Temperature variability in the day–night cycle is associated with further intracranial pressure during therapeutic hypothermia

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Abstract
Background: To assess whether circadian patterns of temperature correlate with further values of intracranial pressure (ICP) in severe brain injury treated with hypothermia.

Methods: We retrospectively analyzed temperature values in subarachnoid hemorrhage patients treated with hypothermia by endovascular cooling. The circadian patterns of temperature were correlated with the mean ICP across the following day (ICP24).

Results: We analyzed data from 17 days of monitoring of three subarachnoid hemorrhage patients that underwent aneurysm coiling, sedation and hypothermia due to refractory intracranial hypertension and/or cerebral vasospasm. ICP24 ranged from 11.5 ± 3.1 to 24.2 ± 6.2 mmHg. The ratio between the coefficient of variation of temperature during the nocturnal period (18:00–6:00) and the preceding diurnal period (6:00–18:00) [temperature variability (TV)] ranged from 0.274 to 1.97. Regression analysis showed that TV correlated with ICP24 (Pearson correlation = −0.861, adjusted R square = 0.725, p < 0.001), and that ICP24 = 6 (4–TV) mmHg or, for 80% prediction interval, ICP24 = 23.9 − 6.22 × TV ± 1.73 × √1.06 + ((TV − 1.1)2/4.49) mmHg. The results indicate that the occurrence of ICP24 higher than 20 mmHg is unlikely after a day with TV ≥ 1.0.

Conclusions: TV correlates with further ICP during hypothermia regardless the strict range that temperature is maintained. Further studies with larger series could clarify whether intracranial hypertension in severe brain injury can be predicted by analysis of oscillation patterns of autonomic parameters across a period of 24 h or its harmonics.

Keywords: Intracranial pressure, Hypothermia, Circadian rhythm, Temperature, Prediction, Multimodality monitoring

Background
Severe brain injury may lead to a progressive worsening of neurological status and consequently to poor outcome. Nonetheless, the intensity of neurological deterioration varies widely in each case and frequently is unpredictable. Such poor outcome occurs in part because an effective neuroprotective therapy is missing and the currently available therapies may lead to significant side effects. Therefore, the treatment of patients with severe brain injury could be improved by the development of new methods to predict neurological status worsening [1–3], which could guide bedside decisions in a tailored manner.

We have previously shown that the adult human brain displays a potential novel mechanism of plasticity that involves a neurogenic system orchestrated in a broad brain area [4]. This system begins from the structures without blood–brain barrier, i.e. the circumventricular organs, located principally in the hypothalamus. Next, we showed that the pattern of hypothalamic functions such as circadian rhythms and thermoregulation anticipates signs of brain injury such as seizures in epileptic patients [5], perhaps reflecting the functioning of the potential neurogenic system. Following the same rationale, here...
we investigated whether the temperature variability (TV) in the day–night cycle anticipates intracranial pressure (ICP) values in subarachnoid hemorrhage patients submitted to intravascular catheter-induced hypothermia. The development of this method may reveal a parameter to anticipate neurological worsening in severe acute neurological conditions.

**Methods**

**Clinical data**

We performed retrospective analysis from subarachnoid hemorrhage patients enrolled in the ongoing project named “ICU Cockpit”, which has been approved from local institutional review boards. Regarding the patients analyzed in this study, ICP and brain temperature (Neurovent-P, Raumedic AG, Helmbrechts, Germany) were used for brain monitoring. Body temperature was monitored by intra-arterial thermistors (PiCCO system, Pulsion Medical Systems SE, Munich, Germany). Hypothermia (target core body temperature 33.0–33.9 °C) was induced and maintained using endovascular cooling (Quattro™, Zoll Medical, Chelmsford, USA) according to a standardized protocol if intracranial hypertension and/or delayed cerebral ischemia refractory to conventional treatment occurred [1]. Glasgow outcome scale (GOS) was assessed after 1 year.

