A new reproducible model of an epidural mass lesion in rodents. Part I: Characterization by neurophysiological monitoring, magnetic resonance imaging, and histopathological analysis

RALF BURGER, M.D., MARTIN BENDSZUS, M.D., GILES HAMILTON VINCÉ, M.D., KLAUS ROOSEN, M.D., PH.D., AND ANTHONY MARMAROU, PH.D.

Departments of Neurosurgery and Neuroradiology, University of Würzburg; Department of Neurosurgery, University of Regensburg, Germany; and Medical College of Virginia, Richmond, Virginia

Object. The goal of this study was to characterize a new model of an epidural mass lesion in rodents by means of neurophysiological monitoring, magnetic resonance imaging, and histopathological analysis.

Methods. Changes in intracranial pressure (ICP), cerebral perfusion pressure (CPP), and laser Doppler flowmetry (LDF) values, intraparenchymal tissue partial oxygen pressure (PtiO₂), and electroencephalography (EEG) activity were evaluated in the rat during controlled, epidural expansion of a latex balloon up to a maximum ICP of 60 mm Hg. The initial balloon inflation was followed by periods of sustained inflation (30 ± 1 minute) and reperfusion (180 ± 5 minutes). Histopathological analysis and magnetic resonance (MR) imaging were performed to characterize the lesion.

The time to maximum balloon expansion and the average balloon volume were highly reproducible. Alterations in EEG activity during inflation first appeared when the CPP decreased to 57 mm Hg, the LDF value to 66% of baseline values, and the PtiO₂ to 12 mm Hg. During maximum compression, the CPP was reduced to 34 mm Hg, the LDF value to 40% of baseline, and the PtiO₂ to 4 to 5 mm Hg. The EEG tracing was isoelectric during prolonged inflation and the values of LDF and PtiO₂ decreased due to accompanying hypotonia. After reperfusion, the CPP was significantly decreased (p < 0.05) due to the elevation of ICP. Both the LDF value and EEG activity displayed incomplete restoration, whereas the value of PtiO₂ returned to normal. Histological analysis and MR imaging revealed brain swelling with a midline shift and a combined cortical–subcortical ischemic lesion beyond the site of balloon compression.

Conclusions. This novel model of an epidural mass lesion in rodents closely resembles the process observed in humans. Evaluation of pathophysiological and morphological changes was feasible by using neurophysiological monitoring and MR imaging.

KEY WORDS • trauma • mass lesion • ischemia–reperfusion • laser Doppler flowmetry • partial pressure of oxygen • magnetic resonance imaging • rat

Extraxial mass lesions account for 37% of severe head injuries. Over the past decades prognosis with respect to functional outcome and mortality has been improved. This mainly has been achieved by improvements in emergency rescue, transport, and care of patients, and by new diagnostic modalities such as computerized tomography scanning. Nevertheless, 6 to 19.5% of patients with epidural hematomas and 19.5 to 50.3% of those with acute SDHs have still died of their injuries in the last decade.

So far, the experimental evaluation of dynamic pathophysiological changes during induction of an extraxial mass lesion by epidural or subdural balloon expansion has been described in large animals (primates, dogs, and cats). Until now, a reproducible balloon model in rodents has not been reported.

An SDH model created by injection of subdural autologous blood was established in rodents and the ensuing pathophysiological changes caused by this lesion have been extensively studied. Heterogeneous distribution of blood over the hemisphere, delayed clotting of the injected blood, and assessment of pathophysiological interactions during hematoma evacuation and reperfusion are more difficult to evaluate than the circumscript mass lesion induced by a balloon.

Multimodal neurological monitoring has been introduced to reduce secondary brain damage in the sequela of severe head injuries and, thus, improve outcome. These recent developments necessitate the determination of methodological thresholds affecting brain homeostasis during and after induction of an extraxial focal mass lesion. Therefore, we revised and evaluated a new epidural balloon expansion model introduced by the Richmond group.

