腦創傷後腦溫的變化對於顱內壓腦灌流壓及預後的影響

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摘要

本研究主要在探討當腦傷病人試圖維持正常腦溫的狀態下，腦壓、腦灌流壓、昏迷指數及顱內溫度改變的關係。共收集 28 位腦傷病人，依標準手術程序將腦壓及腦溫監視器植入受傷大腦半球的腦實質 3 公分深，腦壓、腦灌流壓、腦溫及肛溫每小時記錄共記錄三天，三個月後再次評估病人的格拉斯哥預後指數 (Glasgow Outcome Scale, 以下簡稱 GOS)。在存活及死亡病例中發現腦溫、腦壓及腦灌流壓有明顯的差異。在存活病人中則看不到腦壓及腦溫(Rho=0.373, p=0.080)、腦灌流壓和腦溫(Rho=0.334, p=0.119)的相關性。腦溫對於腦壓(p<0.001)及腦灌流壓(p=0.021)則有明顯的影響。在 GOS 2 至 3 分的病人中，24 小時內(p=0.043)及 96 小時內(p<0.001)有較高的機會出現腦高溫(相對於 GOS 為 4 至 5 的病人)。全身體溫及腦溫差在不同的 GOS 病人中(GOS 1, GOS 2+3, and GOS 4+5)也可看到明顯的差異(p<0.001)。腦溫的改變比腦溫監測對於腦壓及腦灌流壓有較明顯的影響。入院後 24 及 96 小時內出現高溫跟三個月後較差的 Glasgow 預後指數有關。腦溫調控的異常將造成較高的腦溫及體溫的差異也預告著較差的預後。

關鍵詞 ： 腦溫，腦灌流壓，腦壓，格拉斯哥預後指數

The Effects of Brain Temperature Changes on Intracranial Pressure, Cerebral Perfusion Pressure and Prognosis After Traumatic Brain Injury

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Abstract

The aim of study was to assess the relationship between intracranial pressure (ICP), cerebral perfusion pressure (CPP), Glasgow Outcome Scale (GOS) and intracranial temperature change (ΔICT) when attempting to keep the brain in normothermia in patients with brain injury. Totally 28 patients were enrolled. ICP, CPP, ICT and rectal temperature (Tr) were recorded every hour for 4 days. A standardized procedure was followed, in

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which an ICP/ICT coupled probe was implanted at 3-cm depth in the parenchyma of the injured hemisphere, and GOS at three months was evaluated. There were significant differences in ICT, ICP, and CPP between surviving and non-surviving patients. Spearman's correlation revealed no link between ICP and ICT (Rho=0.373, p=0.080), and CPP and ICT (Rho=0.334, p=0.119) in surviving patients. When considering the temperature change, ICT had a significant influence on ICP (p<0.001) and CPP (p=0.021). The incidence of brain hyperthermia in patients with GOS of 2 or 3 was higher than patients who scored 4 or 5 within 24 hours (p=0.043), and within 96 hours of admission (p<0.001). The relationship between systemic-brain temperature gradient $\Delta T_{brain\text{-}rectal}$ with outcomes (GOS 1, GOS 2+3, and GOS 4+5) was also shown to be significant (p<0.001). Brain temperature change had more significant effects on ICP and CPP than brain temperature monitoring. Hyperthermia within 24 hours and 96 hours of admission was associated with a worse GOS at 3 months. A loss of temperature regulation, indicating high gradient of $\Delta T_{brain\text{-}rectal}$ was accompanied with a poor outcome.

Keywords*:* Intracranial Temperature, Cerebral Perfusion Pressure, Intracranial Pressure, Glasgow Outcome Scale

I. Introduction

Brain hyperthermia is frequently seen in patients following traumatic brain injury (TBI). The causes may result from posttraumatic cerebral inflammation, direct hypothalamic damage, or secondary infection resulting in fever [1]. Because high temperatures are associated with a longer stay [2] in intensive care units and increase mortality [3], temperature management in the acute stage after TBI is an important issue.

