Temporal Patterns of Body Temperatures in the Acute Stage of Stroke

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Abstract-

Objective: The present study aimed to describe the day-by-day temporal patterns of body temperatures in acute stroke and to delineate the differences in serial daily changes in body temperatures between intracerebral hemorrhage (ICH) and cerebral infarct (CI).

Methods: We retrospectively enrolled 90 patients (32 with ICH and 58 with CI), admitted within 12 hours after the onset of stroke. Body temperatures were measured as the tympanic temperatures during the initial 6 days of hospitalization. Patients with clinical infections were excluded. The severity of stroke was assessed by Scandinavian Stroke Scale (SSS). SSS score ≤30 was defined as severe stroke, and SSS score >30 as mild-to-moderate stroke.

Results: Mean body temperature was significantly higher in patients with ICH than those with CI in 0~12 hours, 12~24 hours, 24~48 hours, and 48~72 hours (all $p<0.05$) after the onset of stroke. Among patients with ICH, the body temperature was significantly higher in the severe group than the mild-to-moderate group during 24~48 hours and 48~72 hours (both $p<0.05$) after the onset of stroke. No significant difference in body temperatures was observed between patients with severe stroke and patient with mild-to-moderate CI.

Conclusions: The serial time course of body temperature in the acute stage of stroke differs between ICH and CI. This study showed that, in ICH but not in CI, the elevation of body temperature has significant association with the stroke severity. Our results may help in the management of hyperthermia during acute stroke.

Key Words: Body temperature, Acute stroke, Intracerebral hemorrhage, Cerebral infarct

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INTRODUCTION

In laboratory animals the relationship between body temperatures and stroke has been studied extensively for many years. Spontaneous hyperthermia following cerebral infarct (CI) was considered to be a natural consequence of brain infarct[1-3]. Both the progress of biochemical and inflammatory ischemic mechanisms in the

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brain associated with the development of cerebral infarct were deemed to be the underlying mechanisms for the appearance of hyperthemia[4]. He et al.[5] demonstrated that the occlusion of the hypothalamic and/or anterior choroidal arteries by inserting an intraluminal suture induced hyperthermia due to the selective hypothalamic infarction. However, hyperthemia caused by hypothalamic injury was relatively rare in humans.

In human subjects, it was observed that the body temperature on admission within 6 hours after stroke was independently related to the initial stroke severity[6]. Boysen et al.[7] investigated body temperatures in patients with acute stroke and found a significant rise in body temperatures over the first 10-12 hours after the onset of stroke, and the elevation of body temperatures only occurred in patients with severe strokes, but not in the mild-to-moderate ones. It was assumed that the hyperthemia was caused by the infarct or hemorrhage itself and that the size of the lesion and probably subsequent necrosis and edema were of relevant importance. However, the initial body temperatures (within hours of stroke onset) in patients with severe strokes was observed to be slightly below normal[8]. There were only limited studies investigating the evolutional change in body temperatures 24 hours after acute stroke. The differences in the temporal course of body temperatures between patients with intracerebral hemorrhage (ICH) and those with CI were not clear.

In this study, we sought to describe the day-by-day temporal changes in body temperatures during the first 6 days of acute stroke. We also aimed to delineate the differences in serial daily variations of body temperatures between ICH and CI. The results should provide new insights into how ICH and CI affect body temperatures and how the brain responds to the acute injuries caused by the cerebrovascular insults. The understandings of the natural course of changes in body temperatures during the acute stage of stroke also provide treatment guides in clinical practice.

METHODS

We retrospectively analyzed 90 patients with acute ischemic or hemorrhagic stroke admitted to a university hospital within 12 hours after the onset of stroke during a 33-month period from July 2001 to March 2004. The approval was given by the Human Experiment and Ethics Committee, National Cheng Kung University Hospital. No selection of patients was performed with regard to age, severity of stroke, or medical condition before admission. The patients were discharged after at least 6 days of admission and at that time, no further in-hospital improvement could be expected. Those with transient ischemic attacks, hemorrhagic infarction, or subarachnoid hemorrhage were exluded for analysis. All patients with clinical evidence of infections during hospitalization were also excluded, by the criteria of febrile episodes accompanied with white blood cell (WBC) count >12000/mm^3, C-reactive protein (CRP) level >7 mg/dl, pneumonia patch identified on chest X-ray, WBC count >5/mm^2 in urinalysis, tissue growth of microorganisms in sputum, urine, or blood specimens, or the necessity of antimicrobial treatment.