Abbreviations used in this paper: CPP = cerebral perfusion pressure; EEG = electroencephalography; ICP = intracranial pressure; LDF = laser Doppler flowmetry; MABP = mean arterial blood pressure; MR = magnetic resonance; PaCO₂ = arterial partial pressure of CO₂; PaO₂ = arterial partial pressure of oxygen; PtiO₂ = tissue partial O₂ pressure; SD = standard deviation; SDH = subdural hematoma.
Epidural mass lesion model in rodents

Materials and Methods

Animal Preparation

The experimental protocol was approved by the Animal Care Committee of the University of Würzburg. The study included 29 Sprague-Dawley rats that were randomized into one of two groups: a group composed of sham-operated animals (Group A, seven rats with a mean weight of 505 ± 73 g) and a group with focal mass lesions (Group B, 22 rats with a mean weight of 466 ± 85 g). The animals received intubation and artificial ventilation with a gas mixture of 1 to 2% isoflurane, 33% O₂, and 66% nitrous oxide. The left femoral artery was catheterized for measuring systemic MABP and PaO₂, PaCO₂, pH, and arterial O₂ saturation throughout the course of the experiment. Rectal body temperature was maintained between 36.5 and 37.5°C by using a heat lamp and a warming blanket. The depth of anesthesia was controlled by monitoring arterial blood pressure and EEG activity.

After the animal had been placed in a stereotactic frame, the skull was exposed by a midline incision that extended from the nasion to the occiput. The epidural balloon device and the monitoring probes were placed according to the schematic drawing shown in Fig. 1. Bone discs with openings of the dura mater that were created during trephination were sealed with dental cement before baseline measurements were obtained.

Data Collection

Cerebral blood flow was measured using LDF with a large-area integrating probe (diameter 3 mm). The probe was positioned over a 2.3-mm burr hole and placed perpendicular to the dura mater at a distance of 1 mm; it emits infrared light with a wavelength of 810 nm. The light is reflected to eight collectors encompassing the light source of the probe in a diameter of 2 mm. The value of the laser Doppler–measured flow (a product of the velocity of flowing blood cells and blood volume in arbitrary units) was recorded as a percentage of drift from initial baseline values. The technical principle and the comparison of LDF to other generally recognized methods for measurement (60 11 minutes in Group A and 18 of 22 animals in Group B) were placed according to the schematic drawing shown in Fig. 1. Bone discs with openings of the dura mater that were created during trephination were sealed with dental cement before baseline measurements were obtained.

A new, commercially available microcatheter for small animals (diameter 0.5 mm; O₂ sensitive area 1 mm in length) was used to measure PtO₂. Apart from a slightly modified length of the PO₂-sensitive area, the architecture of the probe is similar to catheters used in experimental studies of dogs, cats, and rodents,6,17,44 and is similar to those used in clinical studies.11,32,48 The sensor was inserted 4 mm into the white matter of the rodent forebrain. The calibration value specific to the catheter was adjusted to the PO₂ device according to recommendations by the manufacturer. The premeasurement zero (2.2 ± 1.3 mm Hg in Group A and 2.36 ± 1.68 mm Hg in Group B) and the sensitivity drift (−0.7 ± 4.2% in Group A and −2.5 ± 2.6% in Group B) were evaluated for both groups. The PtO₂ values were corrected on the basis of the right parietal intraparenchymal brain temperature, which was recorded with a C10 metal thermometer (diameter 0.25 mm). Intraparenchymal ICP was monitored with the aid of a microsensor. Electrocerephalography recordings were quantitatively analyzed using a five-point visual inspection scale.10

Experimental Protocol

The data obtained during animal preparation were recorded and digitally stored using a MacLab device. A time point of baseline measurement (60 ± 2 minutes in Group A and 69 ± 11 minutes in Group B) was followed by an observation period of 179 ± 2 minutes in sham-operated animals. In Group B the epidural latex balloon was inflated with saline until an ICP of 60 mm Hg was reached (flow rate 0.5 ml/hour). Balloon inflation was followed by periods of sustained inflation (30 ± 1 minute), rapid deflation (15 seconds), and reperfusion (180 ± 5 minutes).

During the period of balloon expansion, changes in neurophysiological parameters were recorded as they related to the intracranial balloon volume. Neurophysiological monitoring was successful throughout the entire experiment in all animals in Group A and in 18 of 22 animals in Group B. At the end of the observation period the hole created by trephination was immediately closed with a bone flap. After skin closure the animals were perfusion fixed with a solution of 3.7% paraformaldehyde (pH adjusted to 7.3–7.4 with cacodylate buffer) and decapitated. Finally, the PtO₂ microcatheter was checked for a postmeasurement zero (2.59 ± 1.56 mm Hg in Group A and 3.08 ± 1.38 mm Hg in Group B) and sensitivity drift (−1.48 ± 2.4% in Group A and −2 ± 3.4% in Group B).