**Data analysis**

Neuromonitoring and systemic data obtained with Infinity® Delta Monitor (Dräger AG, Lübeck, Germany) were conveyed to and synchronized in Component Neuromonitoring System (CNS) monitor (Moberg Research, Inc., Ambler, Pennsylvania, USA). Continuous parameters were stored at 1–10 Hz. Next, files obtained from CNS monitors were converted into Matlab files (Matlab R2014a, Natick, Massachusetts, USA) for statistical analysis. We selected the cases with ICP monitoring registered during more than 5 days. Because we suspected that the circadian rhythms could be a primary factor that correlates with brain injury, we built a spreadsheet in Excel (Excel 2010, Microsoft Corporation, Redmond, Washington, USA) containing the mean and standard deviation of all parameters in diurnal (6:00–18:00) and nocturnal (18:00–6:00) periods, encompassing all days of monitoring. We used this time to define diurnal and nocturnal periods based on the pattern of intrinsic circadian rhythms, which are related to endogenous oscillation of suprachiasmatic nucleus activity and observed through parameters such as serum level of melatonin and core body temperature [6]. To exclude values that corresponded to artifact, we set upper and lower limits based on clinical knowledge and visual analysis of the graphs plotted from data of each parameter. Days with more than 15% of values out of range were excluded of the analysis. Particularly regarding the assessment of the autonomic nervous system, we obtained as parameter the RR (or NN) interval in milliseconds to calculate the heart rate variability. Regarding temperature, we included for statistical analysis days with mean daily temperature <34.9 °C. This temperature limit includes from the first day of hypothermia (target temperature equals 33–33.9 °C) until the day when slow rewarming began. In this manner, this last day of monitoring comprehended initially a period during which the target temperature for hypothermia was maintained and next a period that corresponded to the beginning of rewarming. Importantly, this rewarming was slow in such a way that the mean temperature of that day was less than 34.9 °C. Statistical analysis to find a parameter that could correlate with ICP was carried out using Excel and Minitab 17 (Minitab Inc., State College, Pennsylvania, USA). Excel was used to perform descriptive statistics, ANOVA, and regression analysis. Minitab was used to obtain the graph of regression analysis including regression line and curves of confidence and prediction intervals (80%).

**Results**

From the initial series containing 11 enrolled patients in the ICU Cockpit Project, we obtained data from 17 days of monitoring during hypothermia induced in three patients with subarachnoid hemorrhage that were treated with aneurysm coiling and sedation (Table 1). The continuous parameters suitable for statistical analysis were ICP, body temperature, blood pressure, and heart rate.

| Case # | Age | Gender | Aneurysm | Admission | Clinical assessment | Fisher grade | Recording in CNS monitor | GOS after 1 year |
|--------|-----|--------|----------|-----------|---------------------|--------------|--------------------------|----------------|
| 1      | 50  | F      | ACoA     | d4        | HH 2                | 3            | From d6                   | 5              |
| 2      | 65  | F      | ACoA     | d4        | HH 4                | 4            | From d9                   | 3              |
| 3      | 53  | F      | ACoA     | d0        | HH 3                | 4            | From d6                   | 5              |

ACoA, anterior communicating artery, CNS, Component Neuromonitoring System, d day after bleeding, F female, GOS, Glasgow outcome scale, HH, Hunt and Hess scale, VS, clinical vasospasm
We did not find correlation between heart rate variability or blood pressure with further ICP (Additional files 1, 2).

**Temperature variability correlated with mean ICP in the following day**

The ratio between the coefficient of variation (standard deviation/mean) of temperature during the nocturnal period (18:00–06:00) and the preceding diurnal period (6:00–18:00) (TV) ranged from 0.274 to 1.97 (Table 2). Mean ICP across the following day (ICP$_{24}$) ranged from 11.5 ± 3.1 to 24.2 ± 6.2 mmHg (Table 2). The principal result was that TV correlated inversely with ICP$_{24}$ (Pearson correlation = −0.861, adjusted coefficient of determination $R^2$ = 0.725, p < 0.001) (Fig. 1). This correlation can be visualized, for example, in the upper right-hand graph of Fig. 1, which shows that the inverse of TV parallels ICP$_{24}$ (i.e., the mean ICP that occurs in the following 24 h).

**A formula correlating circadian pattern of temperature with further ICP derived from the results**

From regression analysis, we obtained the formula 

\[ ICP_{24} = 23.9 - 6.22 \times TV \pm 6.2 \]

This confidence interval determines the slope in which the regression line, confidence interval (inner dashed lines), and prediction interval (outer dashed lines).

**Discussion**

The analysis of the ICP curve in head injury patients has been allowed the development of prediction models with up to 30 min of antecedence [7, 8].

