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Time-dependent ICP-thresholds in patients undergoing decompressive craniectomy

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Inhalt

1. Publication

Intracranial pressure in patients undergoing decompressive craniectomy - new perspective on thresholds

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1.1 Abstract

Objective: Decompressive craniectomy (DC) is an established part of treatment in patients suffering from malignant infarction of the middle cerebral artery (MCA) or traumatic brain injury (TBI). However, no clear evidence for intracranial pressure (ICP)-guided therapy after DC exists. This lack of this evidence might be due to the frequently used, but simplified threshold of 20 mmHg, which determines further therapy. The objective of this study was therefore to evaluate this threshold's accuracy and to investigate the course of ICP-values with respect to the neurological outcome.

Methods: Data on clinical characteristics and parameters of the course on the intensive care unit were collected retrospectively in 102 patients who underwent DC from December 2007 through April 2014 in our institution. The postoperative ICP-course in the first 168 hours was recorded and analyzed. From these findings ICP-thresholds discriminating favorable from unfavorable outcome were calculated using conditional inference tree analysis. Additionally, survival analysis was performed using the Kaplan-Meier method. Prognostic factors were assessed via univariate analysis and multivariate logistic regression. Favorable outcome was defined as a score of 0–4 on the modified Rankin scale.

Results: Multivariate logistic regression revealed that anisocoria, diagnosis and ICP-values differed significantly between the outcome groups. ICP-values in the favorable and unfavorable outcome groups differed significantly ($p < 0.001$), while the mean ICP of both groups lay below the limit of 20 mmHg (17.5 and 11.5, respectively). These findings were reproduced when analyzing the underlying pathologies of TBI and MCA infarction separately. Based on these findings, optimized time-dependent threshold values were calculated, lying between 10 and 17 mmHg. These values significantly distinguished favorable from unfavorable outcome and predicted 30-day mortality ($p < 0.001$).

Conclusions: Our study systematically evaluated ICP-levels in a long-term analysis after DC and

provides new, surprisingly low, time-dependent ICP-thresholds for these patients. Future trials investigating the benefit of ICP-guided therapy should take these thresholds into consideration and validate them in further patient cohorts.

1.2 Introduction

Decompressive craniectomy (DC) has been a well-established neurosurgical intervention for more than 100 years in patients suffering from space-occupying cerebral infarctions of the middle cerebral artery (MCA) and leads to reduced intracranial pressure (ICP).[23] DC verifiably prevents secondary brain injury, optimizes perfusion of the penumbra and results in an overall reduction in mortality and an improvement in functional recovery, especially in younger patients.[22,40] The lifesaving benefit and outcome improvement of the DC has been proven by several randomized-controlled studies in the past.[16,21,22,40] DC is also a common treatment in patients with traumatic brain injury (TBI), although clear evidence from prospective clinical trials is still missing.[10,34]

Regardless of the underlying diagnosis, brain ischemia and injury may lead to an increased ICP caused by cerebral edema.[8] ICP-monitoring is generally recommended for patients with severe TBI.[2,38] There are no guidelines for ICP-monitoring in patients suffering from malignant MCA infarction, but ICP-monitoring after DC is often part of further therapy in the intensive care unit (ICU).[20]

Although ICP-monitoring is a common practice, there is no level I evidence for the benefit of ICP-monitoring and ICP-guided therapy. A recently published prospective-controlled trial failed to fill this void.[9] BEST TRIP showed that ICP-guided treatment does not lead to increased therapeutic success compared with a CT-based clinical assessment.[9] The authors of this study expressed concern that these findings may lead to a premature end of ICP-monitoring in ICUs and noted that the failure of ICP-guided therapy may be due to simplified strategies and the lack of evidence for 20 mmHg as the threshold, although this determines further therapy.[6,7]

This lack of evidence and the simplified threshold of 20 mmHg should be questioned even more in patients after DC, since the integrity of the skull is compromised and the physical preconditions are completely different. Factors associated with favorable outcome are still a matter of debate and ICP-recordings did not sufficiently correlate with the neurological outcome.[31,37] It is undisputed that ICP decreases rapidly after DC in TBI or MCA infarction patients,[29] but little data is available on the ICP-course following DC, since most studies evaluated only a small number of patients with a limited recording of ICP-values.[24,28,30,31,37] In particular, the validity of the ICP-threshold has not been addressed thoroughly. The present recommendations regarding ICP-thresholds do not take surgical interventions into consideration or the lack of clear evidence.[3,20]

The aim of this single-center study was to analyze the ICP-level and -course after DC in cerebral infarction and TBI patients and to correlate these parameters with the neurological outcome. Particular emphasis was placed on the evaluation of the commonly accepted threshold of 20 mmHg.

1.3 Material and Methods

This single-center study retrospectively analyzed patients who underwent unilateral decompressive craniectomy from December 2007 through April 2014. In order to increase comparability, only TBI patients with an acute subdural hematoma causing a critical mass effect on the brain were enrolled in this study. Procedures that were not comparable due to the use of a different surgical technique (bifrontal decompressive craniectomy) or patient criteria (age < 14 years, death before arriving on ICU) were excluded. The patients' postsurgical ICP-values for the next 168 hours following DC as well as their functional outcome, assessed via the modified Rankin Scale (mRS) at the end of rehabilitation, were analyzed. Favorable outcome was defined as a score of 0–4 on the mRS according to Vahedi et al. (2007).[40] This study was conducted according to the Declaration of Helsinki, local and institutional laws and was reported to the local ethics committee.

Clinical data

Demographic and clinical data were collected, including sex, age, primary diagnosis, side and size of DC, pupillary status, duration of sedation, Glasgow Coma Scale (GCS) and National Institutes of Health Stroke Scale (NIHSS), respectively.

The patients' level of sedation was measured using the Richmond Agitation Sedation Scale (RASS), and logged initially after DC and subsequently once every 24 hours.[36] The presence of postoperative anisocoria was recorded.

To determine the patients' morbidity, the Simplified Acute Physiology Score (SAPS II) on the day of surgery was analyzed.[25] SAPS II was calculated semi-automatically via the clinical information system (Integrated Care Manager, Dräger, Lübeck, Germany), which filters all relevant data in a given 24-hour period for the worst value.

The size of the trepanation (A) was calculated by $A = \pi/4 \times b \times c$, where b is the maximal fronto-occipital and c the maximal parieto-temporal extent of the defect.[11] These data were collected on postoperative CT-scans.

Treatment

Indication for surgical decompression in TBI patients with acute subdural hematoma followed the recommendations of Bullock et al. and/or the German TBI Guidelines (AWMF 2015) based on the clinical status (age, GCS, anisocoria) and CT-scan (thickness of SDH, midline shift) in an interdisciplinary case-by-case discussion.[4,14] If a DC was indicated, surgery started as soon as possible. Concurrently, conservative treatment started following a standardized protocol. Blood gases were analyzed frequently (at least every 4 hours). Continuous monitoring of electrocardiography, oxygen saturation, arterial blood pressure and respiratory minute volume and tidal volume was performed.

In patients suffering from MCA infarction at risk for a malignant clinical course, the indication for early DC was verified by the senior neurosurgeon and the senior neurologist in charge. The decision was based on the patient's characteristics (age, medical history, laboratory findings), neurological condition (clinical examination, NIHSS, GCS), imaging, exhausted conservative

treatment, time since onset of the neurological symptoms and clinical deterioration according to the treatment guidelines.[18]

Postsurgical treatment on ICU included ICP-guided therapy according to current guidelines.[20] This treatment included elevation of the head by 20°–30°, hemodynamic stabilization in order to avoid hypotension (systolic blood pressure <90 mmHg) and hypoxia (paO_2 < 60 mmHg), sedation and hyperosmolar therapy. Patients were ventilated in BIPAP-mode (Evita Infinity® V500 Ventilator – Dräger, Lübeck, Germany) with the aim of maintaining physiological pH and lower normal $PaCO_2$ (35–38 mmHg).

Decompressive craniectomy and ICP-monitoring

A question mark-shaped skin incision was made fronto-parieto-temporal, ending approximately 10 mm anterior of the tragus, followed by retraction of the musculocutaneous flap, removal of the bone flap and dural opening.[19,34] Before readapting the temporalis muscle and scalp flap, an intraparenchymal ICP-monitor (Codman MicroSensorTM, Johnson & Johnson Professional Inc., Rayham, MA) was placed ipsilaterally at the end of surgery according to the recommendations of the Milan consensus conference on ICP-monitoring and current guidelines.[20,38]

ICP-values and mean arterial pressure were measured continuously. Based on these measurements, CPP-values were calculated. These measurements were performed automatically and stored in the clinical information system (ICM) beginning at arrival in the ICU. Hourly ICP- and CPP-values were extracted for the first 168 hours following DC and used to perform further statistical analyses. A total of more than 22000 ICP- and CPP-values were analyzed in this study.

Statistical analysis

Continuous data are presented as means and range. The Wilcoxon rank-sum test was used to compare non-parametric values. Comparisons including multiple ICP-values were corrected for repeated measures. Categorical data are presented as counts and percentages and were compared using chi-square and Fisher's exact test. The prognostic significance of the models was analyzed via multivariate logistic regression. ICP-thresholds were assessed using conditional inference

tree analysis.[17] Survival analysis was performed using the Kaplan-Meier method and log-rank test. Statistical analyses were performed using IBM SPSS® v. 19 (IBM Corp., Armonk, NY, USA) and MATLAB R2014b® (The MathWorks, Inc., Natick, MA, USA). Probability values of $p < 0.05$ were considered statistically significant.

1.4 Results

A total of 102 patients (38 females; 37.3%) were included in this study. The mean age of the cohort was 53.2 years (range 14 - 79). Fifty-seven patients underwent DC due to a space-occupying MCA infarction and 45 patients suffered from an acute subdural hematoma due to severe TBI. In detail, 33 patients (73.5%) suffered from an acute subdural hematoma (SDH) with a thickness of more than 10mm and/or a midline shift of more than 5mm regardless of the patients' Glasgow Coma Scale (GCS), while eight comatose patients (17.8%) presented with a SDH of less than 10mm thickness and a midline shift of less than 5mm but presented with either a drop in the GCS of more than 2 points or asymmetric or fixed and dilated pupils. In four patients the decision was based on a clinical decision according to the German TBI guidelines.

Forty-two patients (41%) showed a favorable outcome at the end of rehabilitation (mean follow-up of 129 days after DC). No statistically significant differences between the outcome groups were detected regarding sex, age, side of DC, size of trepanation, GCS, NIHSS, RASS, SAPS II or presence of an external ventricular drain (Table 1). External ventricular drains were only present in four patients in the unfavorable outcome group (two patients with mRS 6). Univariate analysis revealed that anisocoria and diagnosis differed between the outcome groups.

In 91.2% of the MCA infarction patients, DC was performed within the first 72h after onset of the neurological symptoms and 75.4% within the first 48h.[18] We performed a subgroup analysis and compared clinical characteristics and outcome in patients with DC <48h versus patients in whom DC was performed >48h after stroke onset. We found no significant differences regarding

age (p=0.977), NIHSS (p=0.231), anisocoria (p=0.708), mean ICP (p=0.330), SAPS II (p=0.992) or mRS (p=0.303).

ICP-analysis of the first 168 hours:

The mean ICP-values in both outcome groups were analyzed. Figure 1 shows an ICP-versus-time plot of the first 168 hours after DC. The ICP-values of the favorable outcome group started and remained at lower levels than those of the unfavorable group. Values did not exceed 14 mmHg (mean 11.5 mmHg; maximum 13.4 mmHg) at any point.

The ICP-values in the unfavorable group were higher, but rarely exceeded 20 mmHg (mean (168h) 17.5 mmHg, range 10.7–25.0). In the first 72 hours, the ICP-values of the unfavorable group were below 20 mmHg (mean (72 h) 17.2 mmHg). The mean ICP-values crossed the 20 mmHg threshold on only 11 (15.1%) occasions. In 31 (51.7%) patients with an unfavorable outcome, the ICP-values did not exceed 20 mmHg at any point during the first 3 days. When corrected for repeated measures, statistical analysis revealed a significant difference ($p < 0.001$) between the two groups. In the last few hours of ICP-measurement, the curves began to approximate each other. The mean ICP-curves were also analyzed separated by diagnosis. In both subgroups the mean ICP in the first 168 hours was below 20 mmHg in the favorable and unfavorable outcome group. More precisely, the ICP-values of the favorable outcome remained below 15 mmHg regardless of the underlying diagnosis. For more details see Figure 2.

In the following sections, only the results of analyses of ICP-values are presented since the analysis of CPP-values did not provide additional information in our cohort (for an overview of the CPP-course see Supplementary Fig. 1).

Predictive power analysis (ROC):

Based on the results of the univariate analysis, diagnosis, anisocoria and the mean ICP in the first 12 hours were tested further regarding their prognostic value using multivariate logistic regression. Figure 3 shows the predictive power of diagnosis, ICP and anisocoria compared with diagnosis and SAPS II as a validated score to assess hospital mortality regardless of the

underlying diagnosis.[15,25,33] Combining diagnosis, ICP and anisocoria resulted in a significantly larger AUC (0.837 vs. 0.707; $p < 0.001$), while adding SAPS II to the calculation did not further improve its significance (data not shown).

Threshold analysis:

Since the mean ICP-values of both outcome groups lay clearly below 20 mmHg and their predictive power could be demonstrated, new threshold values discriminating the outcome groups were calculated. These optimized threshold values were determined by conditional interference tree analysis in several time periods (Figure 4). Twelve-hour time frames were used for the calculation. Due to the dynamics of the ICP-values, 6-hour intervals were chosen in order to achieve better resolution during the first 48 hours. These new thresholds lay between 9.8 mmHg and 16.9 mmHg and were able to significantly distinguish favorable from unfavorable outcome. Between hours 12 and 24 the calculated values were not quite significant. After 120 hours, no significant threshold values could be calculated.