Magnetic Resonance Imaging and Histological Analysis

Magnetic resonance imaging measurements of the rat skull were performed using a 1.5-tesla MR imaging device with a round surface coil (4 cm diameter) within the first 3 days after perfusion fixation. The protocol consisted of T₂-weighted sequences (coronal plane, angulation rectangular to the anterior skull base, slice thickness 1 mm, TE 4000 msec, TR 96 msec, field of view 60 mm). Volumetric analysis of lesion size was performed using a workstation equipped with postprocessing software to delimit manually the hyperintense area on every imaging slice.

Afterward, the brain was removed for a histopathological workup to evaluate the extent of tissue damage in Group B, as described by Morikawa and colleagues,50 by using a camera microscope and SigmaScan software. Histological and MR imaging volumetric analyses were performed in 15 of 22 animals in Group B.

Statistical Analysis

Intracranial pressure, PtO₂, MABP, blood gas values, EEG visual inspection scores, temperature values, and histological and MR imaging volumetric data are presented as mean values ± SDs. The LDF values are given as mean percentages of baseline values. One-way repeated-measures analysis of variance was used for statistical evaluation of changes over the observation period in both groups. A paired t-test was used to evaluate significant changes during the time course of balloon expansion in Group B and an unpaired t-test was used to compare the time course between brain and core temperatures in each group and differences in physiological parameters between Groups A and B. The Kolmogorov–Smirnov test (with the Lilliefors correction) was used to test data for normality. Statistical analysis was performed using a commercially available statistical software program (SigmaStat version 2.0) and significance was deemed appropriate for a probability value less than 0.05.

Sources of Supplies and Equipment

The large-area integrating probe used for LDF was obtained from Moor Instruments Ltd. (Devon, UK). The small-animal microwaether (Clark-type C1.R) and the metal thermoelement (model C10) were purchased for use with the Liquox system from GMS Corp. (Kiel, Germany) and are now available from Integra Neurosciences.
(Plainsboro, NJ). The microsensor was acquired from Codman and Shurtleff, Inc., a division of Johnson & Johnson (Randolph, MA). The MacLab device was purchased from AD Instruments (Milford, MA).

The Magneion Vision MR imager and Virtuoso postprocessing software were obtained from Siemens (Erlangen, Germany). The SigmaScan software and the SigmaStat statistical software were obtained from Jandel Scientific and are now available from SPSS Inc. (Chicago, IL).

**Results**

**Physiological Parameters**

Blood pressure in sham-operated and injured animals did not differ at the baseline level (p > 0.05). In the injured animals the MABP increased significantly during maximum inflation (p = 0.003) and dropped to subnormal values during prolonged inflation (p < 0.001). There was no difference between groups during the reperfusion period. Rectal and brain temperatures did not differ in sham-operated animals (p > 0.05), whereas brain temperature dropped below core values during brain compression in Group B (p < 0.001). Values of blood gases were not significantly different, except for hyperventilation in sham-operated animals at the beginning of the investigation (p < 0.05) and slightly higher values of PaO₂ over the course of the experiment (p < 0.05) (Table 1). Hematocrit values were similar in sham-operated and injured animals at both the beginning (p = 0.08) and the end (p = 0.058) of the experiment.

**Neurophysiological Values in Sham-Operated Animals.** Laser Doppler flowmetry showed stable values over time in Group A animals, with a maximum dispersion of 26% from baseline measurements. Initially, measurements of PtO₂ revealed a mean value of 10.9 ± 0.9 mm Hg, which reached a stable value of 22.8 ± 0.4 mm Hg after 90 minutes. The maximum dispersion of PtO₂ during the follow up was 4.42 mm Hg. Intracranial pressure remained stable between 4.4 and 5.9 mm Hg and CPP ranged between 73 and 81 mm Hg over the entire time course. Throughout the investigation EEG activity was normal in all animals.