Therapeutic hypothermia is an accepted strategy that improves outcomes following anoxic brain injury associated with cardiac arrest [4] and neonatal birth asphyxia [5], however, its effects on TBI remain uncertain. Currently, avoiding brain hyperthermia or keeping the brain in normothermic conditions after TBI is recommended [6-7].

Inconsistencies in the relationship between intracranial temperature (ICT) and intracranial pressure (ICP) have been found. A positive correlation between brain temperature and ICP has been demonstrated [2, 8], however, in contrast, Huschak et al. indicated no correlation between them [9]. In both of these studies, the mean ICT were correlated with a high frequency of hyperthermia.

The aim of the present study was to evaluate the relationship between ICT and ICP, cerebral perfusion pressure (CPP), and Glasgow outcome scale (GOS) after 3 months when attempting to keep the brain in normothermic conditions in patients with TBI in an intensive care setting.

II. Materials and methods

Patients with severe TBI were retrospective enrolled from November 2008 to February 2010. This study was approved by the Ethics Committee of our hospital. All patients received computerized tomography (CT) neuroimaging study and were evaluated the initial Glasgow Coma Scale (GCS) scores in the emergency room. All patients underwent craniectomy for hematoma removal. The ICP and ICT were monitored by an intra-parenchymal catheter coupled with a thermistor (110-4BT, Pressure-Temperature Monitoring Kit, Integra Camino, USA) which were implanted 3 cm deep, frontally, in the parenchyma of the injured hemisphere in each patient.

Postoperatively, patients underwent cerebral perfusion-guided management, with the aim of a CPP of 60 mmHg or more and ICP of 25 mmHg or less. The mean arterial blood pressure (MAP) and CPP were monitored using standard pressure transducers. All patients were sedated using propofol (0.5-6 mg/kg/h) with or without atracurium (0.3-1.2 mg/kg/h) if shivering occurred during the postoperative period. Brain hyperthermia [10], defined as an ICT greater than 38℃, was controlled by ice pillows (if ICT > 37.5℃) or acetaminophen 500 mg PO (if ICT > 38℃) or an ice blanket device (if acetaminophen failed) (Gaymar Medi-Therm II Hyper-Hypothermia Machine). Outcomes were determined 3 months after head injury. A GOS score of 4 or 5 was defined as moderate disability or better, and a score of 1 to 3 as death, vegetative state or severe disability [11].

Data were expressed as mean ± standard deviation and compared using one-way ANOVA with Scheffe's method for post hoc comparisons. For the comparisons of categorized data, the chi-square test was used. For other analyses, consecutive measurements of ICT, ICP, and CPP within 96 hours for each patient were averaged to represent the mean levels of the patients' conditions. These mean values were then described as median (inter-quartile range) and compared using the Mann-Whitney U test between two groups. Spearman's correlation method was performed to investigate the association between mean ICT and mean CPP. All data were analyzed using SPSS for Windows, version 17.1 (SPSS Inc., Chicago, Illinois, USA). A *p*-value of less than 0.05 was considered significant.

