Comparison of intracranial pressure measured in the cerebral cortex and the cerebellum of the rat

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Abstract

In this study, we evaluated the accuracy of intracranial pressure (ICP) measurement in rats by insertion of a miniature ICP probe in the parenchyma of the cerebellum. A comparison was made between the ICP values measured simultaneously in the parenchyma of the cerebral cortex and the cerebellum. In order to obtain a wide range of ICP, animals were subjected to a severe closed head injury (CHI), a moderate CHI or to a sham operation. ICP values ranged from 0.8 to 43.9 mmHg. After 15 min stabilisation the first measurement was taken and followed by a second measurement 25 min after onset to allow comparison of ICP changes at the two implantation sites. Linear regression analysis showed a highly significant correlation at 15 min: $Y = 0.919X + 0.655$ ($R^2 = 0.977$), and at 25 min: $Y = 0.931X + 0.698$ ($R^2 = 0.976$). The differences in ICP measurement between cerebellar and cerebral site were not significantly different from zero at both time points. Altman–Bland plots showed that the difference in ICP readings between the two locations could differ maximally by 5.3 mmHg. The largest differences were detected when high ICP values were recorded. We conclude that in rats the ICP measurement in the cerebellum is comparable to the ICP measurement in the cerebral cortex. The cerebellar ICP can be used as a valuable alternative during experimental procedures. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Rat; Cerebellum; Cerebrum; Cortex; Neurotrauma; Intracranial pressure

1. Introduction

During the past 6 years, our research group has developed a rat model of closed head injury (CHI) that features several clinically relevant pathological changes, including increased intracranial pressure (ICP) (Engelborghs et al., 1998; De Mulder et al., 1999), disturbed autoregulation of cerebral blood flow (CBF) (Engelborghs et al., 2000), and increased sensitivity to hypoxia

(van Rossem et al., 1999a,b). Since the introduction of ICP measurement in 1951 (Guillaume and Janny, 1951) ICP has become an essential parameter in the assessment of severe head injuries. The therapeutic regimes are often instituted on the basis of ICP values. Measurement of intracranial pressure can be performed with various techniques based on different principles of pressure transformation. Strain gauge, piezo-resistive and fibre-optic probes are most commonly used today (Morgalla et al., 1999). In our laboratory, we have previously reported results using fibreoptic ICP measurement (Verlooy et al., 1990). Currently, the gold standard for ICP measurement in humans is a fluid-filled ventricular catheter. In small animals like the rat, this method of ICP measurement is difficult. Therefore

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we use a miniature ICP probe that is inserted in the cerebral parenchyma. [Morgalla et al. \(1999\)](#) have tested seven types of current ICP transducers under in vitro conditions for measurement accuracy. They conclude that most accurate probes were Haniset[®], Camino[®] and the Codmann[®]. Measurement accuracy for the Codmann[®] probe could deviate up to 5 mmHg, in the pressure group from 60 mmHg onwards.

In previous studies, we reported the use of the Codman[®] micro sensor probe to measure ICP after CHI in the rat ([Engelborghs et al., 1997](#); [De Mulder et al., 1999](#)). The probe was inserted into the cortical parenchyma of the right hemisphere. Insertion of a miniature probe can induce spreading depressions of cortical activity in the entire hemisphere with concomitant alterations in CBF, vascular responsiveness and metabolism ([Verhaegen et al., 1992](#)). When CBF and metabolism are parameters under investigation, such alterations need to be avoided. Moreover, when optical techniques such as near-infrared spectroscopy (NIRS) are used to evaluate cerebral oxygenation and perfusion, the insertion of a miniature probe may cause unwanted light scattering and induce small bleeds that can interfere with the measurements. In our laboratory we apply NIRS to measure cerebral oxygenation ([van Rossem et al., 1999a,b](#)) and perfusion in the rat ([De Visscher et al., 2002](#)) and study pathophysiological changes after traumatic brain injury ([van Rossem et al., 1999a,b](#)). As ICP probe placement in the cerebellum does not induce spreading depressions of cortical activity, and does not interfere with light transmission through the hemispheres this site is an alternative location for ICP recording, especially when simultaneous evaluation of cerebral oxygenation, CBF and metabolism is required.

