Title: Measuring Brain Temperature While Maintaining Brain Normothermia in Severe Traumatic Brain Injury Patients.

Article Type: Clinical studies

Keywords: Intracranial temperature, superficial temporal artery temperature, rectal temperature, brain normothermia

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Dear editor

We thank all the reviewers’ comments on our submitted article. We all agree to change our previous submitted paper according to reviewer recommendation. This revise article had edited by professoral english language editing yet from http://www.elsevier.com/wps/find/authorsview.authors/languagepolishing as editor suggestion.

Once again, thank you for your consideration of the manuscript for publication in the Journal of Clinical Neuroscience

With best regards

Jinn-Rung Kuo, M.D

Chi-Mei Medical Center
Dear reviewers

Thanks for your comments.

We all agree to change our previous submitted paper according to reviewer recommendation.

The major changes in this revise article include

1. We add Fig 5A, B to demonstrate the relationship between ICP, CPP and the reversal of temperature gradient, and was graphically in a separate figure 5A and B.

2. We add Table 1 to describe demographic and clinical characteristics (present in IOQ methods) of 28 patients with severe traumatic injury in survival and non-survival patients. All the patients underwent craniectomy in our series.

Table 1

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3. We add the fever management protocol in Page 5 and 6.

-> controlled with an ice pillow (if ICT > 37.5°C), the administration of 500 mg PO of acetaminophen (if ICT> 38°C), or with an ice blanket device (if acetaminophen failed)

->We also used atracurium (0.3 to 1.2 mg/kg/hr) if the patient was shivering during
the postoperative period.

4. “About the issue of accuracy of the brain temperature measurements in our study”

   This issue is added in discussion as followings:

   ➔ In the literature review, the temperature gradient from the cortex to the central brain ranges up to 0.9°C. In any study that evaluates brain temperature, the accuracy of brain temperature measurement and the position of the implanted probe must be considered. The measurement methods and calibration of the brain temperature sensors and the monitoring technique used in our study have been reported previously. Our study utilized the following standardized measurement procedure: the ICP/ICT was monitored by implanting an intraparenchymal catheter coupled with a thermistor 3 cm deep, frontally, into the parenchyma of the injured hemisphere.

5. This revise article had ediated by professoral english language editing yet from http://www.elsevier.com/wps/find/authorsview.authors/languagepolishing as editor suggestion.

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   With best regards

   Jinn-Rung Kuo, M.D

   Chi-Mei Medical Center
Measuring Brain Temperature While Maintaining Brain Normothermia in Severe Traumatic Brain Injury Patients.

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Abstract

The aim of this study was to evaluate the relationship between superficial temporal artery temperature (Tt), rectal temperature (Tr) and intracranial temperature (ICT) when attempting to keep the brain in a normothermic condition in patients with severe traumatic brain injury.
We also compared the incidence of the reversal of the temperature gradient in survival and non-survival patients and the difference of the reversal of the temperature gradient in survival and non-survival patients.

Between Nov 2008 and Feb 2010, 28 severe traumatic brain injury patients were enrolled retrospectively in our study. Each patient’s Tt, Tr and ICT was recorded every hour for four days. Our results show that the frequency of brain hyperthermia in our participants (ICT > 38℃) was 17.7%. Using a paired t-test and Bland-Altman plots showed that a significant temperature gradient exists between Tt, Tr and ICT ($P<0.001$). Using Spearman’s correlation method revealed a significant positive correlation between Tt, Tr and ICT ($P<0.001$). Five patients in our study developed brain death at a mean of 9.6 hours (ranging from 8-12 hours) after the reversal of the temperature gradient between Tt, Tr and ICT. The Fisher-exact test showed that the incidence of the reversal of the temperature gradient between Tt, Tr and ICT in survival and non-survival patients was significant ($P<0.001$). We conclude that a significant temperature gradient exists between Tt, Tr and ICT when maintaining brain normothermia. The daily practice of non-invasive Tt measurement the may cause doctors to underestimate ICT; reversal of the ICT and Tt and/or Tr could be an early marker of a poor prognosis for patients with severe traumatic brain injuries.