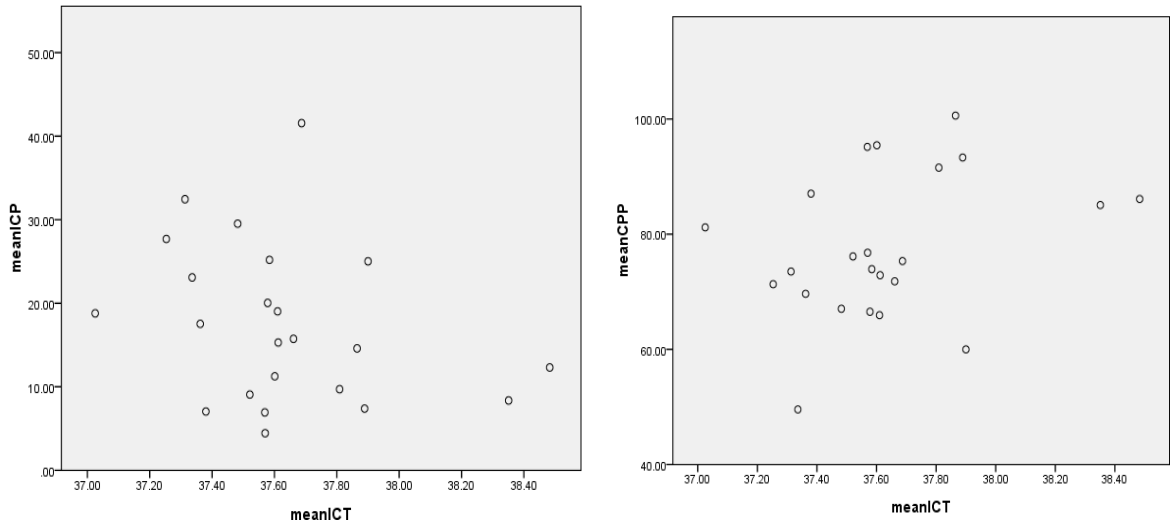
III. Results

Table 1 summarizes the clinical characteristics of the patients. In total, 28 patients were enrolled in this study. The mortality rate was 17.8%. Figure1a showed the relationship between mean intracranial temperature and mean intracranial pressure in survival patients, using Pearson's correlation method (Pearson's correlation coefficient=0.373, p-value=0.080). Fig1b revealed the relationship between mean intracranial temperature and mean cerebral perfusion pressure in survival patients, using Pearson's correlation method (Pearson's correlation coefficient=0.334, p-value=0.119). There was no significant correlationbetween ICT and ICP, and CPP. Changes of ICT/ ICP were calculated by ICT/ICP - ICT/ICP at previous 4 hours in survival patients as figure 2a showed (Dots represent mean, and error bars represent 95% confidence interval; ANOVA test for trend, $p < 0.001$). Fig 2b revealed the changes of ICT/CPP were calculated by ICT/CPP - ICT/CPP at previous hours in survival patients (Dots represent mean, and error bars represent 95% confidence interval; ANOVA test for trend, $p < 0.001$). These results demonstrated changes in ICT were significantly correlated to corresponding changes of ICP and CPP, and the greater thechange in ICT, the greater the change in ICP and CPP (Figures 2).

Table 1 Clinical characteristics of 28 patients with severe traumatic injury

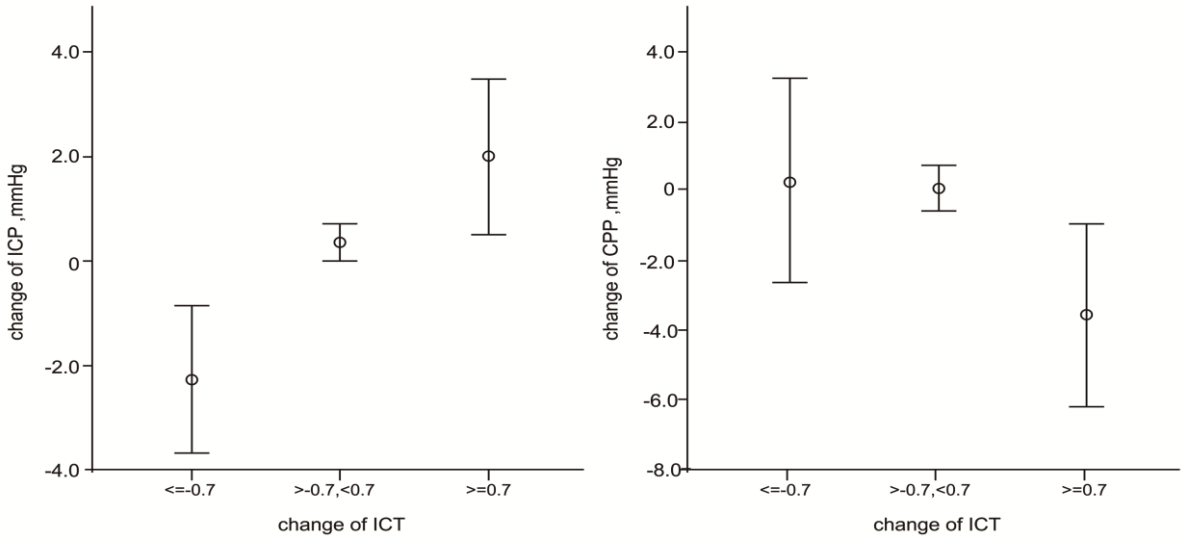
	Survival	Non-survival	
	n=23	n=5	*p*-value
Mean ICT (℃)	37.6(37.0-38.5)	33.3(32.1-37.7)	0.010
Mean Tr (℃)	37.3(36.9-37.9)	36.6(35.4-37.6)	0.186
Mean CPP mmHg	75.3(49.6-100.6)	36.6(10.7-71.8)	0.011
Mean ICP mmHg	17.5(4.4-47.8)	51.2(15.7-82.4)	0.027