Kaplan-Meier survival estimates:

With the aim of detecting an early predictive parameter regarding survival, an ICP-threshold was calculated via conditional inference tree analysis based on the ICP-values of the first 12 hours. As a result, 15 mmHg was determined as the cut-off value between a low- and a high-ICP group. The Kaplan-Meier method was used to analyze both groups' 30-day survival rate, showing a significantly higher survival rate in the low-ICP group ($p < 0.001$; Figure 5).

The survival probability of the low-ICP group lay above 75%. In the high-ICP group, survival probability fell below 40% in the first 10 days following DC.

1.5 Discussion

Our study demonstrates that postsurgical ICP-values in a selected study population differed between the favorable and unfavorable outcome groups. Surprisingly, the ICP-values were

generally below 20 mmHg in both outcome groups. As expected from pathophysiological mechanisms, the ICP-values of the unfavorable outcome group were persistently higher than those of the favorable group.[26] This difference was observed regardless of the underlying diagnosis. In the last few hours of ICP-measurement the curves began to approximate each other due to the dropout of patients who had passed away.

The type of ICP-monitoring was standardized in our study, since only ipsilateral intraparenchymal probes were used. The accuracy and comparability of this technique has recently been proven.[41] Prospective analyses conducted with the utilized ICP-sensor demonstrated an overall small zero drift of 2.0 mmHg over more than 100 hours.[1] Thus, relevant drifts occurred in a small number of cases. Since zero drift increases over time, it is unlikely to confound the results presented here, since the further analysis of the ICP-thresholds was based on the initial period after DC (Fig. 3–5).

To assess the extent of sedation as a possible confounder of the ICP-level, the Richmond Agitation and Sedation Scale was used as an established reliable parameter of sedation status.[13] Since all patients in this study were deeply sedated postoperatively, RASS did not differ between the two outcome groups. The level of sedation was therefore unlikely to be a confounder regarding patients' ICP.

In the next step the early postsurgical ICP-values combined with diagnosis and anisocoria showed a highly predictive power in determining the neurological outcome after rehabilitation. This demonstrates the value of the ICP-level as an independent predictor, whereas SAPS II did not show any additional predictive power. This may be a result of the highly selected subgroup of surgically treated neurointensive care patients. SAPS II primarily focuses on non-neurological parameters and therefore might not be suitable for assessing functional outcome in our cohort.[35,39] GCS alone did not differ in the outcome groups either, reflecting its vague significance in outcome prediction.[32] Anisocoria was associated with an unfavorable outcome as previously demonstrated.[27] In the TBI group, we focused on patients with acute subdural hematoma as the leading radiological finding, since the indication for surgery is well defined in

these cases.[4,14] However, DC is often performed in diffuse TBI as well, and this remains to be studied.

The mean ICP-values of both outcome groups lay well below 20 mmHg. Moreover, the analysis of the ICP-course revealed a surprisingly low range of values in the unfavorable outcome group, predominantly staying below the threshold of 20 mmHg, especially in the first 72 hours after intervention. Therefore, the 20 mmHg threshold was unable to distinguish between the outcome groups. In general 20 mmHg–25 mmHg is recommended as the threshold above which additional therapy should be strongly considered, yet level I evidence is missing due to insufficient studies.[3,26] As a consequence, we calculated new time-dependent threshold values and investigated their correlation with the neurological outcome (Figures 4 and 5). These calculations revealed that a mean ICP-value below 15 mmHg in the first 12 hours was associated with lower mortality. Moreover, our findings suggest a higher probability of favorable neurological outcome in a time-dependent corridor between 10 and 17 mmHg in patients after DC.

Courses of CPP were also evaluated analogously (see supplementary data). Since CPP-values differed significantly in both outcome groups, a confounding effect of lower MAP in patients with unfavorable outcome appears unlikely.

The surprisingly low calculated threshold values may be due to the previously performed DC. This may lead to the missing evidence of the benefit of ICP-monitoring and ICP-guided therapy.[5,6] Studies evaluating the use of ICP-guided therapy in patients suffering from TBI or malignant MCA infarction may have failed due to a higher and fixed threshold that served as the crucial parameter for further therapeutic interventions or clinical assessment.[6,9,31] In the BEST TRIP trial, almost one third of the patients in the pressure-monitoring group and in the imaging-clinical examination group received a craniectomy.[9] This may have influenced the overall findings, since 20 mmHg was the treatment threshold, regardless of neurosurgical procedures.

Although lower ICP-thresholds guiding therapeutic strategies in patients after craniectomy have been discussed previously, this has not had an effect on current guidelines and further studies.[3,12] Our study offers a new perspective on the current nonspecific threshold concept.

However, the question remains whether ICP-guided treatment has a positive impact on clinical outcome. This is beyond the scope of this analysis and will have to be assessed via prospective randomized controlled trials. Our study does not prove the benefit of ICP-monitoring but it provides, for the first time, a systematic analysis of ICP-thresholds in patients undergoing DC. Since we found remarkably low ICP-values in both outcome groups following DC, it will be necessary to reassess the ICP-thresholds used to guide therapy in future studies. Furthermore, there might be a need to review ICP-thresholds at an individual level in all subgroups of neurological patients in which ICP-guided therapy is applied, since ICP-values are likely to differ significantly in patients with an intact cranium. New individualized, multimodal ICP-threshold strategies need to be established based on an improved evidence level. This may prevent the unjustified abandoning of ICP-measurement as an easily accessible real-time tool in the ICU.

Surprisingly the ICP-courses were quite similar for both diagnoses, although they reflect completely different mechanisms of brain injury. The different pathological mechanisms of TBI and MCA infarction are of course beyond question. Yet, our findings regarding ICP-thresholds after DC seem to be valid for both diagnoses as shown by our analyses.

The major limitations of our study are its retrospective design and single center character. Patients who died on emergency department arrival or directly after surgery did not receive an ICP-sensor or no ICP-recordings could be performed. This might be a potential bias in the study results. However, our patient cohort contained those patients in whom ICP-recording after DC might have been in any way relevant and reflects the reality of a specialized neurointensive care unit. We also excluded patients operated on using different surgical techniques (for example bifrontal decompression) and patients with insufficient ICP-recordings or clinical data. The goal of the study was to investigate ICP-thresholds over a period of 7 days in an ICU after DC and

therefore it cannot prove the effectiveness of ICP-guided therapeutic concepts at all. We demonstrated that the ICP-level in almost all patients, regardless of the preexisting brain damage, rarely exceeded 20 mmHg, which does not prove that lowering ICP-levels is clinically useful. Furthermore, our analysis was not designed to determine ICP-cut-offs as an indication for surgery.

Nevertheless we are convinced that our study produced valid and detailed data on ICP-values after DC and will provide an impetus for further investigation of this topic.

1.6 Conclusions

Our study suggests a new time-dependent threshold based on the ICP-analysis of the first 168 hours after DC. This paper cannot provide therapeutic evidence but does give a new perspective on ICP-monitoring. As a consequence, therapeutic concepts based on 20 mmHg as an established but unproven cut-off should be reconsidered and evidence-based thresholds are needed for future trials. Individual thresholds would ensure that the therapeutic concept is more than a paradigm of keeping the pressure below a fixed threshold.

Disclosure of Conflicts of Interest

The authors have no conflicts of interest.

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References

1. Al-Tamimi YZ, Helmy A, Bavetta S, Price SJ: Assessment of zero drift in the Codman intracranial pressure monitor: a study from 2 neurointensive care units. Neurosurgery 64:94-98; discussion 98-99, 2009
2. Brain Trauma F, American Association of Neurological S, Congress of Neurological S, Joint Section on N, Critical Care AC, Bratton SL, et al: Guidelines for the management of severe traumatic brain injury. VI. Indications for intracranial pressure monitoring. J Neurotrauma 24 Suppl 1:S37-44, 2007
3. Brain Trauma F, American Association of Neurological S, Congress of Neurological S, Joint Section on N, Critical Care AC, Bratton SL, et al: Guidelines for the management of severe traumatic brain injury. VIII. Intracranial pressure thresholds. J Neurotrauma 24 Suppl 1:S55-58, 2007
4. Bullock MR, Chesnut R, Ghajar J, Gordon D, Hartl R, Newell DW, et al: Surgical management of acute subdural hematomas. Neurosurgery 58:S16-24; discussion Si-iv, 2006
5. Chesnut R, Videtta W, Vespa P, Le Roux P, Participants in the International Multidisciplinary Consensus Conference on Multimodality M: Intracranial pressure monitoring: fundamental considerations and rationale for monitoring. Neurocrit Care 21 Suppl 2:S64-84, 2014
6. Chesnut RM: Intracranial pressure monitoring: headstone or a new head start. The BEST TRIP trial in perspective. Intensive Care Med 39:771-774, 2013
7. Chesnut RM, Bleck TP, Citerio G, Classen J, Cooper DJ, Coplin WM, et al: A Consensus-Based Interpretation of the Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure Trial. J Neurotrauma 32:1722-1724, 2015
8. Chesnut RM, Marshall LF, Klauber MR, Blunt BA, Baldwin N, Eisenberg HM, et al: The role of secondary brain injury in determining outcome from severe head injury. J Trauma 34:216-222, 1993

9. Chesnut RM, Temkin N, Carney N, Dikmen S, Rondina C, Videtta W, et al: A trial of intracranial-pressure monitoring in traumatic brain injury. N Engl J Med 367:2471-2481, 2012

10. Cooper DJ, Rosenfeld JV, Murray L, Arabi YM, Davies AR, D'Urso P, et al: Decompressive craniectomy in diffuse traumatic brain injury. N Engl J Med 364:1493-1502, 2011

11. Dunisch P, Walter J, Sakr Y, Kalff R, Waschke A, Ewald C: Risk factors of aseptic bone resorption: a study after autologous bone flap reinsertion due to decompressive craniotomy. J Neurosurg 118:1141-1147, 2013

12. Eisenberg HM, Frankowski RF, Contant CF, Marshall LF, Walker MD: High-dose barbiturate control of elevated intracranial pressure in patients with severe head injury. J Neurosurg 69:15-23, 1988

13. Ely EW, Truman B, Shintani A, Thomason JW, Wheeler AP, Gordon S, et al: Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). JAMA 289:2983-2991, 2003

14. Firsching R, Rickels E, Mauer U, Sakowitz O, Messing-Jünger M, Engelhard K, et al: AWMF LEITLINIE SCHÄDEL-HIRN-TRAUMA IM ERWACHSENENALTER, in: AWMF, Deutsche Gesellschaft für Neurochirurgie e.V. (DGNC), 2015, Vol 2016

15. Handschu R, Haslbeck M, Hartmann A, Fellgiebel A, Kolominsky-Rabas P, Schneider D, et al: Mortality prediction in critical care for acute stroke: Severity of illness-score or coma-scale? J Neurol 252:1249-1254, 2005

16. Hofmeijer J, Kappelle LJ, Algra A, Amelink GJ, van Gijn J, van der Worp HB, et al: Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]): a multicentre, open, randomised trial. Lancet Neurol 8:326-333, 2009

17. Hothorn T, Hornik K, Zeileis A: Unbiased recursive partitioning: a conditional inference framework. J Comput Graph Stat 15:651–674, 2006

18. Huttner HB, Schwab S: Malignant middle cerebral artery infarction: clinical characteristics, treatment strategies, and future perspectives. Lancet Neurol 8:949-958, 2009

19. Johnson RD, Maartens NF, Teddy PJ: Technical aspects of decompressive craniectomy for malignant middle cerebral artery infarction. J Clin Neurosci 18:1023-1027, 2011

20. Jüttler E: AWMF Leitlinie Intrakranieller Druck in: Deutsche Gesellschaft für Neurologie, 2012, Vol 2015

21. Juttler E, Schwab S, Schmiedek P, Unterberg A, Hennerici M, Woitzik J, et al: Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery (DESTINY): a randomized, controlled trial. Stroke 38:2518-2525, 2007

22. Juttler E, Unterberg A, Woitzik J, Bosel J, Amiri H, Sakowitz OW, et al: Hemicraniectomy in older patients with extensive middle-cerebral-artery stroke. N Engl J Med 370:1091-1100, 2014

23. Kocher E: Die Therapie des Hirndruckes, in Nothnagel H (ed): Specielle Pathologie und Therapie. Wien: Alfred Hölder, 1901, pp 255-266

24. Kontopoulos V, Foroglou N, Patsalas J, Magras J, Foroglou G, Yiannakou-Pephtoulidou M, et al: Decompressive craniectomy for the management of patients with refractory hypertension: should it be reconsidered? Acta Neurochir (Wien) 144:791-796, 2002

25. Le Gall JR, Lemeshow S, Saulnier F: A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 270:2957-2963, 1993

26. Marmarou A, Anderson RL, Ward JD, Choi SC, Young HF, Eisenberg HM, et al: Impact of Icp Instability and Hypotension on Outcome in Patients with Severe Head Trauma. Journal of Neurosurgery 75:S59-S66, 1991

27. Marmarou A, Lu J, Butcher I, McHugh GS, Murray GD, Steyerberg EW, et al: Prognostic value of the Glasgow Coma Scale and pupil reactivity in traumatic brain injury assessed pre-hospital and on enrollment: an IMPACT analysis. J Neurotrauma 24:270-280, 2007