*Key words:* Intracranial temperature, superficial temporal artery temperature,
rectal temperature, brain normothermia

INTRODUCTION

Traumatic brain injury (TBI) is estimated to effect up to 2% of the population per year and is a major cause of disability and death among young people. Following a TBI, hyperthermia is frequently seen in patients during the acute injury period, and the incidence and duration of the fever are significantly associated with neuronal damage. Previous studies have shown that the incidence of hyperthermic rates was 16% within 24 hours post-admission, 31.7% between 24 to 48 hours post-admission, 42% at 72 hours post-admission, and 60% to 70% between 48 hours to 96 hours post-admission.

The difference between ICT and Tr has been evaluated via invasive temperature monitoring, and it has been shown that brain temperature is 0.5 to 1°C higher than rectal temperature. Tt measurement is a non-invasive procedure that uses technology commonly found in intensive care units. Tt measurement offers potential benefits in critically ill patients. Until now, a relationship between Tr, Tt and ICT has not been well-established in TBI patients. Dissociation or reversal between intracranial and systemic temperatures, defined as when rectal temperature exceeds intracranial temperature, has been demonstrated to be an early sign of brain death. However, the incidence and difference of a reversal of the temperature gradient in...
survival and non-survival patients have not been well-evaluated. The aim of this study is to determine the relationship between Tr, Tt and ICT when attempting to keep the brain in a normothermic condition in patients in the intensive care unit with a TBI. We also compared the incidence and difference of a reversal of the temperature gradient in survival and non-survival patients.

**Material and method**

Patients who were diagnosed with a TBI in a medical center in southern Taiwan were evaluated retrospectively and enrolled in our study from November 2008 to February 2010. This study was approved by the ethics committee of our hospital. A complete history was taken, and a neurological assessment was performed on each patient. All patients received neuroimaging with computerized tomography (CT) and were evaluated based on the initial Glasgow Coma Scale (GCS) in the emergency room. All patients underwent a craniectomy for hematoma removal. The ipsilateral superficial temporal artery was preserved when the craniectomy was performed. The following standardized procedure was performed to monitor the intracranial pressure (ICP) and ICT: an intraparenchymal catheter coupled with a thermistor (110-4BT, Pressure-Temperature Monitoring Kit, Integra Camino, USA) was implanted 3 cm deep, frontally, in the parenchyma of the injured hemisphere. The methods and calibration of the brain temperature sensors and the monitoring techniques used in this
study have been reported previously\textsuperscript{12}. According to the manufacturer of the instruments used to record our temperature, the temperature data are precise within 20 to 40 ± 3.0°C. Postoperatively, patients underwent cerebral perfusion pressure (CPP)-guided management with the aim of maintaining a CPP of 60 mmHg or more and an 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 to 6 mg/kg/hr). We also used atracurium (0.3 to 1.2 mg/kg/hr) if the patient was shivering during the postoperative period.

The room temperature in the intensive care unit (ICU) was set at 25°C. Tr was monitored with a rectal temperature thermistor (Gaymar Medi-Therm II Hyper-Hypothermia Machine), and Tt was obtained with a temporal scanner (TemporalScanner\textsuperscript{TM} TAT-5000, EXERGEN, Boston, MA). All temperature measurements were recorded in degrees Celsius every hour for four days. Tt measurements were performed according to the following ICU standard temperature measurement protocol. The patient’s hair was brushed aside if necessary, and the probe was positioned on the center of the patient’s forehead. The measurement button was pressed, and the measurement was performed by scanning the region from the center midline and sliding the probe across the head to the region behind the earlobe. The button was then released, and the temperature was recorded. The duration of this
procedure was about five seconds. The Tt was evaluated on the side of the head
where the operation was performed (defined as the craniectomy side). The
cranieotomy side was where the hematomas were surgically removed and where the
ICT probe was implanted.

Brain hyperthermia\textsuperscript{13}, defined as an ICT $> 38^\circ C$, was controlled with an ice pillow
(if ICT $> 37.5^\circ C$), the administration of 500 mg PO of acetaminophen (if ICT$> 38^\circ C$),
or with an ice blanket device (if acetaminophen failed) (Gaymar Medi-Therm II
Hyper-Hypothermia Mechine).

