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Progress of intracranial pressure and cerebral perfusion pressure in patients during the development of brain death

Christian Roth[a,b,*], Andreas Ferbert[c], Johannes Matthaei[a], Stefanie Kaestner[d], Holger Engel[e], Markus Gehling[f,g]

[a] Department of Neurology, DRK-Kliniken Nordhessen, Kassel, Germany
[b] Department of Neurology, University of Marburg, Germany
[c] Department of Neurology, Klinikum Kassel, Kassel, Germany
[d] Department of Neurosurgery, Klinikum Kassel, Kassel, Germany
[e] Department of Plastic-Reconstructive, Aesthetic and Handsurgery, Klinikum Kassel, Kassel, Germany
[f] Department of Anesthesiology, University of Marburg, Marburg, Germany
[g] Pain Center, Kassel, Germany

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ABSTRACT

Background: Clinical investigations of brain death are supposed to prove absence of cerebral perfusion. However, only limited data are available documenting intracranial pressure (ICP) and cerebral perfusion pressure (CPP) during the development of brain death. Our study presents additional data to understand the course of ICP and CPP in patients developing brain death.

Material and methods: We analyzed retrospective data of 18 patients with ICP monitoring during the development of brain death due to primary brain lesions. ICP and CPP values were continuously measured between two clinically defined time points: 1. non-reactive and widened pupils, 2. brain death determination. We analyzed ICP and CPP at the above-mentioned end points. Additionally, we investigated maximum ICP and minimal CPP values between these time points.

Results: Patients developed fixed and dilated pupils with a median of 38 h before brain death determination. During brain death determination median ICP and median CPP were 103.5 and –2.5 mmHg, respectively. Maximum ICP before brain death determination was significantly higher and minimal CPP values were significantly lower compared to the time point of brain death. During the investigation period all patients experienced ICP values > 95 mmHg and CPP < 10 mmHg. All but one patient had documented CPP values of ≤ 0 mmHg. This single patient had a minimum CPP of 8 mmHg with a maximum ICP of 145 mmHg.

Conclusion: Cerebral perfusion pressure during brain death determination may be positive in some patients. Our results showed variable values of ICP and CPP. However, extremely elevated ICP values before or during brain death in combination with low CPP values suggest absence of cerebral perfusion. The occurrence of positive CPP values during brain death determination therefore depends on the time point at which brain death determination is performed.

1. Introduction

The concept of brain death is discussed controversially both in the public view and in medical literature, [1–3].

The concept of brain death is defined as irreversible loss of cerebral functions. However, most guidelines consider that cerebral blood flow may be sustained, though cerebral function has terminated, as compatible with brain death. Some authors have raised concerns of persisting cerebral perfusion in some patients. This could result in minimal chance of cerebral survival [4]. On the other hand, a majority of clinicians regard brain death determination as a valued instrument and the brain death concept is emphasized by the law in many countries. Since the consequence of brain death determination are irreversible, any source of mistakes should be ruled out.

Intracranial pressure monitoring is one of the key aspects in neurocritical care and it is recommended, especially in comatose patients who are at risk of elevated intracranial pressure [5,6]. Elevated intracranial pressure (ICP) refractory to treatment and low cerebral

* Corresponding author at: Department of Neurology, DRK-Kliniken Nordhessen, Hansteinstraße 29, 34121 Kassel, Germany.
E-mail addresses: roth99@web.de, roth@drk-nh.de (C. Roth).

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perfusion pressure (CPP) is a strong predictor for poor outcome and high mortality [6]. However, data of ICP and CPP during brain death are very scarce in the literature [3,7–10]. Some authors has suggested ICP monitoring as a complementary test for brain death [11]. However, while there are clear clinical signs of cerebral herniation leading to brain death, threshold values for ICP and CPP determining brain death are missing. Cerebral circulation arrest has been postulated in brain death [12,13]. With ICP exceeding mean arterial pressure, there is no positive CPP. In contrast to these theoretical considerations, real life data has revealed patients with slightly positive CPP values during brain death [7,9].

Based on a retrospective analysis of data from our neurological intensive care patients we have investigated ICP and CPP values during the process of brain death determination.

2. Material and methods

2.1. Study design and setting

We report the results of a retrospective observational study. All patients were treated on our 12-bed Neurological intensive Care Unit in a tertiary hospital in Germany (Department of Neurology and Department of Neurosurgery, Klinikum Kassel). Data analysis was performed retrospectively including charts obtained between 2012 and 2017. The study was approved by the ethics committee of the local state medical chamber (Landesärztekammer Hessen, Germany).