Stroke was defined according to World Health Organization criteria[4]. Computerized tomography (CT) or magnetic resonance imaging (MRI) of the brain was performed routinely on admission. Experienced neuroradiologists read the scans. Patients were categorized into 2 groups with different stroke types, ICH and CI.

Aspirin 100 mg/d was prescribed for patients with cerebral infarct after the CT scan. Anticoagulant treatment was used in cases of chronic atrial fibrillation and some cases of stroke in evolution for individualized consideration. No patient was treated with thrombolytic agent. Antipyretics were not routinely applied.

The stroke severity was assessed with the Scandinavian Stroke Scale (SSS) by the same evaluator who was blinded to the study[9]. The SSS evaluates the level of consciousness; eye movement; power in arm, hand, and leg; orientation; aphasia; facial paresis; and gait for a total score from 0 (worst) to 58 (best). Patients were divided into 2 groups on the basis of stroke severity on admission. SSS score ≤30 was defined as severe stroke (S). The patients in this group suffered from severe neurological deficits. Patients with SSS score >30 were categorized to mild-to-moderate stroke group (M).

Since this was a retrospective study, all the data were measured under clinical necessity. In the routine practice of our hospital, the nursing staff recorded the vital signs, including body temperatures, on a special sheet. Vital values were registered immediately within minutes of hospital arrival, and then they were measured twice to six times within 12 hours of the onset of stroke, and twice to eight times daily throughout the following 6 days of admission. Body temperature was measured as a single ear tympanic temperature with infrared tympanic thermometers (Welch Allyn 9000, Welch Allyn Inc., Skaneateles Falls, NT, USA). The electronic ear thermometer encompassed a preheated probe and sensor for reliable temperature readings on patients of all ages. It provided an active user feedback system to ensure proper positioning and improved accuracy in calculating temperatures with the standard for accuracy between ±0.1°C. The measurements were averaged respectively for the first 0~12 hours, 12~24 hours, and the 2nd, 3rd, 4th, 5th and 6th day after the onset of stroke. The differences in the mean values between groups of patients were analyzed using Student t-test. The level of statistical significance (α value) was set at 0.05. The strength of correlation between body temperature and WBC count and SSS score was expressed as the standard correlation coefficient (CC).

RESULTS

As shown in Table, among the 90 enrolled stroke patients, 32 (mean age of 59 years) had ICH, and 58 (mean age of 65 years) had CI. The mean WBC count was below 8000/mm^3 in both groups. The unexpected high percentage of ICH cases (33%) could be explained by the fact that most patients with lacunar infarct were usually hospitalized for shorter than six days and these patients were not included for analysis.

In the ICH group, 10 (31.3%) belonged to the subgroup of severe stroke (ICH-S) and 22 (68.8%) belonged to the subgroup of mild-to-moderate stroke (ICH-M). There was no difference in mean age (p=0.32) or mean WBC count (p=0.25) on the first day between the two ICH subgroups. For the CI group, 16 (27.6%) belonged to the subgroup of severe stroke (CI-S) and 42 (72.4%) belonged to the subgroup of mild-to-moderate stroke (CI-M). The mean age and WBC count on the first day showed no significant difference between these two CI subgroups (p=0.052 and 0.77, respectively). Correlation between WBC count and body temperature throughout the initial 6 days was small for both groups (e.g. CC was -0.020 for ICH group and 0.063 for CI group for the initial 12-hour period).