Pearson’s correlation methods were used to evaluate the correlation between Tr, Tt
and ICT. The temperature gradient of ICT vs. Tr and ICT vs. Tt at each point was
calculated and plotted as described by Bland and Altman\textsuperscript{14}.

Data were expressed as median (interquartile range) or mean ± standard deviation in
some items. All data were analyzed using qualified statistical software (SPSS for
Windows, Version 16, SPSS Inc., Chicago, Illinois, USA). A p-value of less than 0.05
was considered statistically significant.

RESULTS

In this study, 28 traumatic brain injury patients were evaluated retrospectively (19
male and 9 female; age range of 16 to 80 years; median age of 44.5 years;
interquartile age range of 28 to 77.5 years). Traffic accidents had occurred in 73.8 %
of the cases. The preoperative Glasgow Coma Scale median number for our participants was a six, and the interquartile range of the Glasgow Coma Scale was 3.7 to 7.5. The median injury severity score (ISS) was 25, and the interquartile ISS range was 24 to 28. Five patients expired during the course of treatment. The mortality rate of our participants was 17.8%. Table 1 shows the detailed demographic and clinical characteristics of the survival and non-survival patients.

We used the Bland and Altman plotting analysis to evaluate the temperature difference in ICT minus Tr and ICT minus Tt (Figures 1A and 1B). Our analysis revealed a significant temperature gradient difference between these two sites from postoperative day one to postoperative day four in survival patients. Our paired t-test showed that the mean temperature difference between ICT and Tr (0.23 ±0.45 °C) and ICT and Tt (0.64±0.6 °C) were significantly different (p<0.001). ICT had the highest value of all of the temperature parameters recorded in survival patients (37.6 ± 0.6°C).

Pearson’s correlation methods showed a significant positive correlation (P<0.001) between ICT and Tr (Fig. 2) and ICT and Tt (Fig. 3) in survival patients.

Figure 4 shows the daily mean temperature change from postoperative day one to postoperative day four. The data in Figure 4 reveal that ICT had the highest value followed by Tr and Tt when maintaining the ICT at less than 38°C in survival patients.

In total, the brain hyperthermia frequency was 17.7% in our study. The daily brain
hyperthermia frequency from postoperative day one to postoperative day four was 21.9%, 18.8%, 15.1%, and 13.2%, respectively.

Five patients developed brain death at 8 hours, 8 hours, 10 hours, 10 hours, and 12 hours after a reverse of the temperature gradient in ICT-Tr and ICT-Tt. Each patient died due to an uncontrolled intractable increase in intracranial pressure and brain swelling. An example of this uncontrolled increase in pressure and swelling is shown in Fig 5. In the non-survival patient shown in Fig. 5, the reverse of the temperature gradient in ICT-Tr and ICT-Tt started at 65 hours after the operation (5A). At the same time, the ICP and CPP reversal were accompanied by a reversal of brain temperature and rectal temperature (5B). At this instance, the value of ICT was 34.2°C, Tr was 35.3°C, Tt was 35.9°C, ICP was 58 mmHg, and CPP was 9 mmHg.

Figure 6 shows the incidence of the reversal of the ICT-Tr gradient in survival and non-survival patients from postoperative day one to day four. The mean reversal temperature gradient was -3.0 ± 0.62°C in non-survival patients and 0.2 ± 0.16°C in survival patients.

Discussion

Brain hyperthermia is frequently seen in patients following a traumatic brain injury (TBI). These causes may result from post-traumatic cerebral inflammation, direct hypothalamic damage, or a secondary infection resulting in fever. In our study, the
incidence rate of brain hyperthermia was 17%, which is a lower rate than previous reports that ranged from 16% to 85%\textsuperscript{4-6, 15}. This discrepancy may be due to early intervention in our study to maintain brain temperatures at 38°C or less.