2.2. Patients

We included patients in whom brain death was confirmed and in whom ICP/CPP measurements were available. We excluded patients with incomplete data. Patient's data were enrolled into the study if the medical records included continuous data of ICP and CPP for > 24 h before brain death determination. Patients with insufficient data (missing ICP and CPP values for intervals of > 4 h) were excluded. Pupils reaction are observed and documented in the patients chart hourly on our intensive care unit. The investigation period comprised the time between the first observation of fixed and dilated pupils and definite brain death. The control of pupil reaction was performed by specially trained neuro-intensive care nurses. Direct and indirect reactions were controlled by a standard lamp (0,25 watt = 2,5 lm). All other brainstem reflexes are observed only three times a day by the neuro-intensivist in charge. Therefore, these were not considered in this study. Brain death diagnosis was based on the actual recommendations of the Scientific Advisory Board of the German Federal Chamber of Physicians. After exclusion of confounding factors clinical examination was performed by two neuro-intensivists documenting unresponsive coma, loss of brainstem reflexes and apnoea by reaching a $PaCO_2$ threshold of at least 60 mmHg in blood gas analysis. Irreversibility of brain death was proven using ancillary tests in all patients. The syndrome of isolated brain-stem death does not fulfill the criteria of brain death in Germany. Therefore, in patients with primary infratentorial lesions irreversibility must be shown by one of the following ancillary tests: EEG, CT-angiography, ultrasound of the cerebral vessels or cerebral scintigraphy.

2.3. Monitoring and data recording

ICP measurement was performed using intraparenchymal ICP monitoring (Neurovent-P, Raumedic AG, Muenchberg, Germany). According to the manufacturer's information these ICP tubes are proven for pressure measurement from −40 mmHg up to 400 mmHg with a maximum shift of 2.5 mmHg in the case of values above 100 mmHg. ICP and CPP were recorded continuously (Infinity Delta, Draeger, Germany). The indication for ICP monitoring was based on the underlying brain disease and was confirmed by the neurointensivist in charge. The probe was placed unilaterally at the Kocher point contralaterally to the brain lesion. Blood pressure was measured invasively by percutaneous radial artery cannulation. In our institution the transducer is placed level with the patient's heart to avoid incorrect catecholamine therapy. Supine position with 30° head elevated was maintained in all patients. CPP was calculated automatically as the difference between mean arterial pressure (MAP) and ICP. To exclude false-low measurements of MAP for example in cases of subclavian or axillary artery stenosis we previously conducted a non-invasive blood pressure measurement on both sides. In cases with strongly elevated ICP values reaching values higher than MAP negative CPP may be calculated. ICP and CPP values as well as pupil size and their light reaction were hourly documented in the patient's charts.

2.4. Analysis

ICP and CPP values were continuously measured between two clinically defined time points: 1. non-reactive and widened pupils, 2. brain death determination. We analyzed ICP and CPP at the above-mentioned end points. Additionally, we analyzed maximum ICP and minimal CPP values.

2.5. Statistics

Data were analyzed using Graph Pad 6.0. We used a column statistic approach. First, we checked normal distribution (D'Agostino & Pearson omnibus normality test, Shapiro-Wilk normality test and KS normality test). Since normal distribution could not be confirmed for all columns we decided to use normality-free statistical analysis for paired columns (Wilcoxon test). A p value < .05 was assumed to be significant. All values are expressed as mean and standard deviation.

3. Results

During the study period a total of 71 patients underwent brain death determination. 23 patients received additional ICP monitoring. 5 patients were excluded due to missing data, leaving 18 patients for analysis.