The aim of the present study was to determine if the ICP measured in the cerebellum corresponds to the hemispheric ICP, in the rat.

2. Materials and methods

2.1. Animal treatment and preparation

Animal housing and treatment conditions complied with the European Directive #86/609 for animal welfare. Forty-five male Sprague–Dawley rats (Charles River, Sulzfeld, Germany), weighing between 370 and 490 g were used for the experiments. They were allowed free access to food and water and kept under a continuous 12/12-h day-night cycle. Anaesthesia was induced over 4 min with 4% isoflurane in a mixture of 30% O₂ and 70% N₂O. Subsequently, rats were endotracheally incubated and anaesthesia was maintained with 2% isoflurane during surgical procedures. The animals were divided into three groups of 15 animals. Each

animal of the 1st group received a severe CHI, those of the 2nd group received a moderate CHI whilst the final group received sham operations.

In the sham and moderate CHI group a 2 cm midline incision of the scalp was made and the periost removed to expose the bregma. After identification of the impact place on the bregma, the rat was transferred to the trauma device as previously described ([De Mulder et al., 1999](#)). To induce moderate closed head injury (CHI), a 400 g weight was dropped from a height of 50 cm. Shams underwent all of the above except the weight drop. Severe head injury was induced using similar apparatus, however with a silicon tip on the steel cylinder and the absence of an incision in the scalp of the rat. The rats were placed on a table and positioned using fixed ear bars. To induce severe CHI, the 400 g weight was dropped from a height of 70 cm ([Engelborghs et al., 1998, 2000](#)).

After CHI or sham procedure the head of the rats was fixed in a stereotaxic apparatus (model DK1962; Ultra Precise Small Animal Stereotaxic, Kopf Instruments, Germany) and a thermistor inserted into the tip of an ear bar was used to measure the tympanic temperature, providing an accurate measurement of brain temperature ([Brambink et al., 1999](#)). A rectal temperature probe was inserted to monitor body temperature, which was controlled with a heating pad connected to a temperature controller unit. The end tidal CO₂ (EtCO₂) and breathing rate were continuously monitored with an EtCO₂-monitor (Capnogard, Novametric, USA). The left femoral artery was cannulated to allow continuous monitoring of the mean arterial blood pressure (MABP) and heart rate (Argon Transducer, Maxxim Medical, Greece). Neck muscles were retracted and dissected until the occipital bone was exposed. In the severe CHI group, the scalp was removed at this time point. Possible sites of bleeding were cauterised to prevent excessive blood loss.

To measure cerebellar ICP, a burr hole of 2 mm was drilled into the right part of the occipital bone, 2 mm caudal of the cranial edge and 2 mm lateral from the midline, avoiding damage to the sagittal sinus. The first microsensor ICP probe (ICP Neuro microsensor; diameter 1.2 mm, length 4 mm; Codman & Shurtleff Inc., Randolph, MA) was attached to a micromanipulator. The tip was positioned in the sagittal plane with an angle of 35° relative to the horizontal plane and carefully inserted in the cerebellar parenchyma.

To measure cerebral ICP, a 2 mm burr hole was drilled into the right interparietal plate of the rat's skull 4 mm from the midline and 2 mm caudal to the bregma suture. The second microsensor probe attached to a micromanipulator was inserted in the cortical parenchyma with the sensor facing towards the midline. In a frontal plane, the probe was placed at a 70° angle to the

Table 1
Physiological variables at 25 min after onset of ICP measurement

	Sham	Moderate CHI	Severe CHI
Weight (g)	396 (384–430)	392 (384–402)	410 (394–430)
PO ₂ (mmHg)	130 (123–139)	108 (94.7–126) ^a	106 (96.4–128) ^a
PCO ₂ (mmHg)	46.4 (43.3–49.0)	48.4 (44.4–52.5)	50.6 (44.0–54.5)
pH	7.40 (7.39–7.40)	7.37 (7.36–7.42)	7.37 (7.33–7.39) ^a
MABP (mmHg)	104 (98–112)	90 (86–102) ^a	91 (81–103) ^a
Heart rate (BPM)	349 (323–393)	353 (318–407)	387 (309–412)
EtCO ₂ (mmHg)	54 (50–55)	55 (52–59)	58 (57–62) ^a
Breathing rate (BPM)	58 (55–62)	62 (57–65)	56 (49–59) ^b
Ear temp. (°C)	36.4 (36.1–36.7)	35.7 (35.0–36.2)	35.4 (34.8–36.1) ^a

Data are presented as median (95% CI). Except for the weight that was measured at the onset of the experiment, all variables were measured at 25 min after onset of ICP measurement. PaCO₂: arterial CO₂ pressure; PaO₂: arterial O₂ pressure; MABP: mean arterial blood pressure; EtCO₂: end tidal CO₂.