28. Munch E, Horn P, Schurer L, Piepgras A, Paul T, Schmiedek P: Management of severe traumatic brain injury by decompressive craniectomy. Neurosurgery 47:315-322; discussion 322-313, 2000

29. Olivecrona M, Rodling-Wahlstrom M, Naredi S, Koskinen LO: Effective ICP reduction by decompressive craniectomy in patients with severe traumatic brain injury treated by an ICP-targeted therapy. J Neurotrauma 24:927-935, 2007

30. Paldor I, Rosenthal G, Cohen JE, Leker R, Harnof S, Shoshan Y, et al: Intracranial pressure monitoring following decompressive hemicraniectomy for malignant cerebral infarction. J Clin Neurosci 22:79-82, 2015

31. Poca MA, Benejam B, Sahuquillo J, Riveiro M, Frascheri L, Merino MA, et al: Monitoring intracranial pressure in patients with malignant middle cerebral artery infarction: is it useful? J Neurosurg 112:648-657, 2010

32. Potts MB, Chi JH, Meeker M, Holland MC, Claude HJ, 3rd, Manley GT: Predictive values of age and the Glasgow Coma Scale in traumatic brain injury patients treated with decompressive craniectomy. Acta Neurochir Suppl 102:109-112, 2008

33. Raj R, Skrifvars M, Bendel S, Selander T, Kivisaari R, Siironen J, et al: Predicting six-month mortality of patients with traumatic brain injury: usefulness of common intensive care severity scores. Crit Care 18:R60, 2014

34. Sahuquillo J, Arikan F: Decompressive craniectomy for the treatment of refractory high intracranial pressure in traumatic brain injury. Cochrane Database Syst Rev:CD003983, 2006

35. Sakr Y, Marques J, Mortsch S, Gonsalves MD, Hekmat K, Kabisch B, et al: Is the SAPS II score valid in surgical intensive care unit patients? J Eval Clin Pract 18:231-237, 2012

36. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, et al: The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 166:1338-1344, 2002

37. Sharda P, Haspani S, Idris Z: Factors prognosticating the outcome of decompressive craniectomy in severe traumatic brain injury: A Malaysian experience. Asian J Neurosurg 9:203-212, 2014

38. Stocchetti N, Picetti E, Berardino M, Buki A, Chesnut RM, Fountas KN, et al: Clinical applications of intracranial pressure monitoring in traumatic brain injury : report of the Milan consensus conference. Acta Neurochir (Wien) 156:1615-1622, 2014

39. Suistomaa M, Niskanen M, Kari A, Hynynen M, Takala J: Customized prediction models based on APACHE II and SAPS II scores in patients with prolonged length of stay in the ICU. Intensive Care Med 28:479-485, 2002

40. Vahedi K, Hofmeijer J, Juettler E, Vicaut E, George B, Algra A, et al: Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. Lancet Neurol 6:215-222, 2007

41. Zacchetti L, Magnoni S, Di Corte F, Zanier ER, Stocchetti N: Accuracy of intracranial pressure monitoring: systematic review and meta-analysis. Crit Care 19:420, 2015

Tables:

Table 1: Demographic and clinical parameters separated by outcome and diagnosis.

Characteristic	mRS 0 - 4	mRS 5 – 6	*p*-value
	n = 42	n = 60	
sex - no. (%)			ns
male	23 (54.8)	41 (68.3)	
female	19 (45.2)	19 (31.7)	
diagnosis - no. (%)			0.003 *
TBI	11 (26.2)	34 (56.7)	
MCA infarction	31 (73.8)	26 (43.3)	
age (years)			ns
mean (range)	52.2 (23 - 72)	53.9 (14 - 79)	
side - no. (%)	23 (54.8)	37 (61.7)	ns
right	19 (45.2)	23 (38.3)	
left			
GCS - no. (% valid)	36 (85.7)	57 (95.1)	ns
mean GCS (range)	9.5 (3 - 15)	8.8 (3 - 15)	
anisocoria - no. (%)	20 (47.6)	42 (70.0)	0.026 **
size of trepanation (cm^2)			ns
mean (range)	128.8 (82.5 - 168.0)	122.7 (64.0 - 165.7)	
RASS			ns
mean (range)	-3.7 (-5 - 0)	-3.9 (-5 - 3)	
SAPS II			ns
mean (range)	40.3 (17 - 68)	45 (21 - 91)	
EVD - no. (%)	0 (0)	4 (6.7)	ns
mean ICP (mmHg) of the first 168h (std)	11.5 (±1.4)	17.5 (±3.4)	< 0.001#

	TBI - mRS 0 - 4	MCA-I - mRS 0 - 4	TBI - mRS 5 – 6	MCA-I (mRS 5 – 6)	
	n = 11	n = 31	n = 34	n = 26	
sex - no. (%)					ns
male	5 (45.5)	18 (58.1)	26 (76.5)	15 (57.7)	
female	6 (54.5)	13 (41.9)	8 (23.5)	11 (42.3)	

age (years)					
mean (std)	50.7 (±16.6)	52.7 (±9.7)	54.4 (±19.6)	53.3 (±12.0)	ns
side - no. (%)					ns
right	7 (63.6)	16 (51.6)	21 (61.8)	16 (61.5)	
left	4 (36.4)	15 (48.4)	13 (38.2)	10 (38.5)	
GCS					ns
mean GCS (std)	5.8 (±4.3)		7.7 (±4.7)		
					} <0.001
		10.9 (±4.2)		10.4 (±4.3)	
NIHSS					ns
mean NIHSS (std)		16.2 (±6.6)		15.7 (±4.1)	
anisocoria - no. (%)	4 (36.4)	16 (51.6)	23 (69.7)	19 (73.1)	ns
size of trepanation (cm^2)					ns
mean (std)	129.8 (±27.7)	128.5 (±20.0)	116.8 (±25.5)	130.6 (±16.3)	
RASS					ns
mean (std)	-2.8 (±2.6)	-3.7 (±0.7)	-4.2 (±0.9)	-3.3 (±1.5)	
SAPS II					ns
mean (std)	47.6 (±12.0)		48.4 (±14.8)		
					} 0.008
		37.5 (±13.5)		40.0 (±14.5)	
EVD - no. (%)	0 (0)	0 (0)	3 (9)	1 (4)	ns

std = standard deviation; mRS = modified Rankin Scale; GCS = Glasgow Coma Scale; RASS = Richmond Agitation Sedation Scale; SAPS = Simplified Acute Physiology Score; EVD = External Ventricular Drain; NIHSS = National Institutes of Health Stroke Scale;
* in multivariate analysis $p<0.01$; ** in multivariate analysis $p<0.05$;
[#]assessed with Wilcoxon rank sum test

Supplementary table 2: Risk of unfavorable outcome depending on ICP separated by diagnosis.

Estimation of unfavorable outcome	OR	CI	p-value
diagnosis: MCA infarction	0.23	0.17 – 0.30	<0.001
ICP in TBI	1.04	1.02 – 1.07	0.001
ICP in MCA infarction	1.11	1.05 – 1.19	<0.001

OR = Odds ratio; CI = confidence interval

Figures:

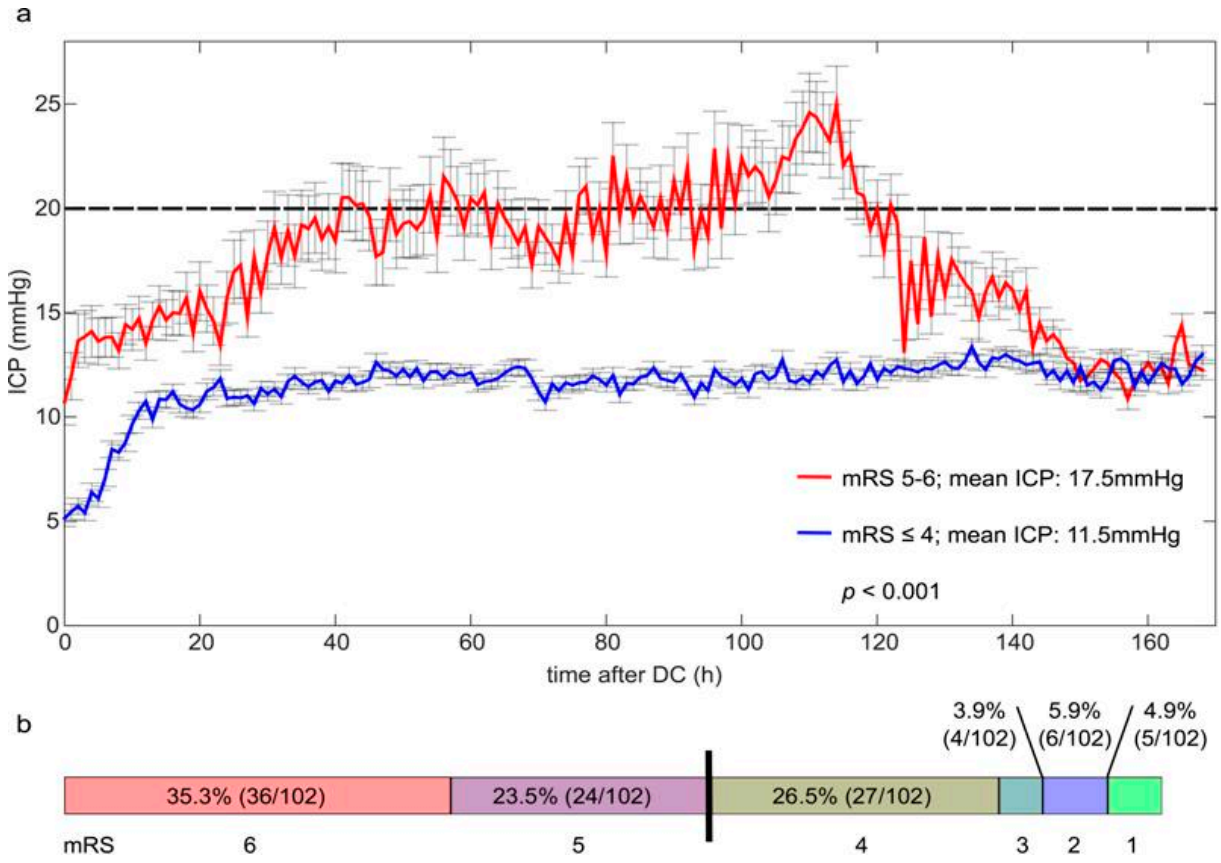


Figure 1: Mean intracranial pressure in the first 168 hours after decompressive craniectomy.
a) In the favorable outcome group (blue) the mean ICP was 11.5 mmHg compared to 17.5 mmHg in the unfavorable group (red; $p < 0.001$). The blue curve does not exceed 14 mmHg and even the red curve stays predominantly below the limit of 20 mmHg. In the first 72 h the red curve barely exceeds 20 mmHg. Error bars indicate the standard error of the mean.
b) Distributions of the scores on the mRS in the entire cohort (mRS = modified Rankin Scale).

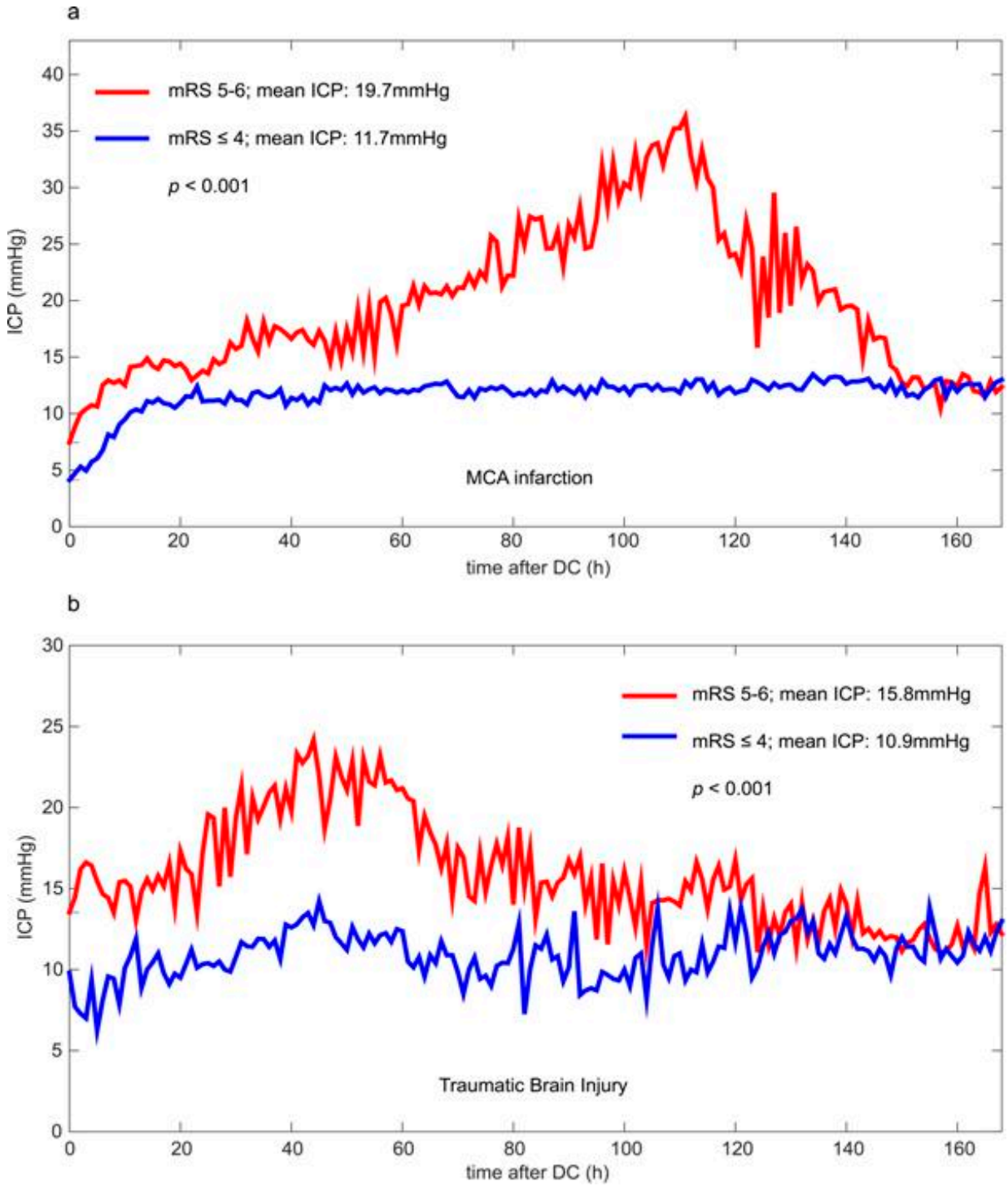


Figure 2: Mean intracranial pressure separated by diagnosis.

a) Mean intracranial pressure in the first 168 hours after decompressive craniectomy in patients with malignant middle cerebral artery infarction. The mean ICP was 11.7 mmHg in the favorable group (blue curve) and 19.7 mmHg in the unfavorable group (red curve; $p < 0.001$). No crossing of the 20 mmHg threshold occurred during the first 57 hours.

b) Mean intracranial pressure in the first 168 hours after decompressive craniectomy in patients with traumatic brain injury. Mean ICP was 10.9 mmHg in the favorable group (blue curve) compared to 15.8 mmHg in the unfavorable outcome group (red curve; $p < 0.001$). The mean ICP did not exceed 20 mmHg in the first 31 hours after DC (mRS = modified Rankin Scale).