The patients median age was 56 years, ranging from 26 to 71 years (female:male = 11:7). Brain death was diagnosed with a median of 5 days after hospital admission (range 1–16 days). The underlying diseases were subarachnoid hemorrhage (n = 9), intracerebral hemorrhage (n = 5), traumatic brain injury (n = 3) and malignant cerebral stroke (n = 1). Decompressive hemicraniectomy was only performed in one patient with intracerebral hemorrhage. Thirteen patients had primary supratentorial brain lesions and 4 patients had combined supra- and infratentorial brain lesions. Only one patient suffered from primary infratentorial brain lesion. Irreversibility of brain death was confirmed by ancillary tests in all patients. In one patient CT-angiography was performed whereas in all other patients EEG was used. Twelve patients developed central diabetes insipidus. Organ donation was performed in 12 cases after brain death determination. Median apnoea time was 10 min (range 7–21 min). During apnoea ventilation a median pCO2 of 63.5 mmHg (range 60–81 mmHg) and a median pO2 of 320.5 mmHg (range 90–501 mmHg) was reached, respectively. Fixed and dilated pupils were documented with a median of 38 h before brain death determination (range 1–96 h). Maximum ICP and minimum CPP were observed 17 h (range 1–53 h) and 14 h (range 1–53 h) before brain death determination, respectively.

The results are shown in Tables 1 and 2. Half of the patients showed positive CPP values during brain death determination, with a median CPP of −2.5 mmHg ranging from −43 to 32 mmHg. ICP at this time point ranged from 62 to 158 mmHg (median 103.5 mmHg). ICP during brain death determination was significantly lower than previous values of maximum ICP (103.5 mmHg versus 148.5 mmHg, p < .0001) (Fig. 1). All patients experienced a maximum ICP value of at least

Table 1
Intracranial pressure (ICP) values of 18 patients developing brain death. Significant differences were found when comparing the different time points of fixed and dilated pupils, maximum intracranial pressure and brain death determination with one another.

	Pupils fixed and dilated	Maximum ICP	Brain death determination
Number of values	18	18	18
Median ICP (mmHg)	70,5	148,5	103,5
Std. Deviation	25,36	31,2	27,8
Minimum ICP (mmHg)	10	96	62
Maximum ICP (mmHg)	102	192	158
p-value compared to fixed pupils		0.0001	0.0001
p value compared to max. ICP	0.0001		0.0001
p value compared to brain death	0.0001	0.0028	

Table 2
Cerebral perfusion pressure (CPP) values of 18 patients developing brain death. Significant differences were found when comparing the different time points of fixed and dilated pupils, maximum intracranial pressure and brain death determination with one another.

	Pupils fixed and dilated	Minimal CPP	Brain death determination
Number of values	18	18	18
Median CPP (mmHg)	29	−18	−2,5
Std. Deviation	25,97	24,93	21,4
Minimum CPP (mmHg)	1	−101	−43
Maximum CPP (mmHg)	96	10	32
p-value compared to fixed pupils		0.0001	0.0001
p value compared to min CPP	0.0001		0.0125
p value compared to brain death	0.0001	0.0125	

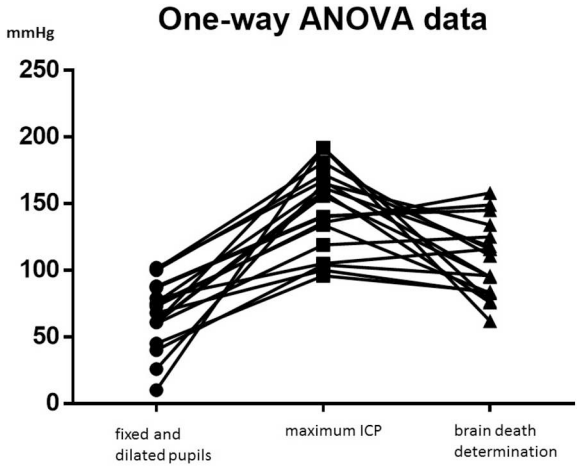

Fig. 1. ICP of all patients during three different time points showed significantly different values.

96 mmHg.

CPP values decreased significantly until brain death determination. CPP during brain death determination was significantly higher than previously obtained values of minimal CPP (−2.5 mmHg versus −18 mmHg, $p < .0125$) (Fig. 2). All but one patient reached CPP values of ≤0 mmHg. A single patient with a supratentorial lesion had a minimum CPP of 8 mmHg and a maximum ICP of 145 mmHg. Overall, all patients had either ICP > 100 mmHg or CPP ≤ 0 mmHg.