The present results indicate that an alteration in the circadian rhythm may anticipate intracranial hypertension. One should bear in mind that the period during which a neurological patient undergoes therapeutic hypothermia is the most critical period of treatment, when episodes of intracranial hypertension are likely to occur. The results of this study seem to be particularly useful during this

**Table 2 Circadian patterns of temperature and intracranial pressure under hypothermia**

| Case # | Day of T monitoring | Diurnal T     | Nocturnal T   | TV          | Predicted ICP$_{24}$ | ICP$_{24}$ |
|--------|---------------------|---------------|---------------|-------------|-----------------------|------------|
| 1      | 1                   | 33.1365 ± 0.1016 | 33.1805 ± 0.0897 | 0.882       | 18.5 (16.7–20.3) | 16.9 ± 3.6 |
| 1      | 2                   | 33.0117 ± 0.212 | 33.1603 ± 0.0583 | 0.274       | 22.2 (20.3–24.1) | 24.2 ± 6.2 |
| 1      | 3                   | 33.1089 ± 0.0634 | 33.1012 ± 0.021  | 0.331       | 21.9 (20–23.8)  | 20.5 ± 3.8 |
| 1      | 4                   | 33.111 ± 0.0361 | 33.1035 ± 0.0247 | 0.684       | 19.7 (17.9–21.5) | 20 ± 2.5  |
| 1      | 5                   | 33.1142 ± 0.0388 | 33.1234 ± 0.0405 | 1.044       | 17.5 (15.7–19.3) | 20 ± 2.3  |
| 1      | 6                   | 33.1145 ± 0.1375 | 33.0374 ± 0.0694 | 0.506       | 20.8 (19–22.6)  | 24 ± 1.6  |
| 1      | 7                   | 33.0858 ± 0.0476 | 33.0935 ± 0.0938 | 1.970       | 11.7 (9.8–13.6) | 13.7 ± 6.9 |
| 1      | 8                   | 33.0643 ± 0.0342 | 33.0427 ± 0.0584 | 1.709       | 13.3 (11.5–15.2) | 11.5 ± 3.1 |
| 1      | 9                   | 33.1612 ± 0.0859 | 33.4189 ± 0.1192 | 1.377       | 15.4 (13.6–17.2) | 15 ± 2.3  |
| 1      | 10                  | 33.7116 ± 0.1166 | 34.2782 ± 0.2091 | 1.764       | 12.9 (11–14.7)  | 14 ± 2.5  |
| 2      | 6                   | 33.1231 ± 0.0954 | 33.0969 ± 0.0641 | 0.672       | 19.8 (18–21.6)  | 20.8 ± 2.3 |
| 3      | 1                   | 33.5335 ± 0.1086 | 33.5147 ± 0.0845 | 0.779       | 19.1 (17.3–20.9) | 16.8 ± 3.1 |
| 3      | 2                   | 33.5118 ± 0.078  | 33.5112 ± 0.068  | 0.872       | 18.5 (16.8–20.3) | 14.9 ± 1.7 |
| 3      | 3                   | 33.485 ± 0.0364  | 33.5293 ± 0.0555 | 1.523       | 14.5 (12.7–16.3) | 14.7 ± 2.4 |
| 3      | 4                   | 33.4787 ± 0.0831 | 33.7156 ± 0.1312 | 1.568       | 14.2 (12.4–16)  | 14.4 ± 2.4 |
| 3      | 5                   | 34.0214 ± 0.1698 | 34.55 ± 0.1982 | 1.149       | 16.8 (15–18.6)  | 15.9 ± 1.7 |
| 3      | 6                   | 34.7498 ± 0.105  | 35.0813 ± 0.1652 | 1.558       | 14.3 (12.4–16)  | 13.5 ± 2.6 |
ICP24 = 6(4 - TV) mmHg

ICP24 = (23.9 - 6.22 x TV) ± 1.73 \sqrt{1.06 + \frac{(TV - 1.1)^2}{4.49}}

(80% PI)
period, in cases in which a strict temperature control is maintained (please note that the maximum standard deviation of temperature in 12 h periods was 0.2).

The analysis of the ICP_{24} formula may guide the therapy in severe cases of subarachnoid hemorrhage. A caveat in this analysis is that ICP_{24} is a mean ICP value, and along a 24 h period it is possible that intracranial hypertension episodes take place. However, in our results we found a variability in ICP that in general did not exceed 20% of ICP_{24}. For example, the third quartile of the coefficients of variability of the 17 analyzed days equals 0.192, which means that in 75% of the analyzed days the standard deviation of ICP_{24} did not exceed 19.2% ICP_{24}. In this manner, it is highly probable that the patient will experience a day with episodes of intracranial hypertensive after a day with TV \leq 0.333. On the other hand, a day without episodes of intracranial hypertension is highly probable after a day with TV \geq 1. These predictions are suitable while the patient undergoes a relatively constant treatment and a strict mild hypothermia. Therefore, a clinical implication of this study may be that endovascular catheter-induced hypothermia may lead to more predictable ICP [9, 10].

