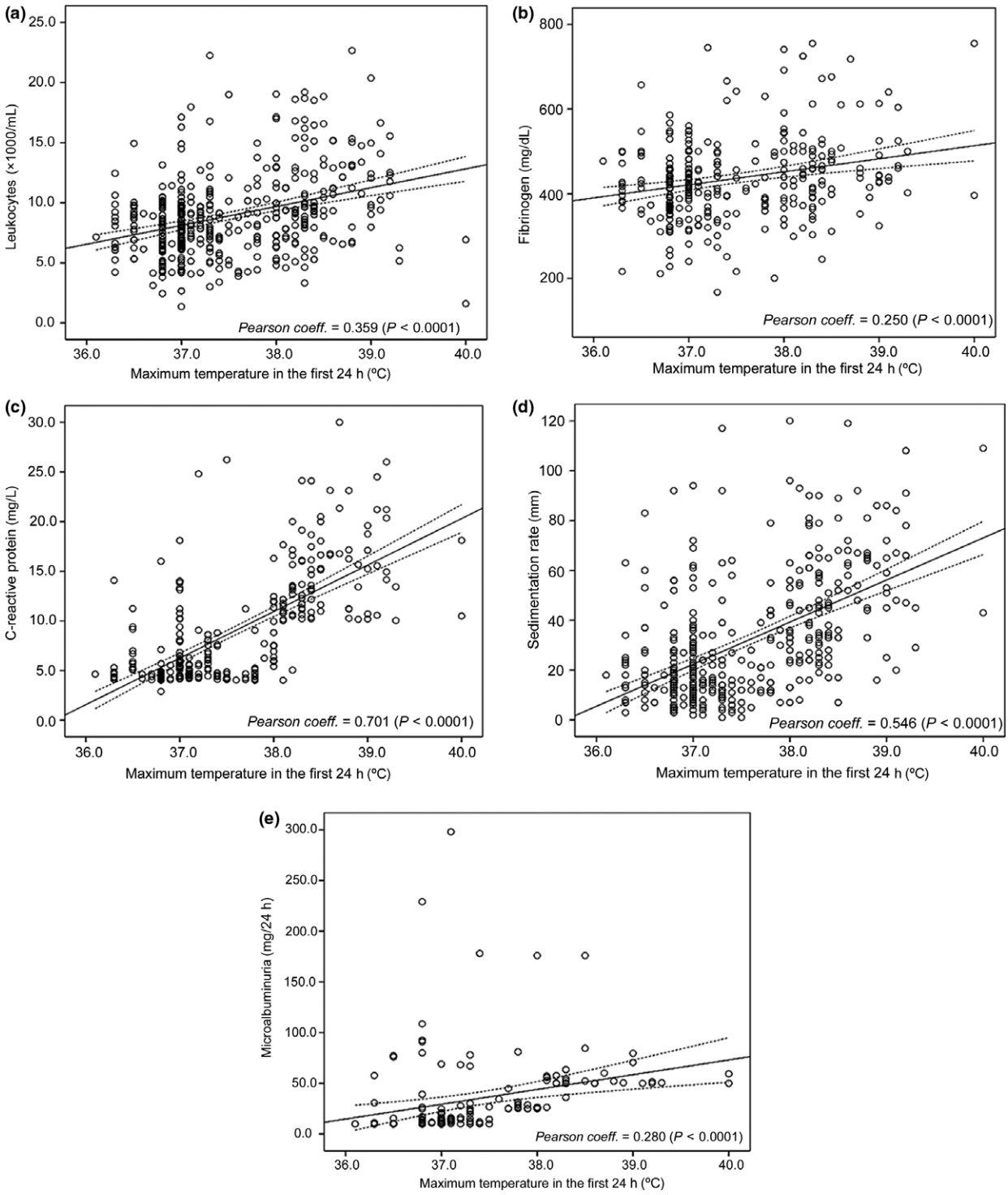

Figure 2 Correlation between maximum temperature during the first 24 h and different inflammation (a–d); and endothelial dysfunction (e) markers in patients with intracerebral hemorrhage of hypertensive etiological origin.

but not by endothelial dysfunction markers (microalbuminuria, $r = 171$, $P = 0.072$). Table S2 details the regression coefficients of edema volume at day 4–7 with molecular markers of inflammation.