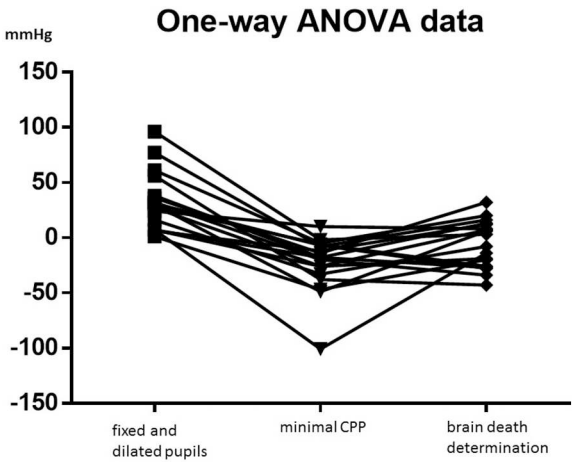

Fig. 2. CPP of all patients during three different time points showed significantly different values.

Fig. 3 shows typical progression of ICP, CPP and MAP values until brain death determination and before organ donation.

4. Discussion

In our study we investigated ICP and CPP development continuously between the time points of fixed and dilated pupils, and brain death determination. Although ICP at brain death determination ranged from 62 to 158 mmHg, all patients experienced highly elevated ICP values of ≥96 mmHg during the total observation period, supporting the notion of brain death. Median CPP at brain death determination was −2.5 mmHg, suggesting cerebral circulation arrest. However, half of the patients showed slightly positive CPP values at this time point. Interestingly, all but one patient showed CPP values equaling zero before brain death determination.

Although animal models exist [14–17], there are only few studies investigating ICP and CPP during brain death in humans [7,9,10,18,19]. Comparable to our findings, they all showed elevated ICP. ICP reached values of about 100 mmHg or more during brain death determination. This was also true for patients with decompressive hemicraniectomy [8]. Based on single cases ICP monitoring has been suggested as complementary test for brain death [11]. However, larger studies have yet to be performed. On the other hand, there are a few cases in the literature with severe brain lesions, transient highly elevated ICP values up to 50 mmHg, and acceptable clinical outcome [20]. Von Leyden was the first to recognized the relationship between increased ICP and dilated pupils in his experimental animal studies in 1866 [17]. Therefore, fixed and dilated pupils if evolving under observation in association with a space-occupying brain lesion are accepted as sign of cerebral herniation due to increased ICP [16]. In our intensive care unit it is evaluated regularly every hour. Therefore, we chose fixed dilated pupils as a clear starting point for our investigation.

CPP represents the pressure gradient driving cerebral blood flow. A CPP equal to zero indicates absence of cerebral perfusion, which has been postulated in brain death [21,22]. However, some patients show slightly positive CPP values during brain death, even in patients without confounding factors such as decompressive hemicraniectomy or external ventricular drainage. The collapse of cerebral veins has been proposed to lead to stasis of blood flow with further increase of ICP [23,24]. This mechanism might also lead to cerebral circulation arrest due to secondary brain edema. Different explanations have been considered. Some authors prefer the hypothesis of critical closing pressure [9] which is defined as the arterial pressure threshold below which arterial vessels collapse. We suggested the phenomenon of stasis filling [7] leading to positive CPP which has been described in CT-