1. Digits in cells represent median (inter-quartile range) or count
2. Variables were compared by Mann-Whitney U test
3. ICT=intracranial temperature; Tr= rectal temperature; CPP=cerebral perfusion pressure; ICP=intracranial pressure



(a) The relationship between mean ICT and ICP (b) The relationship between mean ICT and CPP

Figure 1 The relationship between mean ICT-ICP and ICT-CPP in patients after traumatic brain injury



(a) The relationship between changes of ICT and ICP (b)The relationship between changes of ICT and CPP

Figure 2 The relationship between changes of ICT- ICP and ICT-CPP in patients after traumatic brain injury.

Patients with brain hyperthermia, defined as a brain temperature greater than 38℃, within 24 and 96 hours of admission had poor outcomes in survivors (Table 2). In addition, the mean value of body-brain temperature gradient $\Delta T_{brain\text{-}rectal}$ in patients with a GOS score of 1 was significantly lower than in those with a GOS2 or 3 and those with a GOS score of 4 or 5 (Table 3). Similarly, $\Delta T_{brain\text{-}rectal}$ in patients with a GOS score of 2 or 3 was significantly lower than those with a GOS score of 4 or 5.

ICT in patients who survived was higher than in non-survivors (Figure 3a). The daily changes of ICT remained at a stable temperature (around 33.3℃) (Figure 3b). Extremely and progressively high ICP and low CPP values were verified in patients who did not survive.

Table 2 The relationship between GOS at 3 months and brain hyperthermia within 24 and 96 hours of admission in survivors

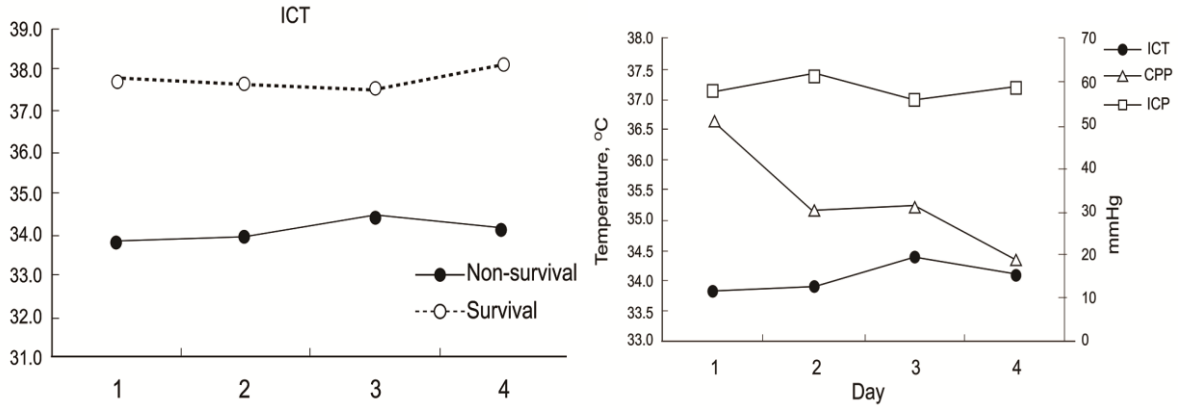
		GOS		
Time interval postoperative	Intracranial Temperature	2+3	4+5	*p*-value
Within 24 hours	ICT<=38	305 (75.1)	120 (83.3)	0.043
	ICT>38	101 (24.9)	24 (16.7)	
Within 96 hours	ICT<=38	1167 (80.5)	491 (89.8)	<0.001
	ICT>38	56 (19.5)	282 (10.2)	