^a Significantly different from sham ($\alpha < 0.05$).

^b Significantly different from moderate CHI ($\alpha < 0.05$).

horizontal plane to avoid perforation of the lateral ventricle. Insertion depth of both probes was 4 mm.

After surgical preparation and the insertion of the ICP probes, anaesthesia was maintained with 1.5% isoflurane. ICP was then monitored continuously for 25 min. Subsequently an arterial blood sample (195 μ l) was collected for blood gas analysis (HBL 725, Radiometer), then the animal was sacrificed with a lethal dose of Nembutal. All data were collected with a MacLab[®] computer system (MacLab/8 MK3 Version 3.5, ADInstruments, Australia). Fifteen and 25 min after the onset of the ICP registration the mean value was calculated over a 30 s period. Statistical analysis was performed on two different time points, respectively 15 and 25 min after onset of the ICP measurement.

Statistical computations were performed using a commercially available software package for exact statistical inference (STATXACT 4.0.1 for Windows). The three groups were first compared using a Kruskal–Wallis test and when a significant difference was found ($\alpha < 0.05$) a two-sided Wilcoxon–Mann–Whitney rank-sum test was used for analysis between pairs of groups separately. Two-sided probability values of less than 0.05 were regarded as statistically significant. Bland and Altman (1986) analysis was used to evaluate the differences between the two ICP measurement sites and linear regression graphs were made to illustrate the correlation of the two measurements. A Wilcoxon signed rank test was used to test if the differences between both methods were significantly different from zero ($\alpha < 0.05$). As a test for normality of these differences, the Shapiro–Wilk W test, combined with a normal quantile plot (NQP) was used ($\alpha < 0.10$). Differences in ICP between 15 and 25 min are also shown in a linear regression graph.

3. Results

Table 1 shows the physiological variables at the end of ICP monitoring. In both the moderate and severe CHI groups, pO₂ and MABP were significantly lower than in sham treated animals. For pH, EtCO₂ and ear temperature only the severe CHI group showed significant differences compared to the sham group. The breathing rate in the severe CHI group was significantly lower than in the moderate CHI group.

Fig. 1 shows the data from the cerebral and cerebellar ICP measurement, at both 15 and 25 min. The four graphs are comparable and show similar distributions within each group. The ICP measurements from both the moderate and severe CHI group show a significant increase compared to the sham group.

Bland and Altman analysis, using both the 15 and 25 min ICP measurements, was used to compare the two methods for measuring the same variable (Fig. 2). The x -variable is an average of the two ICP measurements, because the average is a better estimate of the real value compared to both individual values. The y -variable is the difference between the new method and the established one, cerebellar ICP and cerebral ICP respectively. At 15 min, there was no indication that the differences were not normally distributed. At 25 min, however, both the Shapiro–Wilk W test and the NQP did not show a normal distribution. At both 15 and 25 min, the average value did not significantly differ from zero indicating that both methods of measurement are not significantly different and actually measure the same ICP.

Regression analysis from both the 15 and 25 min ICP measurements resulted in good correlation between both measurement sites (Fig. 2). The x variable was the established cerebral ICP and the y variable was our novel method; the cerebellar ICP. At 15 min the

Fig. 1. The four panels represent the data from the cerebral and cerebellar ICP measurement at 15 (left) and 25 min (right). Each panel contains the individual data ($n = 45$) divided into their treatment groups respectively. Next to the individual data the median with the 95% confidence interval is given. *Significantly different from sham ($\alpha < 0.05$).

following formula was calculated: $Y = 0.919X + 0.655$ ($R^2 = 0.977$). At 25 min: $Y = 0.931X + 0.698$ ($R^2 = 0.976$). As indicated by the R^2 -values, regression ana-

lyses on both time points resulted in a high correlation between the two methods of ICP measurement. The slope of both regressions is somewhat lower than 1, this