Eight (8.9%) patients took acetaminophen (paraceta-

Table. *Basic characteristics of patients*

	ICH			CI		
Severity		S	M		S	M
No. of patients	32			58		
		10	22		16	42
Age (years)	59±10.1			65 ±10.4		
		62±10.8	58±9.6		69±10.1	63±10
Male (%)	19 (59%)			37 (64%)		
		5 (50%)	14 (63%)		11 (69%)	26 (62%)
*Mean SSS score	36±14.5			38±12.3		
		17±8.2	44±6		21±7.3	44±6
*WBC	7.8±2.6			7.4±1.9		
(×1000/mm^3)		8.7±1.7	7.5±2.9		7.5±2.1	7.3±1.9

Note: ICH: intracerebral hemorrhage, CI: cerebral infarct, S: severe stroke, M: mild-to-moderate stroke, SSS: Scandinavian Stroke Scale, WBC: white blood cell.

*SSS scores and WBC counts were the values on the admission day.

mol) temporarily for headache or myofascial pain. Four of these patients were in the ICH group with equal distribution in the ICH-S and ICH-M subgroups. The same distribution was observed in the CI group. One in the ICH-S subgroup was treated for 6 days (500 mg tid), another in the CI-M subgroup for 4 days (500 mg tid) and the remaining 6 patients were only treated with one single dose (500 mg) of acetaminophen (paracetamol).

The time course of body temperatures in the ICH and CI groups is shown in Fig. 1. The mean body temperature of the ICH group was significantly higher compared to that of the CI group during 0~12 hours (36.74 ±0.37 ˚C versus 36.52±0.40 ˚C, p=0.01), 12~24 hours (36.91±0.42 ˚C versus 36.65±0.42 ˚C, p=0.005), 24~48 hours (36.93±0.42 ˚C versus 36.70±0.34 ˚C, p=0.006), and 48~72 hours (36.91±0.37 ˚C versus 36.74±0.35 ˚C, p=0.04) after the onset of stroke (Fig. 1). The rise of body temperature was observed in ICH group from 12~24 hours after stroke onset. After 72 hours following the onset of stroke, body temperatures declined gradually to the baseline value as those during the first 0~12 hours. On the other hand, a substantial decrease in body temperatures was observed in the CI group during the initial 0~12 hours after the onset of stroke (baseline body temperatures not shown). Afterwards, body temperatures increased gradually toward the baseline values during 72 hours after the onset of stroke. For the ICH group, CC of initial SSS score and body temperature in each time period became more negative when the mean body temperature was higher, which indicated that later hyperthermia was negatively correlated with initial SSS score. On the contrary, for the CI group, CC of initial SSS score and body temperature remained small throughout the first 6 days. It was noted that all CCs were negative for the ICH group and positive for the CI group.

Fig. 2 shows the time course of body temperature in the ICH-S and ICH-M subgroups. Body temperatures started to rise within 12~24 hours for both subgroups. The trends continued until 72 hours after the onset of stroke in the ICH-S subgroup, but declined to the baseline level within 24~48 hours after the onset of stroke in the ICH-M subgroup. Body temperature was significantly higher in the ICH-S subgroup as compared with that in the ICH-M subgroup during 24~48 hours (37.15±0.4 ˚C versus 36.83±0.39 ˚C, p=0.05) and 48~72 hours (37.17±0.35 ˚C versus 36.79±0.31 ˚C, p=0.006) after the onset of stroke. It went downward to the baseline value on the fourth day after the onset of stroke. Body temperatures tended to be higher in the ICH-S subgroup than the ICH-M subgroup throughout the fourth to sixth day after the onset of stroke.

For the CI group, no significant difference was found in body temperature between the CI-S and CI-M

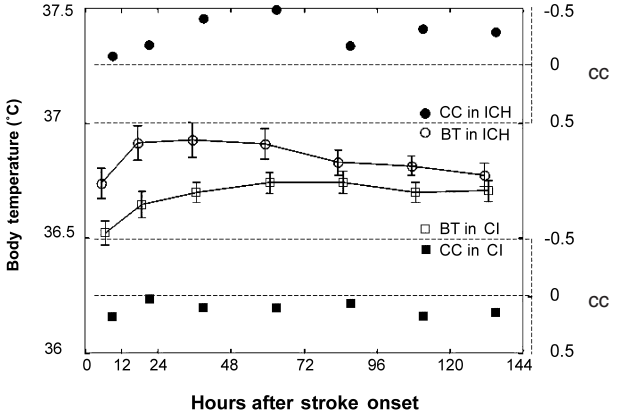

Figure 1. Time course of body temperature and correlation coefficient between initial Scandinavian Stroke Scale and body temperature in intracerebral hemorrhage and cerebral infarct groups.