Chi-square test; GOS=Glasgow Outcome Scale

Table 3 Relationship between $\Delta T_{brain\text{-}rectal}$ and GOS at 3 months after admission

							overall	GOS 1 vs. 2-3	GOS1 vs. 4-5	GOS 2-3 vs. 4-5
GOS	N	Mean	SD	Median	Min	Max	*p*-value	*p*-value	*p*-value	*p*-value
1	351	-2.43	1.93	-2.6	-8	1	<0.001	<0.001	<0.001	<0.001
2-3	546	0.04	0.28	0	0	2				
4-5	1394	0.31	0.49	0.2	-4	3				
Total	2291	-0.17	1.29	0.1	-8	3				

One-way ANOVA, followed by Sheffe's test for multiple comparisons



(a) Daily changes of mean ICT in survival and non-survival patients

(b) Daily changes of mean CPP, ICP and ICT in non-survival patients

Figure3 Daily changes of ICT, CPP and ICT in patients after traumatic brain injury

IV. Discussion

1. Keep the brain normothermic in severe TBI patients

Hypothermia is not currently standard treatment for TBI patients because the results are not consistent compared to normothermia[12-13]. However, early hypothermia therapy for more than 72 hours, during which period brain swelling occurs, is widely accepted [7, 12, 14]. The brain hyperthermia was frequently seen in

patients following TBI [1]. Farag and his colleagues [7] reported that satisfactory results could be obtained by maintaining normothermia and avoiding hyperthermia in cases involving patients with TBI. In our study, when attempting to maintain brain normothermia (median 37.3℃) to avoid hyperthermia (brain temperature > 38℃) using systemic cooling devices for successive 4 days in patients with severe TBI, the mortality rate was 17.8% (5/28). Compared with our previous report in which the mortality rate was 37% in patients with severe TBI but without brain temperature monitoring [15]. We proposed that attempting to keep the brain in normothermia might be a promising strategy for the treatment in patients with severe TBI.

2. The relationship between ICT and CPP/ICP when keeping the brain normothermic in the patients who survived

Since many causes raised ICP and decrease CPP such as brain swelling, mass effect and hyperthermia, it was not surprising that when ICP, CPP and ICT values were plotted together, there were no significant correlations when keeping brain ICT at 36.9-37.9℃ (Figures 1). In subgroup analysis using generalized estimating equations with a binary logistic model, we did not find any significant correlations between ICT (ICT > 38℃, ICT≦38℃) and ICP > 20 mmHg (odds ratio 0.97, p=0.816), or ICT (ICT > 38℃, ICT≦38℃) and CPP < 60 mmHg (odds ratio 0.62, p=0.052). These findings were consistent with report by Huschak et al, in which the brain temperature was maintained at 37-39℃ [9]. Nevertheless, when ICT changes were considered, a reduction in ICT especially a temperature gap greater than 0.7℃ produced a concomitantly significant reduction in ICP and increased in CPP (Figures 2). These results supported the concept that treating pyrexia would bring some beneficial effects in reducing ICP and deep venous stasis, increase brain flow perfusion and cells oxygen saturation, to some extend[8, 16].