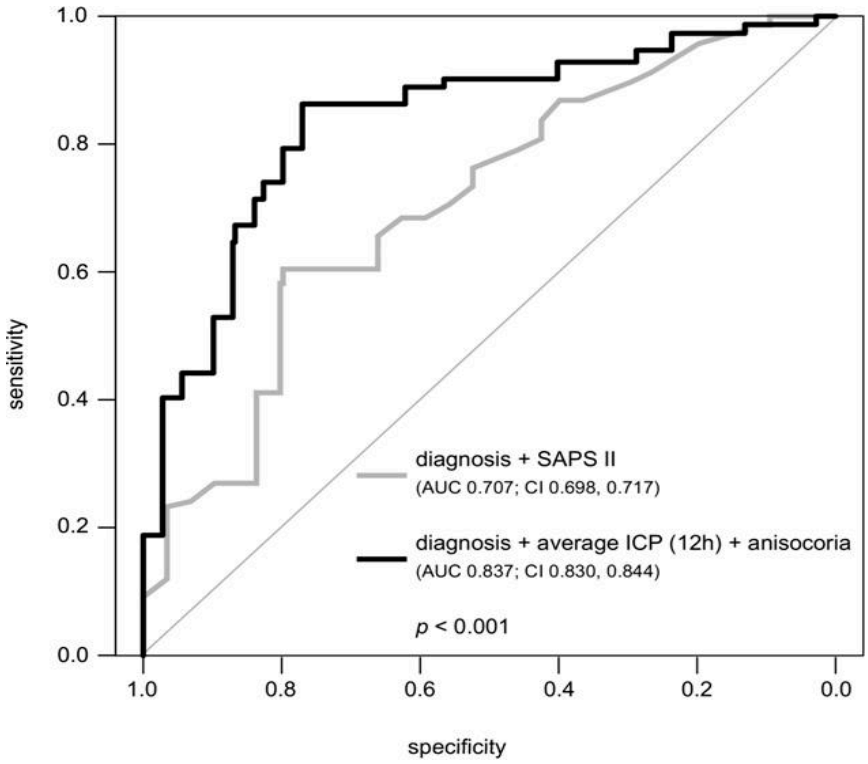


Figure 3: Significance of mean intracranial pressure (12h) in outcome prediction. In this ROC-curve, the models for outcome prediction detected via multivariate logistic regression are displayed. Models were tested for correct outcome prediction against the null hypothesis. Diagnosis and SAPS II showed an area under the curve (AUC) of 0.707. Including diagnosis, ICP and anisocoria resulted in a significantly higher AUC of 0.837 ($p < 0.001$; DeLong test; CI = Confidence Interval; SAPS II = Simplified Acute Physiology Score).

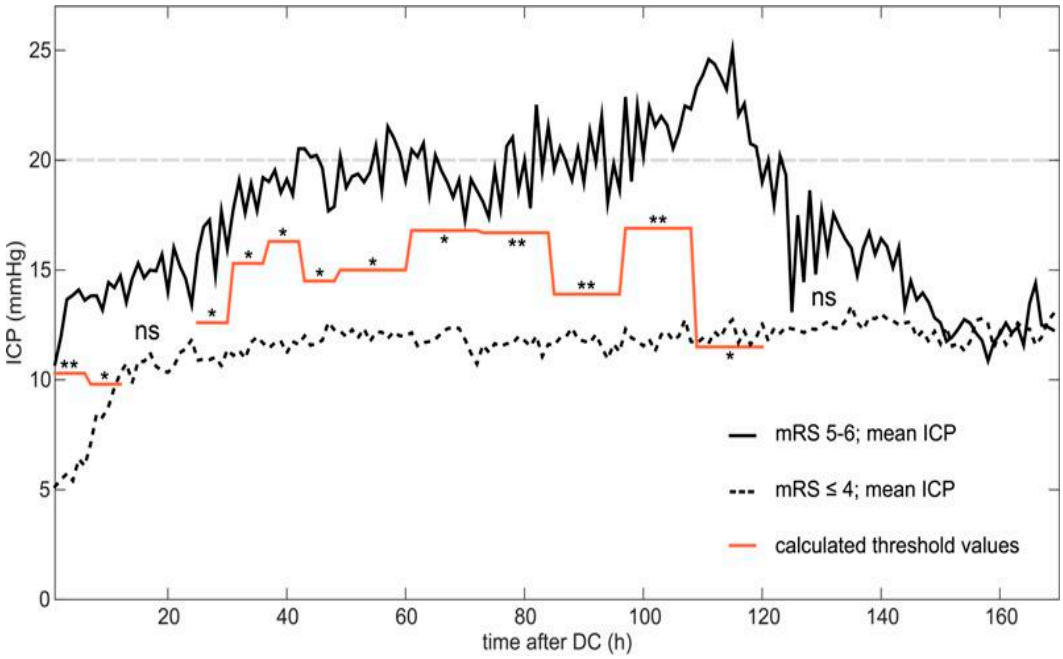


Figure 4: Calculated intracranial pressure-thresholds in the first 168 hours after decompressive craniectomy.
(* $p < 0.05$; ** $p < 0.01$; ns = not significant; conditional inference tree analysis; mRS = modified Rankin Scale, merged diagnoses)

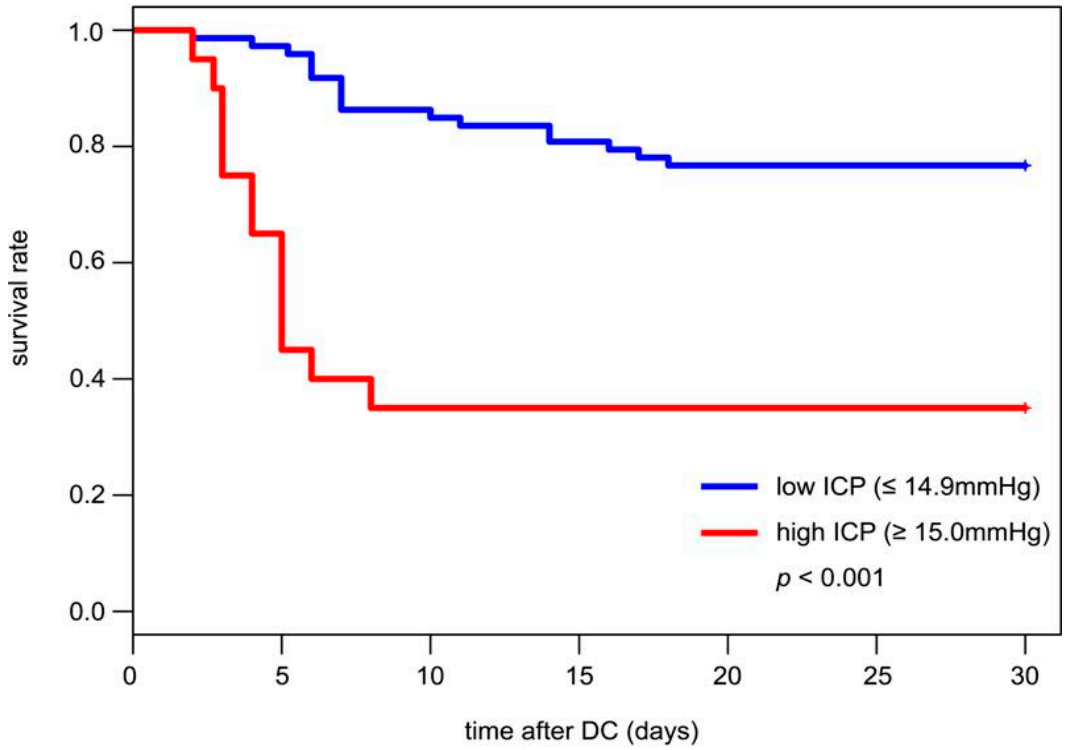
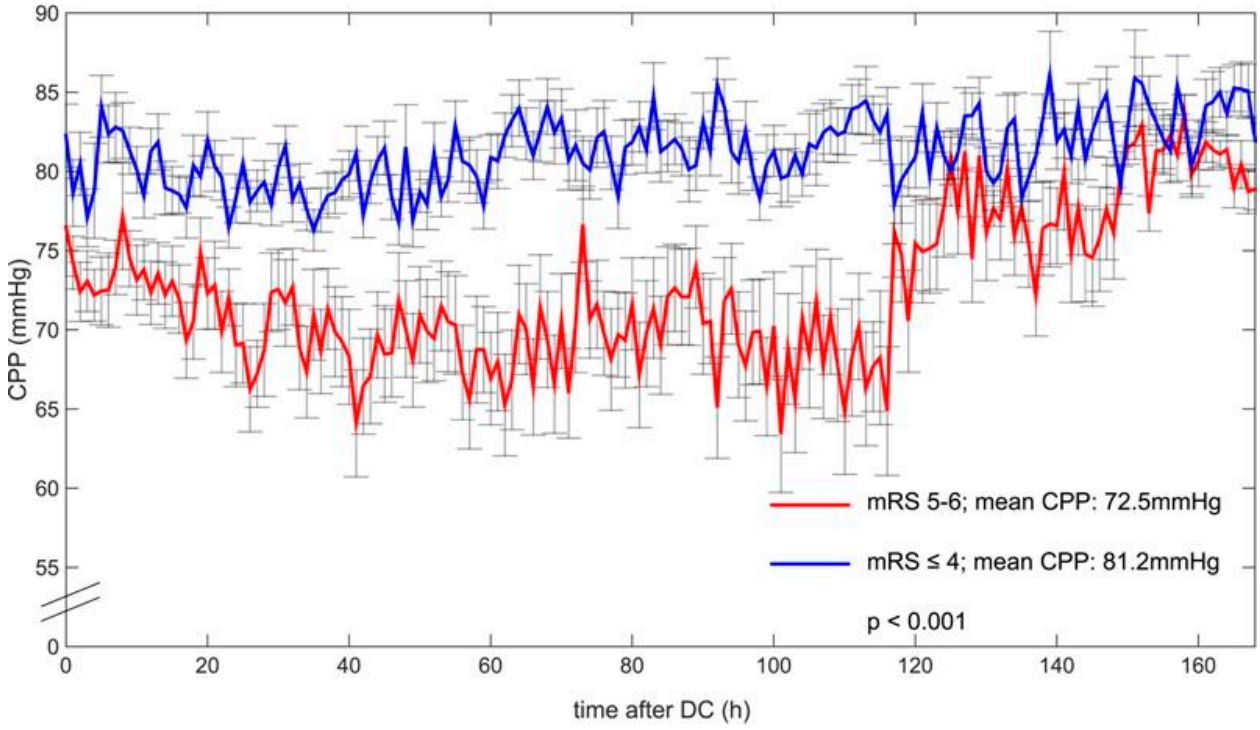
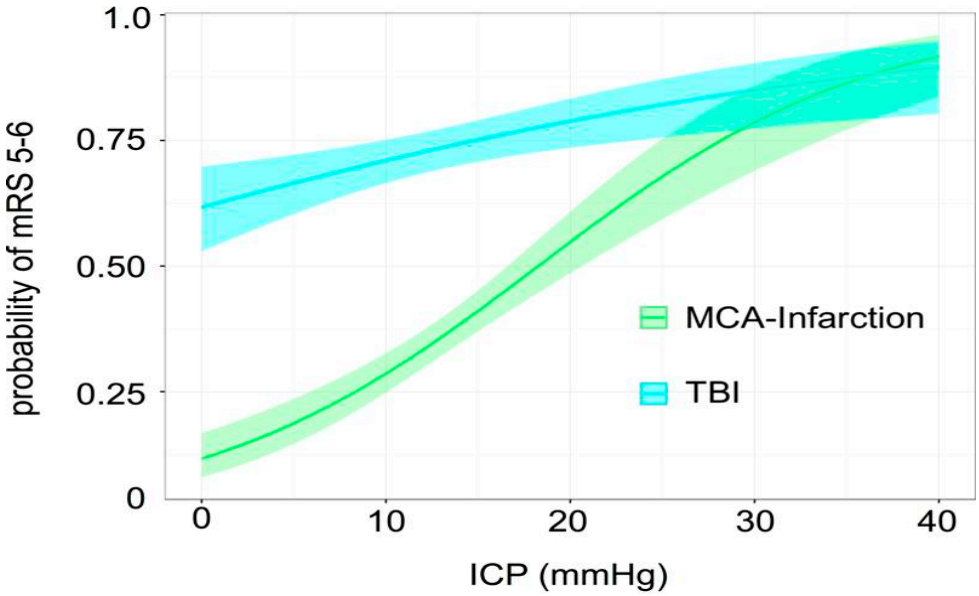


Figure 5: Kaplan-Meier survival curves for the first 30 days after decompressive craniectomy.
Comparison of the 30-day survival probability of patients with low ICP (mean ICP ≤ 14.9 mmHg; blue curve) with that for patients with high ICP (mean ICP ≥ 15.0 mmHg; red curve) showed significantly higher survival in the low ICP-group ($p < 0.001$, log-rank test, merged diagnoses).