Hypertensive patients with intracerebral hemorrhage

Approximately 40.9% of hypertensive patients with ICH presented hyperthermia in the first 24 h. The

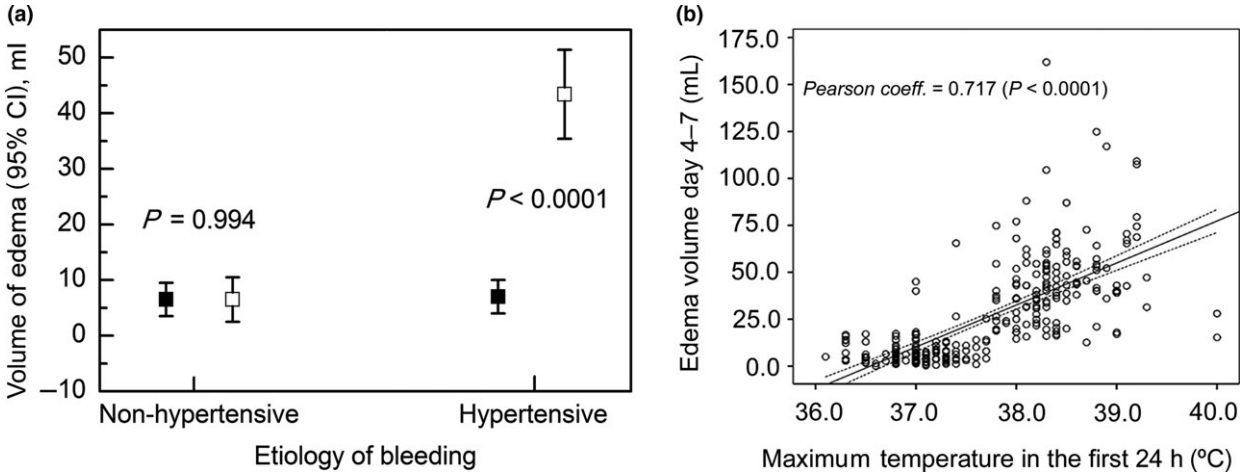

Figure 3 (a) Edema volume in hypertensive and non-hypertensive etiological groups and presence (□) or absence (■) of hyperthermia. (b) Relationship between temperature and edema volume at day 4–7 in patients with intracerebral hemorrhage of hypertensive etiological origin. CI, confidence intervals.

univariate study showed that these patients had higher levels of leukocytes (9.8 ± 3.8 vs. 8.4 ± 2.5×10^3/mL, $P < 0.0001$), fibrinogen (449.8 ± 96.5 vs. 431.6 ± 91.6 mg/dL, $P < 0.0001$), microalbuminuria (50.6 ± 32.9 vs. 31.2 ± 57.5 mg/24 h, $P < 0.0001$), C-reactive protein (10.8 ± 6.1 vs. 5.3 ± 1.5 mg/L), sedimentation rate (39.9 ± 23.2 vs. 17.6 ± 15.2 mm, $P < 0.0001$), hematoma volume on admission (45.2 ± 52.3 vs. 28.1 ± 21.8 mL, $P < 0.0001$), edema volume in the control neuroimaging (43.8 ± 20.4 vs. 6.1 ± 7.0 mL, $P < 0.0001$) and early neurological deterioration (60.0 vs. 93.0%, $P < 0.0001$). Multivariable analysis is detailed in Table S3.

Discussion

In this study, we found that the maximum axillary temperature within the first 24 h after admission is a factor associated with poor outcome in a large unselected series of patients with non-traumatic ICH. We determined that each °C of body temperature is associated with about 30% more risk of dying or being dependent at 3 months. Results are in line with clinical and pre-clinical studies on the deleterious effect of hyperthermia and fever in different neuronal pathologies [3–15,25]. This study shows that hypertensive patients with ICH with a body temperature in the first 24 h ≥ 37.5°C have a 5.3-fold higher risk of poor outcome at 3 months. In addition, in hypertensive ICH, each °C of body temperature increase in the first 24 h increased the proportion of patients with poor outcome at 3 months by 3.3 times. Our clinical data suggest that hyperthermia is a factor in poor outcome mainly in hypertensive ICH, in agreement with recent findings related to fever in patients with ICH [8,10]. Other studies have shown correlations between lesion size and hematoma location with the development of fever after brain injury [26,27]. To the best of our knowledge, independent association of hyperthermia (within 24 h after admission) with bleeding etiology in patients with ICH has not been previously accurately evaluated.