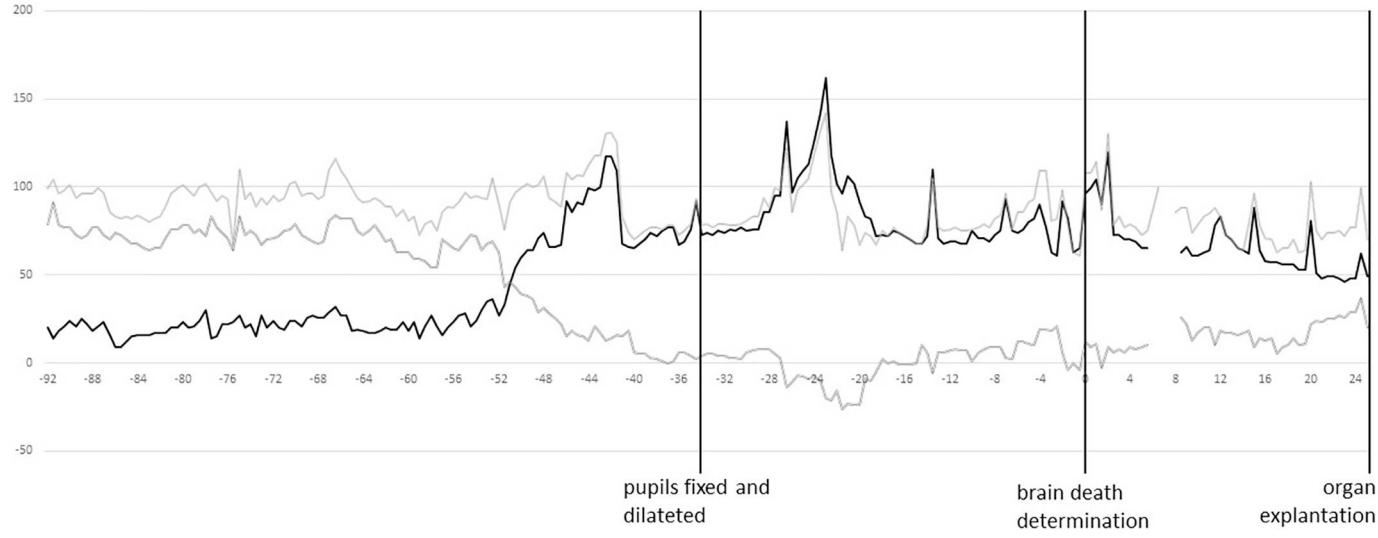

Fig. 3. Example of a patient during intensive care treatment. ICP (black), CPP (mid-grey) and MAP (light grey) values in mmHg before and after brain death determination up until organ donor. X axis indicates time interval in hours. Time of brain death determination is defined as 0. Maximum ICP values and negative CPP values are reached hours before brain death determination. During brain death determination CPP values were positive.

angiography studies [13]. A low cerebral blood flow beyond the detection level of conventional angiography is supposed to fill segments of the medial cerebral artery. In our study, all but one patient developed CPP values of ≤ 0 mmHg hours before brain death determination. In this single patient the minimal CPP was very low with a minimal value of 8 mmHg. This value may be explained by the fact that we placed the MAP transducer at the level of the heart. Generally, lower CPP values could be expected with the MAP transducer placed at level of foramina of Monro. Furthermore, the maximum ICP was highly elevated with a value of 146 mmHg. Overall, all patients had either ICP $>$ 100 mmHg or CPP $\leq$ 0 mmHg. Thus, we consider that these values do not represent persisting brain tissue perfusion in any of our patients.

ICP and CPP values vary within the course of brain death development and even after brain death determination, as shown in Fig. 3. Time point of brain death determination is set freely and might even be influenced by availability of clinicians to do the tests. It differs from the time point brain death occurs, which may be at the time of maximum ICP or even shortly after it. The presence of positive CPP values during or after brain death determination therefore depends on the time point at which brain death determination is performed.

Our results highlight further aspects of brain death. Most physicians regard apnoea testing as an integral part of brain death determination. Some authors have postulated an additional rise of ICP due to apnoea testing and therefore a potential hazard in patients with severe brain lesions [4]. Recently, we were able to show that ICP in brain death patients strongly correlates with mean arterial pressure (MAP) [7]. Therefore, ICP may rise under apnoea ventilation in correspondence with increasing MAP values in some patients. Our results provide important information about ICP and CPP development in patients with severe brain lesions before brain death. A potential hazard due to apnoea ventilation seems to be implausible considering the extremely elevated ICP levels or CPP values equal to zero before brain death determination in all patients.

The design of a retrospective analysis has certain limitations. Our study may additionally be limited due to restricted sample size. ICP and CPP values were available from the patient's chart at an hourly interval only. Maximum ICP elevation may not be documented exactly. On this basis, even higher maximum ICP values may be assumed. In addition to absolute ICP values, the total duration of ICP elevation also plays an important role in causing brain damage. However, duration of ICP elevation has not been taken into account in our study. Furthermore, all but one of our patients had primary supratentorial or combined brain lesions, suggesting transtentorial herniation as a common pathophysiological pathway with highest ICP levels in the cerebrum. ICP monitoring was performed by intraparenchymal probes placed in all patients. ICP and CPP may vary in primary infratentorial lesions. Furthermore, this study was not designed to confirm thresholds of ICP and CPP values during brain death determination. Therefore, angiography was not generally performed as ancillary test for brain death irreversibility.

ICP and CPP measurement are not standard diagnostics in brain death determination. We analyzed the values of 18 patients during the course of ICU therapy until brain death. Our results showed variable values of ICP and CPP. However, extremely elevated ICP values before or during brain death in combination with low CPP values suggest an absence of brain perfusion. Even though measurements of ICP/CPP do not represent the true cerebral blood flow, they help us to understand the process of brain death development. Our data support the concept of brain death and cerebral circulation arrest.

Disclosures

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