Fig. 2. The upper panels are the Bland and Altman plots at 15 and 25 min showing the difference between both measurements against their mean value. The dashed line represents the mean difference and the 95% confidence interval of the data lies between the dotted lines. The lower panels are the regression analysis plots for both timepoints. The line represents the regression line and the dashed line the 95% confidence interval of the regression. Linear regressions: ICP cerebellum 15' = $0.919 \text{ ICP cerebrum } 15' + 0.655$ ($R^2 = 0.977$) and ICP cerebellum 25' = $0.931 \text{ ICP cerebrum } 25' + 0.698$ ($R^2 = 0.976$).

Fig. 3. Changes of both cerebral and cerebellar ICP measurements in time plotted against each other. For both ICP measurements the differences (Δ) were calculated by subtracting the 15 min ICP measurement from the 25 min value. The cerebral (X) and cerebellar (Y) differences were then plotted against each other. The line represents the regression line and the dashed line the 95% confidence interval of the regression. Linear regression: $\Delta \text{ICP cerebellum} = 0.876 \Delta \text{ICP cerebrum} + 0.188$ ($R^2 = 0.970$).

is in part due to the fact that the cerebellar ICP underestimates the cerebral ICP when high ICP values are recorded. When we only use the sham data (lower ICP) the slope of the regression is approximately 1 (data not shown).

Regression analysis of ICP changes in time, between $t = 15$ min and $t = 25$ min, gave the following formula: $Y = 0.876X + 0.188$ ($R^2 = 0.970$) for all 45 animals (Fig. 3).

4. Discussion

This study shows that measurement of cerebellar ICP are comparable to those of the cerebral cortex ICP, under both normal and pathological circumstances. Trauma was used to create a wide range of ICP values. The absolute measurement of ICP in both sites correlates extremely well. The divergence is quite small compared to the actual measurement but tends to increase with increasing ICP, because the cerebellar ICP has the tendency to slightly underestimate high cerebral ICP's. The Bland and Altman plots (Fig. 2) show that both methods of ICP measurement do actually measure the same ICP. If the novel technique measures the same ICP as the established technique it should also respond to changes in ICP in the same way. Although this experiment was not specifically designed to study these responses, we looked at normally occurring ICP changes over time with both techniques and compared those. The differences at both time points

were not significantly different from zero. Here we can conclude that the results from both methods of ICP measurement change similarly when the ICP changes. The obtained slope, for time related changes of ICP, is somewhat smaller than 1. This was caused by the somewhat blunted response of the cerebellar ICP when larger cerebral ICP changes occur. Except for one, these larger changes could only be found in the higher ICP measurements where we had already noted that the cerebellar ICP measurement tends to be somewhat lower than the cerebral ICP measurement. The central cloud in Fig. 3 ($n = 40$) which corresponds to small changes in both ICP measurements has a slope that is approximately 1, indicating a good response of the novel method to smaller ICP changes. This implies that the cerebellar site can also be useful to evaluate the effect of pharmacological interventions that influence ICP.

The positioning of the ICP probe in the cerebellum instead of the cerebral parenchyma has several advantages. Firstly, the cortical area remains intact, thus precluding electrophysiological, metabolic or cerebrovascular changes due to spreading depression of cortical activity. These changes are present hours after insertion of a probe with a diameter larger than $50 \mu\text{m}$ (Verhaegen et al., 1992). The Codman probe has a diameter of 1 mm. Secondly, there is no interference with light transmission and scattering in the cortical area when the probe is placed in the cerebellum. Thirdly, bleeding due to drilling and probe insertion that can interfere with NIRS measurements are avoided. Practically, cerebellar ICP probe placement makes positioning the

NIRS optodes easier compared to when the probe is stereotactically placed in the cortex. This experimental set-up makes it possible to simultaneously study CBF, oxygenation and ICP. This may provide very valuable information about the pathophysiologic changes and effects of pharmacological treatment of intracranial hypertension.

To conclude; in experimental studies in rats, where insertion of a cerebral probe should be avoided, cerebellar ICP measurement is a very useful and valuable alternative to the cerebral ICP measurement.

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