Supplementary Figure 1: Mean cerebral perfusion pressure in the first 168 hours after decompressive craniectomy.
In the favorable outcome group (blue) the mean CPP was 81.2 mmHg compared with 72.5 mmHg in the unfavorable group (red; $p < 0.001$). Please note: The zero-point of the mean arterial pressure was defined at the level of the right atrium whereas the zero-point for ICP-measurement was at the level of the nasion. Having regard to the elevation of the head by 20°–30°, this results in a higher range of the CPP of approximately 10 – 15 mmHg compared with a calculation using common zero-points. However, the courses of and differences in the CPP-levels remained unaffected. Error bars indicate the standard error of the mean.



Supplementary Figure 2: Estimation of outcome based on ICP separated by diagnosis.
The risk of unfavorable outcome depending on the mean ICP in the first twelve hours is shown for MCA and TBI separately. In both diagnoses the risk of an unfavorable outcome increases significantly with an elevation of the mean ICP. Both graphs demonstrate a large increase in risk already at ICP values below 20 mmHg. In general patients with MCA infarction have a higher chance of a favorable outcome, whereas the risk of unfavorable outcome depending on the ICP increases even more in these patients.

1.7 Letter of Acceptance

November 11, 2016

Dear Dr. Sauvigny:

We are pleased to inform you that your article entitled "Intracranial pressure in patients undergoing decompressive craniectomy - new perspective on thresholds," submitted to Journal of Neurosurgery, has been accepted for publication.

Editor-in-Chief's comments:

After careful review of your revised manuscript, I am satisfied that you have answered the Reviewers' many comments. Accordingly, your manuscript will now be prepared for publication.

Congratulations to you and your co-authors!

Please note that changes to authorship at this point will no longer be considered.

We will plan to publish the supplemental data online only, and not in the print issue. The JNSPG staff does not edit or proofread any online-only content (OOC). Authors are responsible for the accuracy of their OOC data and its relationship to the rest of the article. If editing queries result in any changes that affect OOC data or other OOC material, please ask the JNSPG staff for the OOC file(s) so that you can make any necessary corrections. Note that, unless requested, OOC files will not be sent to the authors.

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Our production staff will contact you when your manuscript enters the active phase of the editing and production process. Due to the numerous high-quality acceptances that we process, it may take some time before this next phase begins. However, once it begins, the process moves quickly. We would appreciate your prompt response to all queries. This plays a vital part in ensuring rapid online publication.

If any of your user account information changes, please log in to your account on our manuscript submission site and update it.

If you would like to check on the status of your paper, please email our production staff at: production@thejns.org.

Sincerely,

James T. Rutka, M.D., Ph.D.
Editor-in-Chief
Journal of Neurosurgery Publishing Group

2. Summary

2.1 Introduction

The cranium contains three compartments, with brain parenchyma measuring approximately 1400 ml, followed by cerebrospinal fluid (CSF) and intracranial blood each measuring about 150 ml (1). Since the compartments' sum stays constant, according to the Monro-Kellie-doctrine, an expansion of one leads to the compression of one or both of the remaining (2). Due to the skull's inability to expand and the incompressible nature of the brain parenchyma as well as blood and CSF, the body has only limited ways of compensating an increase in volume, such as reducing the production of CSF and evading the same into the spinal canal (1). After the depletion of compensatory mechanisms, pathologies causing an increase in volume in any compartment, therefore lead to an elevation of intracranial pressure (ICP), whose normal range is 3 – 15 mmHg (1). Moreover, since the relation between intracranial pressure and volume is nonlinear, a disproportionate increase in ICP occurs, once the compensatory mechanisms are exhausted.

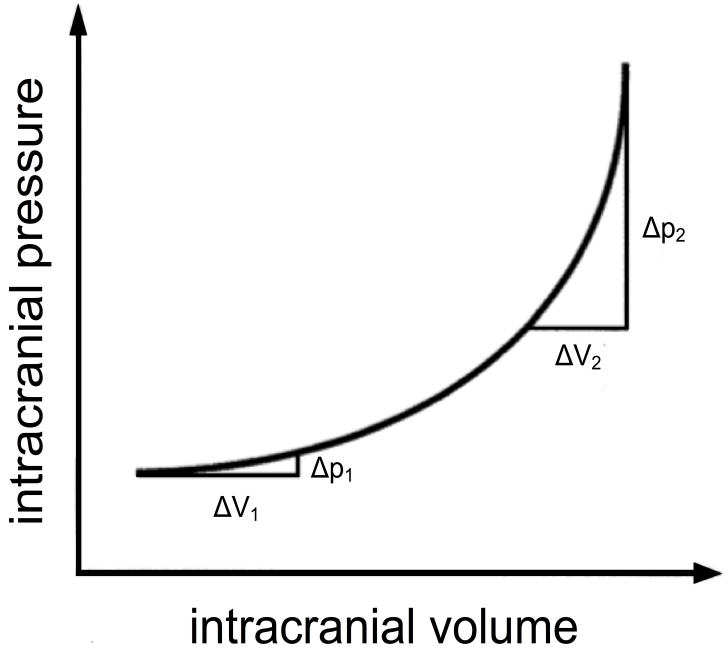

Figure 1: Relationship between intracranial volume and pressure.
A non-linear relationship exists between the increase in intracranial pressure (p) and volume (V). With advanced intracranial volume, intracranial pressure increases faster (Δp2 > Δp1).

Increased intracranial pressure can have various causes; however, all of them have the potential of possibly developing into a life-threatening condition due to herniation and secondary ischemia (1).
Since the cerebral perfusion pressure (CPP) is calculated as the difference between the mean arterial pressure (MAP) and the ICP (CPP = MAP - ICP), elevated ICP may lead to impaired cerebral perfusion and therefore to ischemia.

Possible causes for elevated ICP are space-occupying infarctions, such as malignant middle cerebral artery (MCA) infarction, intracranial hemorrhages and traumatic brain injury (TBI) resulting in brain edema (3).
Therapeutic approaches in the management of elevated ICP aim at preventing secondary ischemic brain damage, which could arise from a decrease of CPP.
Current guidelines recommend the extension of treatment in patients with ICP above 20 – 25 mmHg (4, 5). This treatment includes the avoidance of hypotension (systolic blood pressure < 90 mmHg) and hypoxia (Pa O_2 < 60 mmHg or saturation < 90%) as well as sedation, hyperosmolar therapy with mannitol (0.25 – 1g/kg) and moderate hyperventilation (Pa CO_2 30 – 35 mmHg) (5, 6).
Furthermore, decompressive craniectomy (DC) is an option in the management of elevated ICP. In young patients suffering from malignant infarction of the middle cerebral artery treated with DC, prospective randomized trials were able to show a reduction of mortality and an improvement in clinical outcome (7-10). Decompressive craniectomy is recommended within the first 48 hours from the onset of symptoms in patients suffering from malignant MCA infarction (5).
DC is also frequently performed in TBI patients suffering from refractory elevated ICP, although data are controversial (11-14). The RESCUEicp study revealed DC in patients with TBI to result in lower mortality and higher rates of vegetative state, lower severe disability, and upper severe disability than conservative treatment (15).

Severe injury of the brain, independent of the underlying diagnosis, frequently induces cerebral edema causing an increase in ICP. ICP-monitoring and ICP-guided therapeutic interventions are generally performed in clinical practice. While ICP-monitoring is generally recommended for patients with severe TBI (16, 17), corresponding guidelines for patients with malignant MCA infarction are missing. ICP-monitoring after DC is nevertheless often part of the further therapy on the intensive care unit (ICU) (5).

Although commonly performed, no class I evidence for the benefit of ICP-monitoring and ICP-guided therapy exists so far. The objective of a multicenter controlled trial published in 2012 was to assess the efficacy of ICP-guided treatment in improving the outcome of patients suffering from severe TBI (18). In this trial, patients were randomly assigned to either a "pressure-monitoring"- or "imaging-clinical examination" group. Patients in the "pressure-monitoring" group were treated with the aim of maintaining an ICP at or below 20 mmHg. Counterintuitively, no significant differences between these groups could be found with regards to their outcomes. Despite the failure of this trial to provide this evidence, the authors still emphasize the likely benefit of ICP-guided therapy and ICP-guided therapy has not been abandoned in clinical practice (17-19).
Missing evidence for the simplified threshold of 20 mmHg, which determines further therapy, should be considered as a possible cause for these results. In the BEST TRIP trial almost one third of the patients in the "pressure-monitoring group" and in the "imaging-clinical examination group" received a craniectomy. This may have influenced the study's results, since 20 mmHg served as the general treatment threshold regardless of neurosurgical interventions.

The effectiveness of DC in lowering ICP has been proven in various studies (12, 20), but only limited data are available for the postsurgical ICP-course. So far, only a few studies focused on

this topic, of which most evaluated only a small number of patients or recorded a limited number of ICP-values (21-25).
Hence, objective of this study was to analyze the ICP-level and -course of the first week after DC in patients suffering from malignant MCA infarction and TBI and to correlate these parameters with their neurological outcome. A special focus was put on the evaluation of the commonly accepted threshold of 20 mmHg.

2.2 Methods

Patients undergoing unilateral DC due to malignant MCA infarction or acute subdural hematoma from December 2007 through April 2014 were analyzed retrospectively. Hourly postsurgical ICP-values of the first 168 hours and the clinical outcome were evaluated. Functional outcome was assessed via modified Rankin Scale (mRS) at the end of rehabilitation. Favorable outcome was defined as a score of 0 – 4 on the mRS according to Vahedi et al. (2007) (9).
Demographic and clinical data, including sex, age, primary diagnosis, side (and size) of DC, postoperative pupillary status Glasgow Coma Scale (GCS) and National Institutes of Health Stroke Scale (NIHSS), respectively.
Furthermore, the patients' level of sedation was assessed regularly via the Richmond Agitation Sedation Scale (RASS) and collected initially after DC and subsequently once every 24 hours (26). The Simplified Acute Physiology Score (SAPS II) on the day of surgery was analyzed to determine the patients' morbidity (27). Furthermore, frequent blood gas analyses were performed as well as continuous monitoring of electrocardiography, oxygen saturation, arterial blood pressure, respiratory minute volume and tidal volume.
After the ipsilateral placement of an intraparenchymal ICP-probe at the end of DC, according to the recommendations of the Milan consensus conference on ICP-monitoring and current guidelines, ICP-values and mean arterial pressure were measured continuously (5, 16). CPP-values were calculated, based on these measurements.

2.3 Summary of results

A total of 102 patients (64 males; 62.7 %) were included in this study. Mean age of this cohort was 53.2 years (range 14 – 79). DC was performed due to a space-occupying MCA infarction in 57 (55.9 %) cases, whereas severe traumatic brain injury led to DC in 45 (44.1 %) cases. A favorable outcome at the end of rehabilitation (on average 129 days after DC) was assessed in 42 (41 %) patients.
Statistical analysis detected no significant differences between the outcome groups regarding sex, age, side of DC, size of trepanation, GCS, NIHSS, RASS, SAPS II and presence of an external ventricular drain. External ventricular drains were present in 4 patients of the unfavorable group. Univariate analysis revealed anisocoria and diagnosis to differ significantly in the outcome groups.
Additionally, multivariate logistic regression was used to analyze the prognostic value of diagnosis, anisocoria and mean ICP. Early postsurgical ICP-values combined with diagnosis and anisocoria showed a highly predictive power in determining the neurological outcome after rehabilitation.

We analyzed ICP-values of the first 168 hours after DC of both outcome groups.
ICP-values in the favorable outcome group started and remained lower than those of the unfavorable group. Mean ICP in the favorable outcome group was 11.5 mmHg compared to 17.5 mmHg in the unfavorable outcome group. In the latter, ICP-values stayed in a higher range, but barely exceeded 20 mmHg. Particularly during the first 72 hours, ICP-values of the unfavorable outcome group only crossed the 20 mmHg threshold at 11 (15.1%) measuring points. In 31 (51.7%) patients with unfavorable outcome, ICP-values did not exceed 20 mmHg at any point during the first 72 hours.
Statistical analysis, corrected for repeated measures, revealed a significant difference ($p < 0.001$) between the outcome groups. Figure 2 shows the ICP-courses in both groups plotted over 168 hours.