3. Brain hyperthermia within 24 and 96 hours of admission was associated with poor outcomes in patients who survived

The incidence of hyperthermia within 96 hours post admission after TBI had been reported with an increasing mortality tendency from 16% on day one post-admission, 31.7% on day two post-admission, 42% on day three post-admission, and 60% to 70% from 48 to 96 hours post-admission [17-19]. In our data, within 96 hours post-admission in patients who survived, the incidence of brain hyperthermia (16.9%, 338/1996) (Table 2) was far less than in previous reports. The daily incidence of brain hyperthermia decreased by day, from 22.7% on post-operative day one, to 18.8% on day two, 15.1% on day three, and 13.2% on day four. These results demonstrated that attempting to maintain normothermia was effective in reducing fever burden and might offer a means to attenuate secondary injuries as evidence by the decrease in mortality. These results might be due to our aggressive attempts at avoiding brain hyperthermia. Brain hyperthermia within 24 and 96 hours of admission was associated with a poor prognosis in our data (Table 2). Therefore, we considered early avoidance of brain hyperthermia by maintaining normothermia for at least 96 hours might be a promising strategy for treating patients with severe TBI. We emphasized the crucial point that in the absence of monitoring brain temperature, pyrexia might be under-diagnosed and under-treated, and the outcome would be more devastating.

4. Dissociation of brain and rectal temperature in the patients (GOS 1)

The regional warm blood perfusion [20-21] and the byproducts of heat production during brain tissue high metabolic activity were the major sources of brain temperature [22]. In general, following an acute brain injury, the human brain temperature was higher than the systemic temperature [23]. Previous reports had demonstrated

that dissociation or reversal of brain temperature and systemic temperature was an early marker of poor prognosis [20-21, 24]. The current study further supported this point of brain and systemic temperature dissociation (Table 3). The mean intracranial and systemic ($\Delta T_{brain\text{-}rectal}$) temperature gradient in patients with a GOS score of 1 was -2.43℃. The $\Delta T_{brain\text{-}rectal}$ of these patients at 3-month outcome was significantly poorer than those with GOS scores of 2 or 3 and those with GOS scores of 4 or 5. In addition, the $\Delta T_{brain\text{-}rectal}$ of patients with GOS scores of 2 or 3 at 3- month outcome was also poorer than those with GOS score of 4 or 5 with statistically significant. These results highlighted that simultaneously measuring brain and rectal temperatures provided more information about the severity of injury and the likelihood outcome. Compared to the patients who survived, the brain temperature was lower (mean 33.3℃) with a low CPP (mean 33.6 mmHg) in patients who did not survive (Figures 3). The CPP decreased and ICP increased in progression, yet, the ICT remained within similar value as shown in Figure 3b. We speculated the brain temperature was not dependent on regional blood perfusion alone. The causes might result from a higher severity of brain injury with possible irreversible cells damage, and subsequently without heating production by metabolism in these groups. We considered the mechanisms in dys-regulating cerebral temperature was concomitant with a decrease of regional cerebral blood flow and diminished in cerebral metabolism. This observation was consistent with previous published reports [20-22]. However, the critical values of brain temperature and CPP leading to a poor prognosis or even death needed to be clarified in the future.

Our study had some limitations. The results were based on normothermic brain conditions mostly, and the relationship between clinical parameters and brain temperature in hyperthermic conditions was not evaluated. In spite of the statistical data we provided was meaningful and significant, the small number of patients, 23 survivors and 5 non-survivors, limited our ability to draw merits about the decisive values of brain temperature and CPP.

V. Conclusions

Based on the observations, we concluded that brain temperature had a significant effect on ICP and CPP when the temperature change was estimated. Brain hyperthermia within 24 hours and 96 hours of admission was associated with a worse GOS score at 3 months, and a loss of temperature regulation with high temperature shiftΔT brain -rectal was also associated with a poor outcome in severe TBI.

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