In general, following an acute neurological injury, the human brain is at a higher temperature than other body temperatures, such as the rectal temperature.\textsuperscript{16} Rossi et al. has demonstrated that ICT is significantly higher than core temperature, especially in the condition of a fever after a brain injury.\textsuperscript{15} However, Childs et al. indicated that brain temperature could not be predicted from rectal temperature at all times because brain temperatures are not always higher than core temperatures.\textsuperscript{12} Figure 1A shows that in our study, when the brain temperature was controlled at a temperature of less than 38°C, the invasive Tr measurement may cause doctors to underestimate ICT (mean gradient of 0.23°C), despite a strong positive correlation between these two parameters in survival patients (Fig. 2). Therefore, our results support Child’s study by indicating that brain temperature cannot always be predicted from rectal temperature in survival patients.\textsuperscript{12} We also want to emphasize the importance of monitoring brain temperature during the acute post-TBI period because rectal temperature measurement may cause doctors to underestimate ICT when the brain is vulnerable to a secondary injury.

Tt measurement is a common practice in the ICU because it is noninvasive, does
not require contact with the mucous membrane, and is not significantly affected by
thermoregulatory changes. In our study, Fig. 1B shows that when we maintained a
brain temperature of less than 38°C, a significant temperature gradient existed
between the ICT and Tt (mean gradient of 0.64°C), despite a strong positive
correlation between these two parameters in survival patients (Fig 3). These results
suggest that the daily practice of non-invasive temporal artery temperature
measurement may cause doctors to underestimate ICT in survival patients. Our
results also remind us that neither rectal nor temporal artery thermometers provide
adequate accuracy to replace monitoring ICT if a highly accurate ICT measurement
is desired, such as in selective brain hypothermia.

Under normal conditions, brain temperature is dependent on heat production
during brain parenchymal metabolism and regional blood flow perfusion.
Fountas et al. demonstrated that the ICTs in 11 patients became lower than their
systemic temperatures (median time of 4.43 hours) prior to any changes in intracranial
and cerebral perfusion pressure. Fountas concluded that dissociation between the
intracranial and rectal temperatures is an early sign of brain death. In our study, five
patients developed brain death at 8 hours, 8 hours, 10 hours, 10 hours, and 12
hours after the reversal of the temperature gradient in ICT-Tr and ICT-Tt (Fig. 5).
This reversal phenomena (decreased cerebral temperature relative to the patient’s
systemic temperature) is also observed between the intracranial and superficial temporal artery temperatures. As Figure 5 shows, the value of CPP was less than 40 mmHg when reversal phenomena occurred postoperatively. We consider the diminished ICT might be due to a concomitant decrease in regional cerebral blood flow and a diminished cerebral metabolism.

Figure 6 shows the incidence of the reversal phenomenon in survival and non-survival patients. The Fisher-exact test revealed a significant difference between survival and non-survival patients (p<0.01). We also found that the mean (STD) reversal temperature gradient in ICT-Tr was -3.0°C (0.62) in non-survival patients and 0.2°C (0.16) in survival patients. These results confirm a previous report showing that the reversal of ICT and Tr, and/or the ICT and Tr gradient may be an early marker of a poor prognosis in patients with a severe head injury. However, the small number of patients in our study limited our ability to draw conclusions about the threshold at which the reversal point was likely to affect patient outcome after a TBI. The exact temperature gradient that will lead to death needs to be clarified in future studies.

Recently, Chio et al. successfully demonstrated that selective brain cooling (33 to 35°C) induced by an infusion of 4°C normal saline via the external jugular vein is associated with a minimal decrease in rectal-temperature-attenuated
cell ischemia and damage in rats. Forte et al. \(^{19}\) also suggested that regional brain cooling (mean of 35.2°C) was effective in controlling the ICP in patients who had previously undergone a decompressive craniectomy. However, based on our findings that reversal of the ICT and Tr could be an early marker of poor prognoses in patients after a TBI, our data do not support the widely-held view that a low brain temperature is beneficial for TBI patients. The optimal brain temperature and how to monitor the patient’s brain condition need to be clarified if selective brain cooling is to be performed.