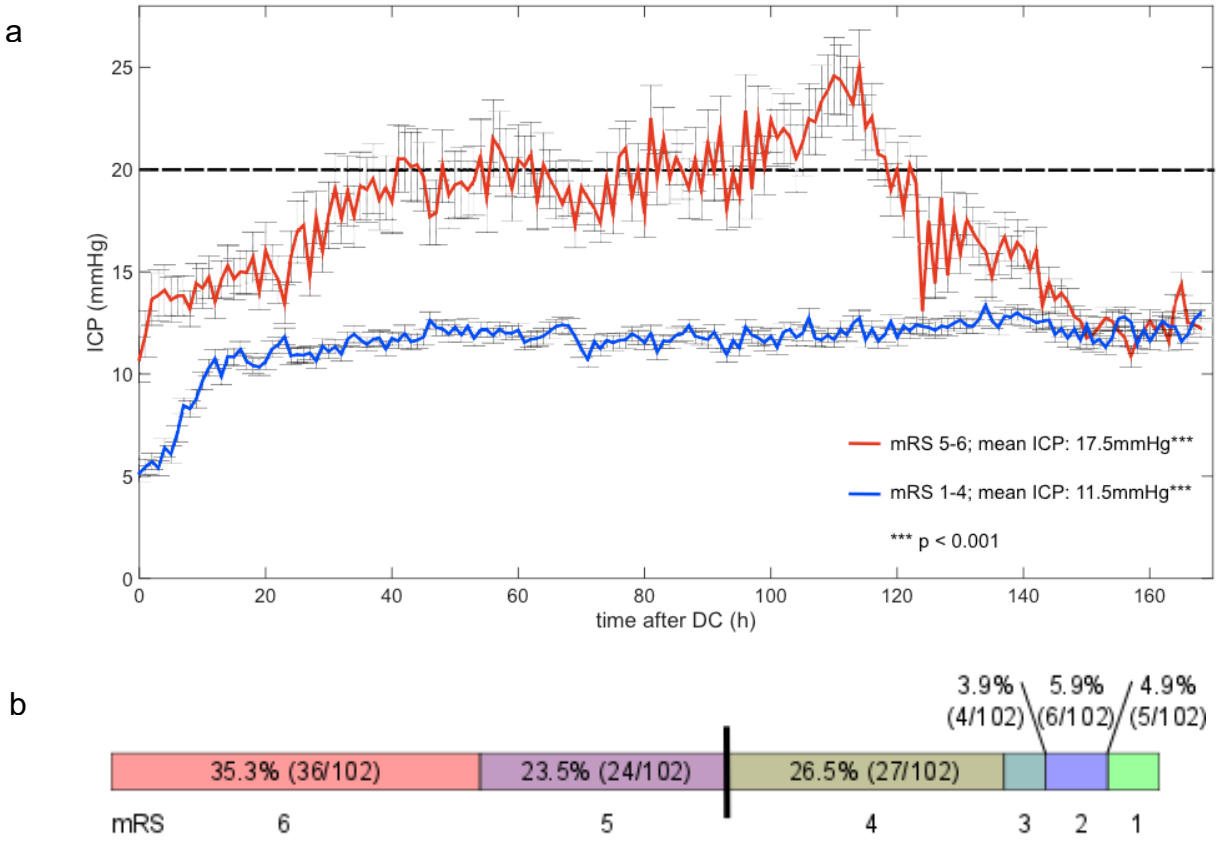

Figure 2: Intracranial pressure of the first 168 hours after decompressive craniectomy.
a) In the favorable outcome group (blue) the mean ICP was 11.5 mmHg compared to 17.5 mmHg in the unfavorable group (red; $p < 0.001$). Univariate comparisons between the patient groups were calculated using the Wilcoxon rank-sum test. The blue graph does not exceed 14 mmHg while the red curve predominantly respects the limit of 20 mmHg. In the first 72 h the red curve barely exceeds 20 mmHg. In the last hours of ICP-measurement the curves approximate to each other. Error bars indicate the standard error of the mean.
b) Distributions of mRS-scores of the entire cohort

Since the underlying diagnosis was found to differ significantly between the outcome groups in univariate as well as multivariate analysis (data not shown), ICP-courses were also analyzed separated by diagnosis (Figure 3 and 4). In MCA infarction patients mean ICP of the favorable group was 11.7 mmHg in comparison to 19.7 mmHg in the unfavorable outcome group. During the first 57 hours mean ICP-values do not exceed 20 mmHg at any point. Mean ICP in both

outcome groups was also found to be below 20 mmHg in patients suffering from TBI (10.9 mmHg and 15.8 mmHg, respectively). In the TBI cohort mean ICP does not cross the 20 mmHg threshold in the first 31 hours after DC. Statistically significant differences between the outcome groups were detected in both subgroup analyses.

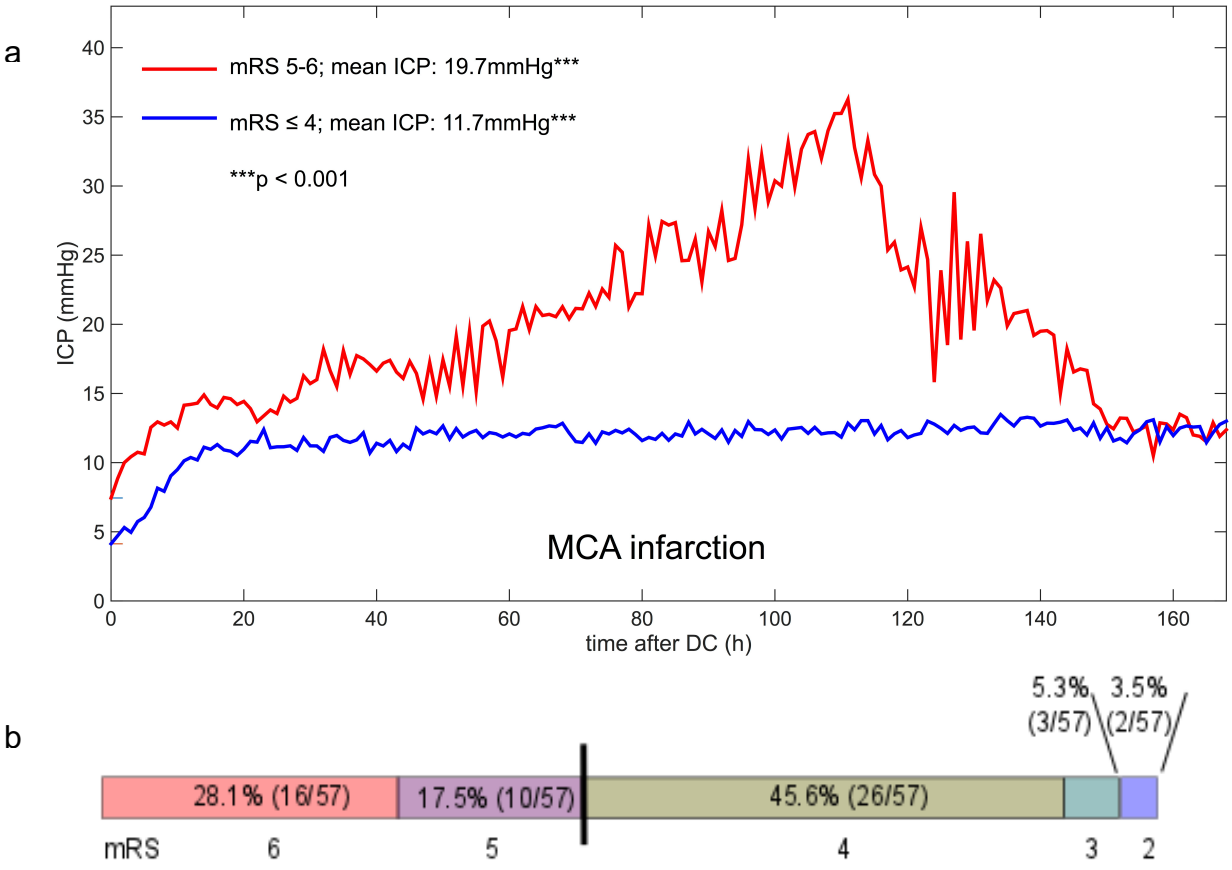

Figure 3: Postsurgical ICP-course in MCA infarction patients.

a) Mean ICP in the favorable group was 11.7 mmHg (blue curve) and 19.7 mmHg in the unfavorable group (red curve; $p < 0.001$) (Wilcoxon rank-sum test). No crossing of the 20 mmHg threshold occurred during the first 57 hours.

b) Distributions of mRS-scores of MCA infarction patients

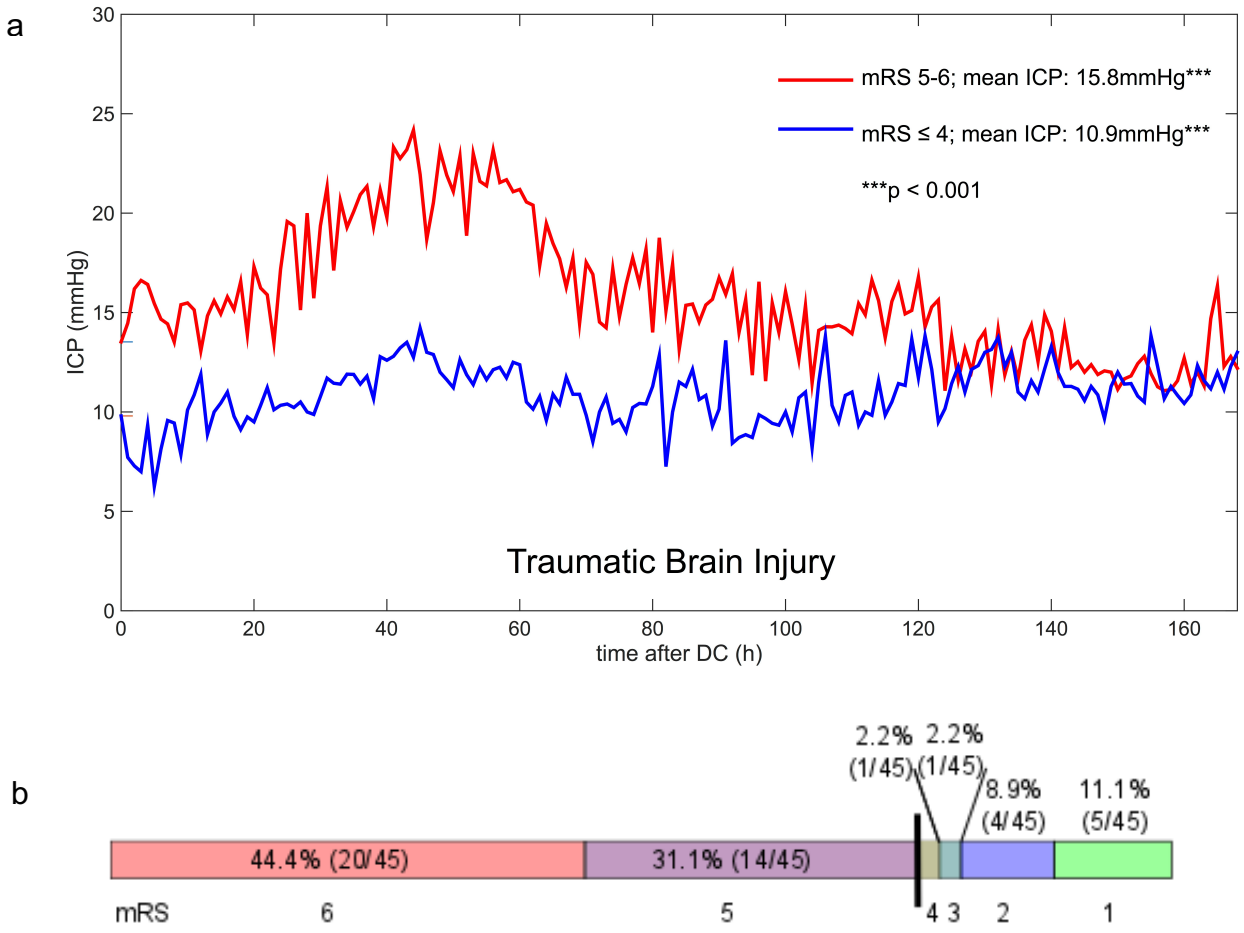

Figure 4: Postsurgical ICP-course in patients with traumatic brain injury.

a) Mean ICP in the favorable group was 10.9 mmHg (blue curve) compared to 15.8 mmHg in the unfavorable outcome group (red curve; $p < 0.001$) (Wilcoxon rank-sum test). The mean ICP does not exceed 20 mmHg in the first 31 hours after DC.

b) Distributions of mRS-scores of the TBI cohort

Since the mean ICP-values of both outcome groups lay clearly below 20 mmHg, new threshold values were calculated in a next step, to discriminate between both outcome groups. These optimized threshold values were determined by conditional inference tree analysis in several time periods using 12-hour time frames. Due to the dynamics of the ICP-values, 6-hour intervals were chosen in order to achieve better resolution during the first 48 hours. The new thresholds lay between 9.8 mmHg and 16.9 mmHg and were able to significantly distinguish favorable from unfavorable outcome as shown in Figure 5. Between hours 12 and 24 the calculated values were not significant. After 120 hours, no significant threshold values could be calculated.