It remains to be determined whether the circadian patterns of temperature correlate with further ICP under normothermia. A further parameter that could be tested according to the results of the ICP prediction under normothermic conditions is the ratio between mean temperature during night and the preceding diurnal period. This parameter was not suitable for ICP prediction due to the strict temperature ranges used to treat the enrolled patients. Nonetheless, this parameter could be assessed in a further study to investigate whether in determined circumstances it may serve to predict intracranial hypertension in the same way it predicts seizure in epileptic patients with 24 h of antecedence [5].

Likewise, perhaps other autonomic parameters correlate with further ICP in a manner not revealed in this study [5]. Blood pressure and heart rate display circadian pattern similar to temperature [11]. Heart rate variability has been shown to be a prognostic factor in conditions such as myocardial infarction [12]. Maybe the balance between the activities of the parasympathetic nervous system assessed by heart rate variability and of the sympathetic nervous system assessed clinically by electrodermal activity [5] may harbor a pattern that correlates with further ICP, although we did not find a correlation between autonomic parameter other than temperature and further ICP.

A major caveat of this study is that the method proposed here remains to be improved after confirmation of the results with the analysis of larger series with patients under different conditions, inclusion of other predictive factors, determination of confounders, and technical improvement of data acquisition and analysis. Accordingly, we studied data from a total of only 17 days of monitoring of three patients. To validate our findings with a retrospective study design, it would be necessary to make up a development cohort and a validation cohort sufficiently large to yield statistically significant results [7]. Moreover, it will be interesting to analyze larger series to test prediction models with different periods, statistical analyses, and neurological parameters. An endpoint of the algorithm could be for example the time when an episode of intracranial hypertension, if any, is likely to occur [13, 14].

Conclusions
In conclusion, the analysis of circadian patterns of autonomic functions may be a paradigm to predict intracranial hypertension in acute brain injury. Temperature seems to be the most remarkable autonomic function to this end, even when maintained in a strict range in patients under deep sedation.

Additional files

Additional file 1. Data regarding heart rate, blood pressure, and ICP. This Table shows the values obtained in the study. The variables obtained for temperature, HR, and mBP data from day 6 of monitoring of patient #2 and HR data from day 3 of monitoring of patient #3 displayed artifact and were not included in the Table. Legend: BPV, blood pressure variability, defined as the ratio between the standard deviation of mean blood pressure during the nocturnal period (18.00 to 6.00) and the preceding diurnal period (6.00 to 18.00); HRV, heart rate variability;
HRV_d, standard deviation of NN interval during the diurnal period; HRV_n, standard deviation of NN interval during 24 h; HRV_n/d, ratio between standard deviation of NN interval during the nocturnal and diurnal periods; ICP_24, mean intracranial pressure during 24 h after the monitoring day of HR and BP; mBP, mean blood pressure during 24 h.

Additional file 2. Statistical analysis (regression analysis, ANOVA) regarding correlation between heart rate and blood pressure variables with ICP_24. This Table shows that there is no statistical correlation between heart rate and blood pressure variables and intracranial pressure across the following day. Legend: BPV, blood pressure variability, defined as the ratio between the standard deviation of mean blood pressure during the nocturnal period (18:00 to 6:00) and the preceding diurnal period (6:00 to 18:00); HRV_d, standard deviation of NN interval during 24 h; HRV_n, standard deviation of NN interval during the nocturnal and preceding diurnal periods; ICP_24 mean intracranial pressure during 24 h after the monitoring day of heart rate and blood pressure.

Abbreviations
GOS: Glasgow outcome scale; ICP: intracranial pressure; ICP_24, mean ICP across 24 h following a day of temperature monitoring; TV: temperature variability.

Authors’ contributions
ABN: wrote the Grant, developed the method, analyzed data, and wrote the paper. EA, OB, FF, CS: collected data and reviewed the manuscript. EK: reviewed Grant application, collected and analyzed data, coordinated the study, and reviewed the manuscript.

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Competing interests
The authors declare that they have no competing interests.

Availability of data and materials
Data necessary for conclusions are available in the manuscript.

Consent for publication
Consent for publication was signed by the person legally responsible for the patient hospitalization.

Ethics approval and consent to participate
The study was carried out after the approval of the local Ethics Committee and the consent in participating in the study was signed by the person legally responsible for the patient hospitalization.

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