In the literature review, the temperature gradient from the cortex to the central brain ranges up to 0.9°C\(^{20}\). In any study that evaluates brain temperature, the accuracy of brain temperature measurement and the position of the implanted probe must be considered. The measurement methods and calibration of the brain temperature sensors and the monitoring technique used in our study have been reported previously\(^{16}\). Our study utilized the following standardized measurement procedure: the ICP/ICT was monitored by implanting an intraparenchymal catheter coupled with a thermistor 3 cm deep, frontally, into the parenchyma of the injured hemisphere.

Our study had several limitations. First, the retrospective nature of this study and the small number of patients limited our ability to draw conclusions about keeping the brain in normothermia and its effect on patient outcome after a TBI. Second, the
results were mostly based on the brain in a normothermia condition. The relationship between brain temperature and superficial artery temperature in a hyperthermia condition was not evaluated. Finally, the study lacked a comparison group to control for other factors that may have influenced the results.

CONCLUSIONS

Based on our findings, we conclude that a significant temperature gradient exists between ICT and Tr and between ICT and Tt. The daily practice of non-invasive temporal artery temperature measurement may cause doctors to underestimate ICT. Reversal of the ICT and superficial temporal artery and/or rectal temperature could be an early marker of patients who have poor prognoses.

References


ACKNOWLEDGMENTS

The authors wish to express their gratitude to all of the participants from neurology, neurosurgery, emergency critical medicine, and the intensive care unit. The authors also thank Ms. Lin Wen-Chun for her help on the statistical analysis.

Figure Legends

Fig. 1. Bland-Altman plots comparing the difference between temperature measurements. Plots as demonstrated for (A), comparison of intracranial and rectal temperature, and (B), comparison of intracranial and superficial temporal artery temperature.

Fig. 2. Relationship between mean intracranial temperature (on the operation side in survival patients) and mean rectal temperature using Pearson’s correlation method.

Fig. 3. Relationship between mean intracranial temperature and mean superficial temporal artery temperature on the operation side in survival patients using Pearson’s correlation method.

Fig. 4. Time course of mean intracranial temperature (ICT), superficial temporal
artery temperature (Tt), and rectal temperature (Tr) in survival patients from postoperative day one to day four.

Fig. 5. Changes of ICT, Tr, and Tt (A), and ICP and CPP (B) in a case from the time of post-operation (0 hours) to 96 hours. The reverse of the temperature gradient in ICT-Tr and ICT-Tt started 65 hours after the operation. At that time, ICT was 34.2°C, Tr was 35.3°C, Tt was 35.9°C, ICP was 58 mmHg, and CPP was 9 mmHg.

Fig. 6. Proportion of rectal temperature exceeds intracranial temperature in survival and non-survival patients.

Fig. 7. Gradient of intracranial temperature minus rectal temperature in survival and non-survival patients.
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Digits in cells represent median (interquartile range) or count.

Continuous variables were compared by Mann-Whitney U test, and categorical ones were by Fisher’s
Fig 1 Bland-Altman plots comparing difference between temperature measurements.

Plots as demonstrated for (A) comparison of intracranial and rectal temperature, (B) comparison of intracranial and superficial temporal artery temperature.
Fig 2 Relationship between mean intracranial temperature and mean rectal temperature in survival patients, using Pearson’s correlation method

Pearson’s correlation coefficient = 0.869, p < 0.001
Fig 3 Relationship between mean intracranial temperature and mean superficial temporal artery temperature in operation side in survival patients, using Pearson’s correlation method

Pearson's correlation coefficient = 0.863, p < 0.001
Figure 4

Time course of mean temperature in intracranial temperature (ICT), superficial temporal artery temperature (Tt), and rectal temperature (Tr) in survival patients from postoperative day 1 to day 4.
Fig 5 Changes of ICT, Tr, Tt (A), ICP and CPP (B) in a case from the time of postoperation 0 to 96 hours. The reverse of the temperature gradient in ICT-Tr and ICT-Tt started at the 65 hours after operation. At this time, the value of ICT is 34.2°C, Tr 35.3°C, Tt 35.9°C, ICP 58 mmHg, and CPP 9 mmHg.
Fig 6
Proportion of rectal temperature exceeds intracranial temperature in survival and non-survival patients.
Figure 7 Gradient between intracranial temperature and rectal temperature in survival and non-survival patients when rectal temperature exceeds intracranial temperature.