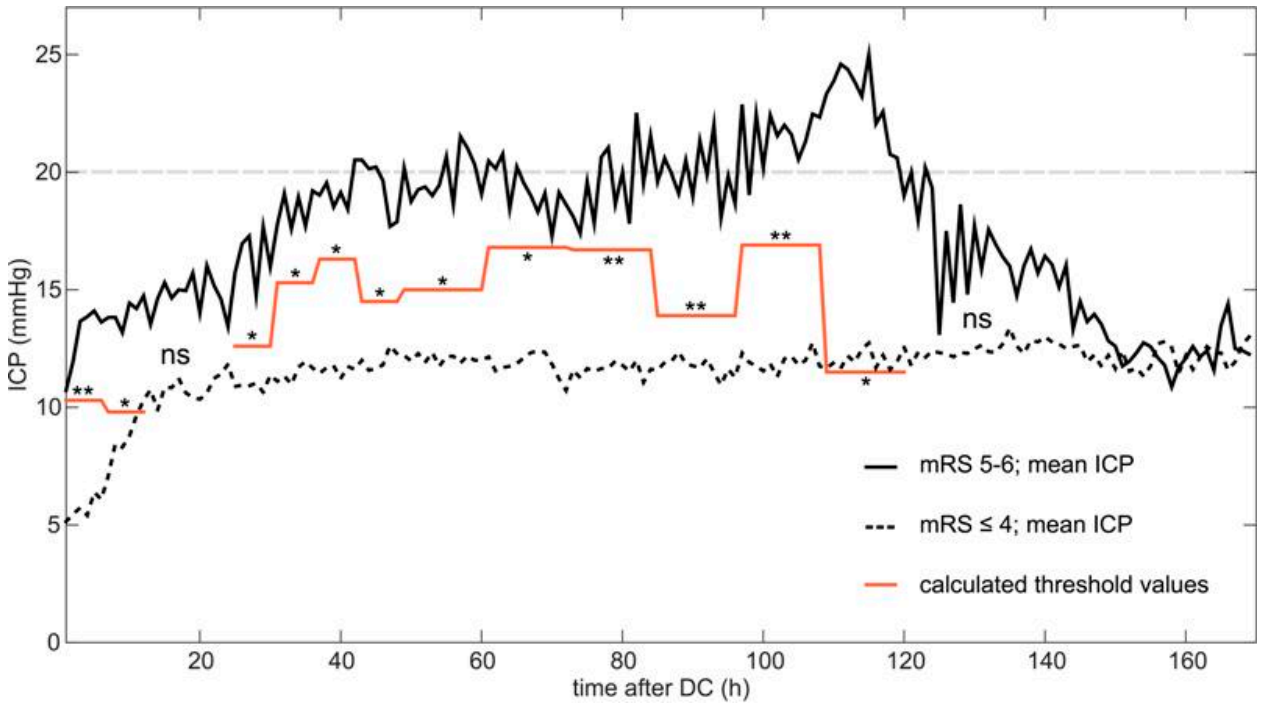

Figure 5: Calculated ICP-thresholds in the first 168 hours after DC.

Postsurgical ICP-courses in the favorable and unfavorable outcome group are shown in addition to calculated ICP-thresholds in 12-hour and 6-hour time frames, respectively. These thresholds lie between 9.8 mmHg and 16.9 mmHg. All thresholds significantly distinguish favorable from unfavorable outcome.

(* $p < 0.05$; ** $p < 0.01$; ns = not significant; conditional inference tree analysis; mRS = modified Rankin Scale, merged diagnoses)

With the aim of detecting an early predictive parameter regarding survival, an ICP-threshold was calculated via conditional inference tree analysis based on the ICP-values of the first 12 hours. As a result, 15 mmHg was determined as the cut-off value between a low- and a high-ICP group. The Kaplan-Meier method was used to analyze both groups' 30-day survival rate, showing a significantly higher survival rate in the low-ICP group ($p < 0.001$). ICU-survival rates are shown in Figure 6.

The survival probability of the low-ICP group lay above 75%. In the high-ICP group, survival probability fell below 40% in the first 10 days following DC.

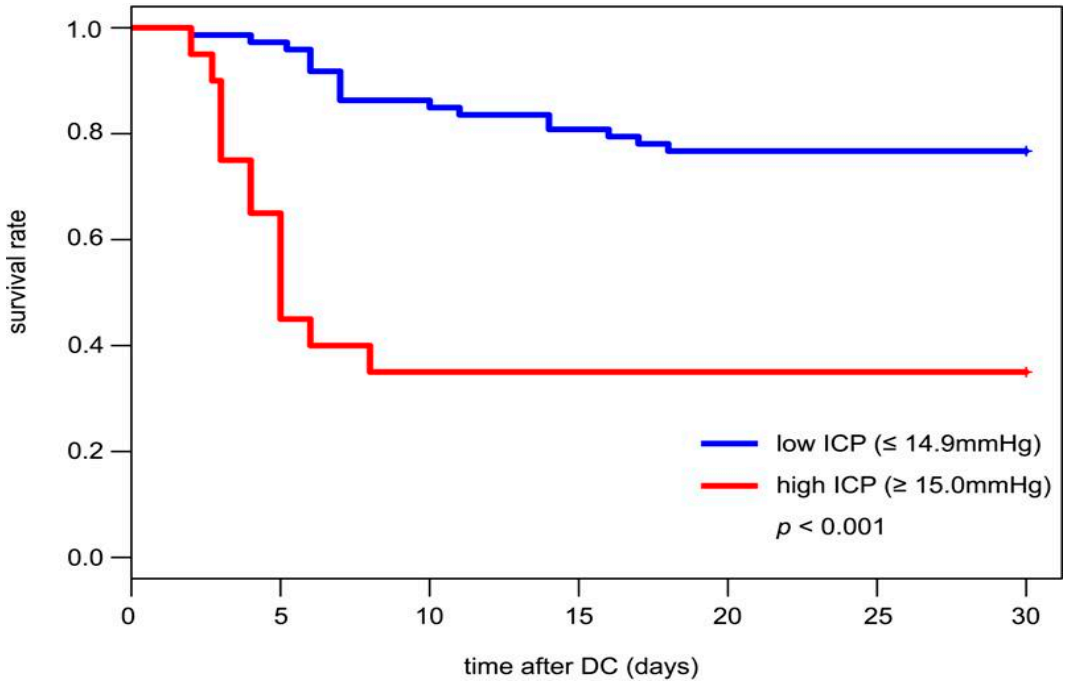

Figure 6: Kaplan-Meier survival curves for the first 30 days after DC.

Patients with low ICP (mean ICP ≤ 14.9 mmHg; blue curve) showed a significantly higher 30-day survival probability compared to those with high ICP (mean ICP ≥ 15.0 mmHg; red curve) ($p < 0.001$, log-rank test, merged diagnoses).

2.4 Discussion

Only a few parameters are known so far to predict patients' functional outcome after DC. According to previous studies, age, postoperative midline shift (MLS) and the difference between pre- and postoperative MLS on CT-imaging seem to be of prognostic value in patients undergoing DC due to malignant MCA infarction (28-31). Heterogeneous data are available regarding the quality of predictive factors in TBI patients with DC (31-34). The recently published RESCUEipc study found that TBI patients treated with DC might profit from lower mortality compared to conservatively treated patients, albeit showing higher rates of vegetative state, lower severe disability and upper severe disability (15). As ethical considerations arise from these findings, it will be necessary to evaluate what conclusions can be drawn from these results.

In this context, this study analyzed ICP-courses after decompressive craniectomy and delivers new time-dependent ICP-thresholds for a selected patient cohort.
ICP-monitoring was standardized, since only ipsilateral intraparenchymal probes were used. This technique's accuracy and comparability has been proven recently (35). Not only does this work provide predictors of functional outcome in patients after DC, but also delivers new time-dependent thresholds regarding ICP-guided therapy.
Postsurgical ICP-values of the first 168 hours were found to differ in patients with favorable and unfavorable outcome. ICP-values values in the unfavorable group started and stayed higher than in patients with favorable outcome. In the last hours of ICP-measurement the curves might approximate to each other due to the drop out of patients passed away. Courses of CPP have

been evaluated analogously (data not shown). Since mean CPP-values also differed significantly in both outcome groups, the conceivable confounding effect of lower MAP in patients with unfavorable outcome appears unlikely.
Due to the fact that mean ICP-values in both outcome groups lay well below 20 mmHg, our study challenges current concepts. Therefore, new time-dependent thresholds were calculated discriminating between favorable und unfavorable outcome (Figure 5).
As a possible confounder regarding the level of intracranial pressure, the extent of sedation was assessed. This was achieved via collecting the Richmond Agitation and Sedation Scale as an established and reliable parameter of sedation status (36). Due to the deep postoperative sedation of all patients in this study (mean RASS -3.7 (range -5 – 0) in the favorable group versus -3.9 (range -5 – 3) in the unfavorable group), no significant difference of RASS between the outcome groups could be detected. The level of sedation is therefore unlikely to be a confounder regarding patients' ICP.
Early postsurgical ICP-values combined with diagnosis and anisocoria showed a high power in predicting functional outcome. This demonstrates the value of the ICP-level as an independent predictor, whereas SAPS II as a validated score to assess hospital mortality, independent of the underlying diagnosis, did not show any predictive power (27, 37, 38). A reason for this finding might be the highly selected subgroup of surgically treated neurointensive care patients in this study. Since SAPS II primarily focuses on non-neurological parameters, it might not be adequate in assessing this cohort's mortality (39, 40). Anisocoria and diagnosis differed significantly in the outcome groups as revealed by uni- and multivariate analyses. The association of anisocoria with unfavorable outcome has previously been demonstrated (41).
Due to the different pathologies causing an increase in intracranial pressure, ICP-courses of the underlying diagnoses were analyzed separately (Fig. 3, 4). Both diagnosis-subgroup analyses independently showed significant differences in mean ICP-values in both outcome groups. Brain swelling during the first few days after malignant MCA infarction can be reproduced in the ICP-courses. The first exceeding of the 20 mmHg threshold occurs on the third day after DC (58^{th} hour) (42). While the 20 mmHg threshold in TBI patients is crossed on day 2 (32^{nd} hour), mean ICP-values in both outcome groups were found to be lower than in patients suffering from malignant MCA infarction. Although underlying pathophysiological mechanisms differ and have to be further investigated, 20 mmHg appears to be an insufficient threshold in the early postsurgical phase in both subgroups, since patients with favorable and unfavorable outcome did not exceed it

However, these new thresholds are only applicable for patients after DC and might be lower here than in a comparison group of conservatively treated patients. The surprisingly low threshold may be due to the previously performed DC.
Although this is a retrospective and single-center study, it nonetheless provides new insights into the field of neurointensive care.
The question is, whether future trials will be able to reproduce our findings. Furthermore, prospective trials should investigate possible new ICP-thresholds in conservatively treated patients.

Should future prospective multicenter studies be able to reproduce our findings in a greater cohort, the currently missing evidence for the benefit of ICP-guided therapy will have to be

revised. As a consequence, a new study may have to be initiated with the aim of re-evaluating the benefit of ICP-guided therapy, taking into account new ICP-thresholds.

2.5 List of abbreviations

CPP	cerebral perfusion pressure
CSF	cerebrospinal fluid
GCS	Glasgow Coma Scale
ICP	intracranial pressure
ICU	intensive care unit
MAP	mean arterial pressure
MCA	middle cerebral artery
MLS	midline shift
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
RASS	Richmond Agitation Sedation Scale
SAPS II	Simplified Acute Physiology Score
TBI	traumatic brain injury

2.6 References

1. Schwab S, Schellinger P, Werner C, Unterberg A, Hacke W. NeuroIntensiv: Springer Verlag; 2008.
2. Mokri B. The Monro-Kellie hypothesis: applications in CSF volume depletion. Neurology. 2001;56(12):1746-8.
3. Cervós-Navarro JF, R. Klinische Neuropathologie: Thieme Verlag; 1989.
4. Brain Trauma F, American Association of Neurological S, Congress of Neurological S, Joint Section on N, Critical Care AC, Bratton SL, et al. Guidelines for the management of severe traumatic brain injury. VIII. Intracranial pressure thresholds. Journal of neurotrauma. 2007;24 Suppl 1:S55-8.
5. Jüttler E. AWMF Leitlinie Intrakranieller Druck Deutsche Gesellschaft für Neurologie; 2012 [Available from: http://www.awmf.org/uploads/tx_szleitlinien/030-105l_S1_Intrakranieller_Druck_2012_verlaengert.pdf] [Accessed: 12.10.2016]
6. Brain Trauma F, American Association of Neurological S, Congress of Neurological S. Guidelines for the management of severe traumatic brain injury. Journal of neurotrauma. 2007;24 Suppl 1:S1-106.
7. Juttler E, Schwab S, Schmiedek P, Unterberg A, Hennerici M, Woitzik J, et al. Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery (DESTINY): a randomized, controlled trial. Stroke; a journal of cerebral circulation. 2007;38(9):2518-25.
8. Vahedi K, Vicaut E, Mateo J, Kurtz A, Orabi M, Guichard JP, et al. Sequential-design, multicenter, randomized, controlled trial of early decompressive craniectomy in malignant middle cerebral artery infarction (DECIMAL Trial). Stroke; a journal of cerebral circulation. 2007;38(9):2506-17.
9. Vahedi K, Hofmeijer J, Juettler E, Vicaut E, George B, Algra A, et al. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. The Lancet Neurology. 2007;6(3):215-22.
10. Hofmeijer J, Kappelle LJ, Algra A, Amelink GJ, van Gijn J, van der Worp HB, et al. Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]): a multicentre, open, randomised trial. The Lancet Neurology. 2009;8(4):326-33.
11. Timofeev I, Kirkpatrick PJ, Corteen E, Hiler M, Czosnyka M, Menon DK, et al. Decompressive craniectomy in traumatic brain injury: outcome following protocol-driven therapy. Acta neurochirurgica Supplement. 2006;96:11-6.
12. Cooper DJ, Rosenfeld JV, Murray L, Arabi YM, Davies AR, D'Urso P, et al. Decompressive craniectomy in diffuse traumatic brain injury. The New England journal of medicine. 2011;364(16):1493-502.
13. Jiang JY, Xu W, Li WP, Xu WH, Zhang J, Bao YH, et al. Efficacy of standard trauma craniectomy for refractory intracranial hypertension with severe traumatic brain injury: a multicenter, prospective, randomized controlled study. Journal of neurotrauma. 2005;22(6):623-8.
14. Guerra WK, Gaab MR, Dietz H, Mueller JU, Piek J, Fritsch MJ. Surgical decompression for traumatic brain swelling: indications and results. Journal of neurosurgery. 1999;90(2):187-96.