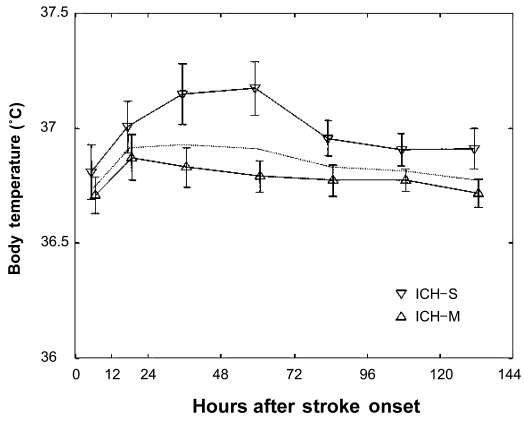

Figure 2. Time course of body temperature in intracerebral hemorrhage subgroups.

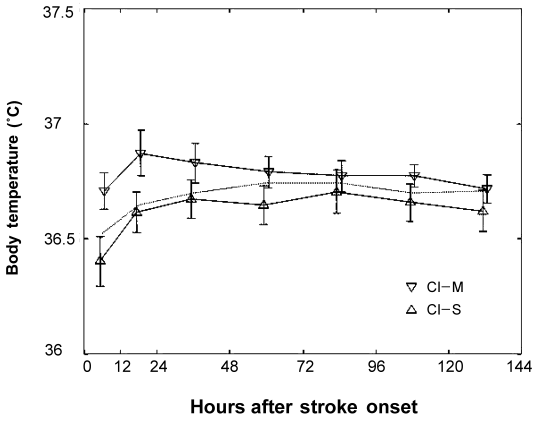

Figure 3. Time course of body temperature in cerebral infarct subgroups.

subgroups throughout the 6 days after the onset of stroke (Fig. 3). The body temperature was lowest in the initial 0~12 hours after the onset of stroke in both subgroups and increased gradually during the following time intervals. The reduction of body temperatures in CI seemed to be more profound in CI-S subgroup, although the difference was not statistically significant.

DISCUSSION

Many studies have been conducted to investigate the normal values of body temperatures after stroke in human subjects with marked variations among these studies. According to a recent review article, normal tympanic body temperatures ranged between 35.4 ˚C-37.8 ˚C[10]. Darowski et al.[11] measured auditory canal temperature in 50 patients whose ages were older than 70 years and concluded that the normal value was between 36.4 and 37.2 ˚C, with a mean value of 36.8 ˚C. Impaired thermoregulation, low activity level in daily life and disease-related changes in the circulatory and nervous systems might contribute to a low body temperature in the elderly[12]. We have also performed measurements of the tympanic temperature in a group of elderly Taiwanese (> 60 years) and the results were comparable to the abovementioned data (unpublished paper). In this study, we defined 36.8 ˚C as a normal value of tympanic temperature in older patients and the elevation and reduction of body temperatures as higher and lower than 36.8 ˚C, respectively.

Some investigators have stated that the body temperature was related to the severity of stroke[6,7]. Suzuki et al.[13] have reported that there was a tendency for the admission body temperature to be higher in those subjects with a larger intracerebral hematoma. They proposed that the mechanism was possibly related to the stimulation of thermoregulatory center of the hypothalamus by the hematoma itself or by blood in the third ventricle after the rupture of the hematoma. In our study, the rise of body temperature in patients with severe ICH was most prominent during the second and third days after the onset of stroke, corresponding to the timing with the highest edematous effect. This suggests that the edematous effect of the hematoma might play a role in the elevation of body temperatures during acute ICH. Yet the relationship between them is subject to future investigation.