We determined that the highest temperature in the first 24 h in patients with hypertensive ICH significantly correlates with well-established cellular and molecular markers of inflammation and endothelial dysfunction. This correlation is less pronounced in other subtypes of hemorrhage. These findings support our previous data, where we found that a biomarker of the blood–brain barrier (matrix metalloproteinase-9) was a mediator between hyperthermia and poor outcome in a heterogeneous population of patients with ICH [9]. Recently, we reported an acute short-term treatment with a new antifibrinolytic agent (CM352), which limits brain damage by reducing hematoma expansion leading to improved functional and neurological recovery in an ICH rat model [28].

Hypertension is a chronic inflammatory disease, where the association between inflammation and hyperthermia is still unclear. The hematoma location, extension and subarachnoid contamination could justify ICH of hypertensive etiology affecting central mechanisms of thermoregulation especially in deep and large lesions [10,11]. Events such as hematoma growth, breakdown of the blood–brain barrier, development of edema, reduced cerebral blood flow or increase in pro-inflammatory cytokines and axonal death could be involved in the adverse consequences

of hyperthermia [6,29–31]. The inclusion of inflammation markers lowered the OR of the temperature for poor outcomes, which suggests the presence of an inter-relationship between temperature and inflammation markers. Due to the selective population analyzed, we can consider that hypertensive patients with ICH have a high probability of a poor outcome only associated with inflammatory mechanisms in the first 24 h.

An association was determined between the edema volume during the first week and body temperature in the first 24 h, which was mediated by inflammation markers. We have not found the same relationship with the hematoma growth during the first week. This result was in contrast to previous studies [8,10] that found a probable association between fever and hematoma growth as early as 24 h.

Our study has limitations. First, this was a monocenter study with a retrospective analysis (data collection was unified in all consecutive patients with ICH) and a prospective and multicenter study could provide more solid results. Secondly, the origin of fever was not identified. However, body temperature was the main variable, not the physiological mechanism involved in the increase of temperature. The negative influence seems similar in patients with hyperthermia of infectious and central origin, as also demonstrated in ischemic stroke [11]. Thirdly, we did not take the location of the lesion into account in our analysis. Fourthly, hematoma growth was estimated between admission and 48 h (44.6% of total patients). A multicenter study showed correlation between hematoma growth determined at 48 h and neurological deterioration [5]. Fifthly, axillary temperature is not the best assessment of core temperature, but the nursing staff of the stroke unit is trained to record axillary temperature. Invasive procedures are not justified in stroke patients with moderate or mild neurological deficits and tympanic or rectal temperature is not always feasible. Lastly, we did not evaluate potential treatments for hyperthermia and possible outcomes. We consider that these parameters should be the subject of therapeutic studies. We specifically focused the analysis on a homogenous population of patients with ICH, with etiological characterization, including a large sample size with several clinical variables analyzed in order to minimize possible analytical gaps.

Conclusions

Our data suggest that hyperthermia is associated with poor outcome, but only in ICH of hypertensive origin. There is a probable relationship between edema volume and elevated body temperature in the first 24 h in hypertensive patients with ICH. This relationship seems to be partially mediated by inflammation markers, but not by endothelial dysfunction markers.

Acknowledgements

We thank the Spanish Ministry of Economy and Competitiveness (SAF2014-56336-R), Xunta de Galicia (GRC2014/027), Instituto de Salud Carlos III (PI13/00292, PI14/01879), Spanish Research Network on Cerebrovascular Diseases RETICS-INVICTUS (RD16/0019) and European Union FEDER Program. T.S. (CP12/03121–CPII17/00027) and F.C. (CP14/00154) are recipients of the Miguel Servet Program, Instituto de Salud Carlos III.

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found online in the supporting information section at the end of the article:

Appendix S1. Materials and methods: clinical variables and statistical analyses.
Table S1. Logistic regression models to determine the involvement of inflammation and endothelial dysfunction in hyperthermia-mediated outcome in intracerebral hemorrhage.
Table S2. Regression coefficients of edema volume at day 4–7 with molecular markers of inflammation.
Table S3. Adjusted odds ratio of poor outcome at 3 months for baseline associated variables of hyperhensive patients with intracerebral hemorrhage.

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