15. Hutchinson PJ, Kolias AG, Timofeev IS, Corteen EA, Czosnyka M, Timothy J, et al. Trial of Decompressive Craniectomy for Traumatic Intracranial Hypertension. The New England journal of medicine. 2016;375(12):1119-30.
16. Stocchetti N, Picetti E, Berardino M, Buki A, Chesnut RM, Fountas KN, et al. Clinical applications of intracranial pressure monitoring in traumatic brain injury : report of the Milan consensus conference. Acta neurochirurgica. 2014;156(8):1615-22.
17. Brain Trauma F, American Association of Neurological S, Congress of Neurological S, Joint Section on N, Critical Care AC, Bratton SL, et al. Guidelines for the management of severe traumatic brain injury. VI. Indications for intracranial pressure monitoring. Journal of neurotrauma. 2007;24 Suppl 1:S37-44.
18. Chesnut RM, Temkin N, Carney N, Dikmen S, Rondina C, Videtta W, et al. A trial of intracranial-pressure monitoring in traumatic brain injury. The New England journal of medicine. 2012;367(26):2471-81.
19. Chesnut RM. Intracranial pressure monitoring: headstone or a new head start. The BEST TRIP trial in perspective. Intensive Care Med. 2013;39(4):771-4.
20. Olivecrona M, Rodling-Wahlstrom M, Naredi S, Koskinen LO. Effective ICP reduction by decompressive craniectomy in patients with severe traumatic brain injury treated by an ICP-targeted therapy. Journal of neurotrauma. 2007;24(6):927-35.
21. Paldor I, Rosenthal G, Cohen JE, Leker R, Harnof S, Shoshan Y, et al. Intracranial pressure monitoring following decompressive hemicraniectomy for malignant cerebral infarction. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia. 2015;22(1):79-82.
22. Munch E, Horn P, Schurer L, Piepgras A, Paul T, Schmiedek P. Management of severe traumatic brain injury by decompressive craniectomy. Neurosurgery. 2000;47(2):315-22; discussion 22-3.
23. Kontopoulos V, Foroglou N, Patsalas J, Magras J, Foroglou G, Yiannakou-Pephtoulidou M, et al. Decompressive craniectomy for the management of patients with refractory hypertension: should it be reconsidered? Acta neurochirurgica. 2002;144(8):791-6.
24. Poca MA, Benejam B, Sahuquillo J, Riveiro M, Frascheri L, Merino MA, et al. Monitoring intracranial pressure in patients with malignant middle cerebral artery infarction: is it useful? Journal of neurosurgery. 2010;112(3):648-57.
25. Sharda P, Haspani S, Idris Z. Factors prognosticating the outcome of decompressive craniectomy in severe traumatic brain injury: A Malaysian experience. Asian journal of neurosurgery. 2014;9(4):203-12.
26. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 2002;166(10):1338-44.
27. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA. 1993;270(24):2957-63.
28. Curry WT, Jr., Sethi MK, Ogilvy CS, Carter BS. Factors associated with outcome after hemicraniectomy for large middle cerebral artery territory infarction. Neurosurgery. 2005;56(4):681-92; discussion -92.
29. Rabinstein AA, Mueller-Kronast N, Maramattom BV, Zazulia AR, Bamlet WR, Diringer MN, et al. Factors predicting prognosis after decompressive hemicraniectomy for hemispheric infarction. Neurology. 2006;67(5):891-3.

30. Tu PH, Liu ZH, Chuang CC, Yang TC, Wu CT, Lee ST. Postoperative midline shift as secondary screening for the long-term outcomes of surgical decompression of malignant middle cerebral artery infarcts. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia. 2012;19(5):661-4.
31. Sauvigny T, Gottsche J, Vettorazzi E, Westphal M, Regelsberger J. New Radiologic Parameters Predict Clinical Outcome after Decompressive Craniectomy. World neurosurgery. 2015.
32. Saade N, Veiga JC, Cannoni LF, Haddad L, Araujo JL. Evaluation of prognostic factors of decompressive craniectomy in the treatment of severe traumatic brain injury. Revista do Colegio Brasileiro de Cirurgioes. 2014;41(4):256-62.
33. Ucar T, Akyuz M, Kazan S, Tuncer R. Role of decompressive surgery in the management of severe head injuries: prognostic factors and patient selection. Journal of neurotrauma. 2005;22(11):1311-8.
34. Takeuchi S, Takasato Y, Suzuki G, Maeda T, Masaoka H, Hayakawa T, et al. Computed tomography after decompressive craniectomy for head injury. Acta neurochirurgica Supplement. 2013;118:235-7.
35. Zacchetti L, Magnoni S, Di Corte F, Zanier ER, Stocchetti N. Accuracy of intracranial pressure monitoring: systematic review and meta-analysis. Critical care. 2015;19:420.
36. Ely EW, Truman B, Shintani A, Thomason JW, Wheeler AP, Gordon S, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). JAMA. 2003;289(22):2983-91.
37. Raj R, Skrifvars M, Bendel S, Selander T, Kivisaari R, Siironen J, et al. Predicting six-month mortality of patients with traumatic brain injury: usefulness of common intensive care severity scores. Critical care. 2014;18(2):R60.
38. Handschu R, Haslbeck M, Hartmann A, Fellgiebel A, Kolominsky-Rabas P, Schneider D, et al. Mortality prediction in critical care for acute stroke: Severity of illness-score or coma-scale? Journal of neurology. 2005;252(10):1249-54.
39. Sakr Y, Marques J, Mortsch S, Gonsalves MD, Hekmat K, Kabisch B, et al. Is the SAPS II score valid in surgical intensive care unit patients? J Eval Clin Pract. 2012;18(2):231-7.
40. Suistomaa M, Niskanen M, Kari A, Hynynen M, Takala J. Customized prediction models based on APACHE II and SAPS II scores in patients with prolonged length of stay in the ICU. Intensive Care Med. 2002;28(4):479-85.
41. Marmarou A, Lu J, Butcher I, McHugh GS, Murray GD, Steyerberg EW, et al. Prognostic value of the Glasgow Coma Scale and pupil reactivity in traumatic brain injury assessed pre-hospital and on enrollment: an IMPACT analysis. Journal of neurotrauma. 2007;24(2):270-80.
42. Kunze S, Hacke W, Schwab S. Klinik und Therapie des raumfordernden Mediainfarktes. Dt Ärztebl. 1999;96(42):A-2670-7.

3. Zusammenfassung in deutscher und englischer Sprache

This doctoral thesis investigated postoperative intracranial pressure (ICP)-levels and their correlation with clinical outcome in patients who underwent decompressive craniectomy (DC). DC is an established part of the treatment in patients suffering from malignant infarction of the middle cerebral artery or severe traumatic brain injury. While the ICP lowering effect of decompressive craniectomy has been proven before, the benefit of ICP-guided therapy remains unclear. Currently, an ICP of 20 mmHg frequently serves as threshold, which determines further therapy. The objective of this study was therefore to evaluate this threshold's accuracy and to investigate the course of ICP-values with respect to the neurological outcome in patients who underwent DC. A retrospective evaluation of ICP-values of the first 168 hours after DC in 102 patients revealed significant differences between patients with favorable and unfavorable outcome. Since mean postsurgical ICP-values in both outcome groups lay below 20 mmHg, a new time-dependent threshold concept was assessed. Kaplan Meier survival estimates were calculated based on this new threshold concept and showed significantly higher survival probability in patients with "low" ICP. Although this study has its biases and limitations due to its retrospective design, it nonetheless provides new insights into the field of ICP-management. However, the question remains whether ICP-guided treatment has a positive impact on clinical outcome. This is beyond the scope of this analysis. Should future prospective multicenter studies be able to reproduce our findings in a greater cohort, the currently missing evidence for the benefit of ICP-guided therapy will have to be revised.

Diese Dissertation untersuchte den postoperativen intrakraniellen Druck und seine Korrelation mit dem klinischen Ergebnis bei Patienten, bei denen eine dekompressive Hemikraniektomie durchgeführt wurde. Die dekompressive Hemikraniektomie ist ein etablierter Bestandteil in der Behandlung von Patienten, welche an einem malignen Infarkt der Arteria cerebri media oder einem schweren Schädelhirntrauma leiden. Während der Hirndruck senkende Effekt der dekompressiven Hemikraniektomie bereits bewiesen werden konnte, bleibt der Nutzen der Hirndruck gesteuerten Therapie an sich unklar. Aktuell dient ein Wert von 20 mmHg häufig als Grenzwert, welcher die weitere Therapie bestimmt. Das Ziel dieser Studie war es daher, die Genauigkeit dieses Grenzwertes sowie die intrakraniellen Druckwerte im Hinblick auf das neurologische Ergebnis bei Patienten nach dekompressiver Hemikraniektomie zu untersuchen. Die retrospektive Analyse intrakranieller Druckwerte der ersten 168 postoperativen Stunden zeigte signifikante Unterschiede zwischen Patienten mit gutem und schlechtem Outcome. Da die mittleren Druckwerte in beiden Outcome-Gruppen unter 20 mmHg lagen, wurde ein neues zeitabhängiges Grenzwertkonzept erstellt. Kaplan-Meier Überlebenszeit Analysen wurden, basierend auf diesem neuen Grenzwertkonzept, berechnet und zeigten eine signifikant höhere Überlebenswahrscheinlichkeit bei Patienten mit "niedrigem" Hirndruck.
Obwohl diese Studie durch ihr retrospektives Design limitiert ist, bietet sie dennoch neue Einsichten in das Feld der Hirndrucktherapie. Die Frage, ob die Hirndruck gesteuerte Therapie einen positiven Effekt auf das klinische Ergebnis hat, bleibt jedoch unbeantwortet. Dies entzieht sich der Aussagekraft dieser Analyse. Sollten zukünftige prospektive Multicenterstudien unsere Ergebnisse in einer größeren Kohorte reproduzieren können, müsste die aktuell fehlende Evidenz für Hirndruck gesteuerte Therapie überdacht werden.

4. Erklärung des Eigenanteils

Die Thematik der Dissertation wurde von Prof. Dr. Jan Regelsberger (Klinik und Poliklinik für Neurochirurgie des Universitätsklinikums Hamburg-Eppendorf) vorgeschlagen.

Weitere konkrete Ausformulierungen, der Entwurf des Studienkonzepts sowie die Erstellung der hier bearbeiteten Hypothesen erfolgten durch Prof. Dr. Jan Regelsberger, Dr. Thomas Sauvigny (Klinik und Poliklinik für Neurochirurgie des Universitätsklinikums Hamburg-Eppendorf) und die Verfasserin dieser Arbeit.

Die gesamte Erhebung der hier analysierten Daten erfolgte durch die Verfasserin.

Aufarbeitung und Analyse der klinischen und demografischen Daten sowie der erhoben ICP- und CPP-Daten erfolgten durch die Verfasserin.

Die statistische Aufarbeitung, inklusive weiterführender Analysen der aufgestellten Hypothesen, erfolgte in interdisziplinärer Arbeit durch Eik Vettorazzi (Institut für Medizinische Biometrie und Epidemiologie des Universitätsklinikums Hamburg-Eppendorf), Dr. Thomas Sauvigny und die Verfasserin.

Auswertung und Interpretation der Daten erfolgten durch Dr. Thomas Sauvigny und die Verfasserin.

Die Verfassung des Papers ("Intracranial pressure in patients undergoing decompressive craniectomy - new perspective on thresholds") sowie die Ausarbeitung der Grafiken erfolgten zu gleichen Teilen durch Dr. Thomas Sauvigny und die Verfasserin.

An der Ausarbeitung des Papers waren Dr. Patrick Czorlich (Klinik und Poliklinik für Neurochirurgie des Universitätsklinikums Hamburg-Eppendorf), Prof. Dr. Jan Regelsberger und Prof. Dr. Manfred Westphal (Klinik und Poliklinik für Neurochirurgie des Universitätsklinikums Hamburg-Eppendorf) beteiligt.

5. Liste der aus der Dissertation hervorgegangenen Veröffentlichungen

Sauvigny T & Göttsche J, Czorlich P, Vettorazzi E, Westphal M, Regelsberger J. Intracranial pressure in patients undergoing decompressive craniectomy - new perspective on thresholds. Journal of Neurosurgery. 2016.

Sauvigny T & Göttsche J, Vettorazzi E, Westphal M, Regelsberger J. New Radiologic Parameters Predict Clinical Outcome after Decompressive Craniectomy. World Neurosurgery. 2015.

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7. Lebenslauf

Lebenslauf aus datenschutzrechtlichen Gründen nicht enthalten.

8. Eidesstattliche Erklärung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.
Ferner versichere ich, dass ich die Dissertation bisher nicht einem Fachvertreter an einer anderen Hochschule zur Überprüfung vorgelegt oder mich anderweitig um Zulassung zur Promotion beworben habe.
Ich erkläre mich einverstanden, dass meine Dissertation vom Dekanat der Medizinischen Fakultät mit einer gängigen Software zur Erkennung von Plagiaten überprüft werden kann.

Unterschrift: .....