Hyperthermia following ischemic stroke has been deemed to be a possible natural consequence of brain infarct[4]. Boysen and Christensen[7,8] claimed that in patients with severe CI, the initial body temperature was below normal values and the rise of body temperature occurred over the first 10 to 12 hours. However, aspiration pneumonia as the cause of higher body temperature could not be ruled out completely[18]. Takagi et al.[19] reported that body temperature decreased immediately within 4 hours after the onset of subarachnoid hemorrhage. In patients with subarachnoid hemorrhage who were admitted beyond 4 hours after the onset, body temperature was significantly higher. They suspected that the global cerebral ischemia triggered by the sudden increase in intracranial pressure might play an essential role in the reduction of body temperatures. They also assumed that the decrease of body temperature might serve as a natural protection system in cases of cerebral ischemia in human subjects. Our data showed an initial reduction of body temperatures in patients of both CI subgroups within 12 hours after the onset of stroke. Body temperatures returned to normal values steadily over the next 2 to 3 days. We speculate that, in acute ischemic stroke, the brain may auto-reduce the set point

of body temperature as a self-protective measure. The acute insult caused by ischemic injury ceased within 3 days after the onset of stroke so that body temperatures returned to the baseline value from the fourth day after the onset of stroke.

In our study, the differential leukocyte counts and chest X-ray were routinely examined. Tissue cultures of pathogens were performed whenever needed. Patients with leukocyte counts greater than 12,000/mm^3 were not enrolled. The number was decided according to Santos-Silva et al.[19], who found an association between ischemic stroke and an increase in leukocytes (8390 $\pm$ 3200/mm^3 in ischemic stroke group versus 6660 $\pm$ 1750/mm^3 in control group). Only patients without clinical and laboratory evidence of infections were included. These results indicate that our data on the natural course of body temperatures during the acute stage of stroke were more convincing than those of previous studies.

A daily dose of 100 mg aspirin was prescribed continuously for patients with CI after the onset of stroke. Sulter G et al.[21] reported that intravenous administration of acetylsalicylic acid (500 mg) was insufficient for reducing an elevated body temperature to a state of normothermia during the acute stage of ischemic stroke. Since the differences in body temperatures between the CI and ICH groups in our study exists only during the first 72 hours after the onset of stroke, factors other than the antipyretic effect of aspirin should be considered. Antipyretics were administered infrequently in our study. The patients who were treated with acetaminophen (paracetamol) were distributed equally in different stroke subgroups. The dosage administered was low. Dippel et al.[22] concluded that treatment with low-dose acetaminophen (3000 mg daily) did not result in the reduction of body temperatures after ischemic stroke. We therefore excluded the effect of antipyretic medications as the cause of body temperature differences in our results.

Most patients with stroke were of old age; they might carry more than one disease or organ dysfunction. The basic difference in body temperatures and deranged circadian rhythm related to the disorders in addition to stroke could not be completely controlled. The differences in body temperatures between two ears were not considered. Finally, the numbers of patients in each group might not be large enough. Further prospective studies of larger scale are necessary to validate our findings.

The results provide a natural course of body temperature during the acute stage of strokes and aid in treatment in clinical practice. Body temperatures elevate significantly in patients with ICH than those with CI within 3 days after the onset of stroke, particularly in the severe stroke group on the second and third days. When managing hyperthermia, defined as a body temperature higher than 36.8 ˚C, in patients with severe hemorrhagic stroke during the acute stage, we should be careful not to give a false diagnosis of infections but consider the increase in body temperatures as a natural course of ICH. For example, a body temperature of 37.5 ˚C can be a normal body temperature in patients with severe ICH but may represent febrile episodes in patients with mild-to-moderate ICH or with CI during 48~72 hours after the onset of stroke. An initial reduction of body temperature occurs in patients with CI during the first 0~12 hours after the onset of stroke, this phenomenon became more prominent in the severe group than in the mild-to-moderate group. Since hypothermia is expected in patients with severe acute CI, an otherwise normal body temperature, 37 ˚C as an example, may prompt clinicians to survey the possibilities of infection, such as aspiration pneumonia. The differences in the course of body temperatures during the acute stage of strokes provide more clinical significance in patients with higher severities than those with lower ones. Though some confusing situation exists, we believe more extensive studies in the future may unveil more clinical indicators or biomarkers to help justify the interpretation of the changes in body temperatures during the acute stage of stroke.

In summary, we studied the natural course of body temperatures during the first 6 days in the acute stage of strokes. The results showed that body temperature elevated in ICH patients during the initial days and the phenomenon was more prominent in patients with higher severity. The changes in body temperatures during the acute stage of strokes abated after 3 days of stroke onset.

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COMPETING INTEREST

We declare here that there is no competing interest in this study.

REFERENCES

1. Li F, Omae T, Fisher M. Spontaneous hyperthermia and its mechanism in the intraluminal suture middle cerebral artery occlusion model of rats. Stroke 1999;30:2464-71.
2. Kato H, Araki T, Kogure K. Role of the excitotoxic mechanism in the development of neuronal damage following repeated brief cerebral ischemia in the gerbil: protective effects of MK-801 and pentobarbital. Brain Res 1990; 516:175-9.
3. Kuluz JW, Gregory GA, Han Y, et al. Fructose-1,6-bisphosphate reduces infarct volume after reversible middle cerebral artery occlusion in rats. Stroke 1993;24:1576-83.
4. Zaremba J. Hyperthermia in ischemic stroke. Med Sci Monit 2004;10:RA148-53.
5. He Z, Yamawaki T, Yang S, et al. Experimental model of small deep infarcts involving the hypothalamus in rats: changes in body temperature and postural reflex. Stroke 1999;30:2743-51.
6. Reith J, Jorgensen HS, Pedersen PM, et al. Body temperature in acute stroke: relation to stroke severity, infarct size, mortality, and outcome. Lancet 1996;347:422-5.
7. Boysen G, Christensen H. Stroke severity determines body temperature in acute stroke. Stroke 2001;32:413-7.
8. Takagi K. Body temperature in acute stroke. Stroke 2002; 33:2154-5.
9. Lindenstrom E, Boysen G, Christiansen L, et al. Reliability of Scandinavian Neurological Stroke Scale. Cerebrovasc Dis 1991;1:103-7.
10. Sund-Levander M, Forsberg C, Wahren LK. Normal oral, rectal, tympanic and axillary body temperature in adult men and women: a systematic literature review. Scand J Caring Sci 2002;16:122-8.
11. Darowski A, Weinberg JR, Guz A. Normal rectal, auditory canal, sublingual and axillary temperatures in elderly afebrile patients in a warm environment. Age Aging 1991; 20:113-9.
12. Nakamura K, Tanaka M, Motohashi Y, et al. Oral temperatures of the elderly in nursing homes in summer and winter in relation to activities of daily living. Int J Biometeorol 1997;40:103-6.
13. Suzuki S, Kelley RE, Dandapani BK, et al. Acute leukocyte and temperature response in hypertensive intracerebral hemorrhage. Stroke 1995;26:1020-3.
14. Wang Y, Lim LL, Levi C, et al. Influence of admission body temperature on stroke mortality. Stroke 2000;31:404-9.
15. Kammersgaard LP, Jorgensen HS, Rungby JA, et al. Admission body temperature predicts long-term mortality after acute stroke. Stroke 2002;33:1759-62.
16. Meden P, Overgaard K, Pedersen H, et al. The influence of body temperature on infarct volume and thrombolytic therapy in a rat embolic stroke model. Brain Res 1994;647:131-8.
17. Deng H, Han HS, Cheng D, et al. Mild hypothermia inhibits inflammation after experimental stroke and brain inflammation. Stroke 2003;34:2495-501.
18. Sharma JC. Re: stroke severity determines body temperature in acute stroke. Stroke 2001;32:1697.
19. Santos-Silva A, Rebelo I, Castro E, et al. Erythrocyte damage and leukocyte activation in ischemic stroke. Clin Chim Acta 2002;320:29-35.
20. Takagi K, Tsuchiya Y, Okinaga K, et al. Natural hypothermia immediately after transient global cerebral ischemia induced by spontaneous subarachnoid hemorrhage. J Neurosurg 2003;98:50-6.
21. Sulter G, Elting JW, Maurits N, et al. Acetylsalicylic acid and acetaminophen to combat elevated body temperature in acute ischemic stroke. Cerebrovasc Dis 2004;17:118-22.
22. Dippel DW, van Breda EJ, van Gemert HM, et al. Effect of paracetamol (acetaminophen) on body temperature in acute ischemic stroke: a double-blind, randomized phase II clinical trial. Stroke 2001;32:1607-12.