**Neurophysiological Values in Injured Animals During Balloon Expansion, Sustained Inflation, and Reperfusion.** The balloon expansion device provoked an ICP of 60 mm Hg in Group B animals within a reproducible time period (34 ± 5 minutes) and at a comparable mean balloon volume (0.31 ± 0.04) (Figs. 2 and 3). At the beginning of balloon

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Measurements of MABP, blood gases, and brain and core temperatures</strong></td>
</tr>
<tr>
<td>Time</td>
</tr>
<tr>
<td>sham-operated animals (Group A)</td>
</tr>
<tr>
<td>B1</td>
</tr>
<tr>
<td>B2</td>
</tr>
<tr>
<td>120 mins</td>
</tr>
<tr>
<td>180 mins</td>
</tr>
<tr>
<td>240 mins</td>
</tr>
<tr>
<td>animals w/ epidural mass lesions (Group B)</td>
</tr>
<tr>
<td>B1</td>
</tr>
<tr>
<td>B2</td>
</tr>
<tr>
<td>BE</td>
</tr>
<tr>
<td>SI</td>
</tr>
<tr>
<td>RP 60 mins</td>
</tr>
<tr>
<td>RP 120 mins</td>
</tr>
<tr>
<td>RP 180 mins</td>
</tr>
</tbody>
</table>

* Values are expressed as the means ± SD. Abbreviations: BE = maximum balloon expansion; B1 = start of baseline; B2 = end of baseline; PaO₂ Sat = PaO₂ saturation; RP = time of reperfusion (in minutes); SI = end of sustained inflation; Tbr = brain temperature; Tc = rectal core temperature.
† p < 0.05.
‡ p < 0.001.

<table>
<thead>
<tr>
<th>TABLE 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physiological parameters during period of epidural balloon expansion in Group B</strong></td>
</tr>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
</tr>
<tr>
<td>ICP (mm Hg)</td>
</tr>
<tr>
<td>CPP (mm Hg)</td>
</tr>
<tr>
<td>LDF (% of baseline)</td>
</tr>
<tr>
<td>PtO₂ (mm Hg)</td>
</tr>
<tr>
<td>EEG score‡</td>
</tr>
</tbody>
</table>

* Values are expressed as the means ± SD.
† Indicates first significant change in parameter during balloon expansion.
‡ Visual inspection scale of DeWitt, et al. (5, normal; 1, isoelectric EEG).
inflation, the MABP was normal. A significant increase in MABP was noted at a balloon volume of 0.3 ml (p = 0.048), which finally ended in a Cushing response with a mild vasomotor component, bradycardia, and respiratory dysfunction. An early increase in the ICP was observed after a balloon inflation of 0.05 ml (p < 0.002), whereas the CPP first dropped at a balloon volume of 0.15 ml (p = 0.037). The PtiO2 (p = 0.007) and the LDF value (p = 0.034) demonstrated significant reductions at a balloon volume of 0.1 ml. Alterations in EEG activity first occurred (p = 0.016) when the CPP was reduced to 57 mm Hg, the PtiO2 to 12 mm Hg, and the LDF value to 66% of baseline values. The PtiO2 reached critical values below 10 mm Hg when the LDF value was reduced to 53% and the CPP to 45 mm Hg. At maximum balloon expansion the EEG activity developed a profound burst suppression, turning into an isoelectric pattern. At this time point the CPP was reduced to 34 mm Hg, the LDF value to 40%, and the PtiO2 ranged between 5 and 6 mm Hg (Table 2).

During prolonged balloon expansion the ICP slowly decreased from 61.3 ± 4.9 mm Hg to 39.4 ± 3.2 mm Hg and the CPP dropped further due to concomitant hypotonia. Consequently, the PtiO2 and LDF values further declined and EEG traces showed no evidence of electric activity (Table 3).

Immediately after reperfusion the ICP dropped to baseline value and then increased up to 17.1 ± 1.7 mm Hg within 5 minutes. Eventually, LDF revealed an incomplete flow recovery to 71 ± 5% of baseline value (p < 0.05) and EEG demonstrated an incomplete functional recovery (p < 0.05), although the PtiO2 increased to normal values (Table 3). Four animals in Group B had to be excluded from data evaluation because of balloon disruption (two animals) and loss of neurophysiological data (two animals).

**Results of MR Imaging and Histological Analysis**

On T2-weighted MR images a hyperintense lesion was demonstrated in the ipsilateral cortex, including the upper portions of the basal ganglia, and a midline shift could be observed (Fig. 4). The mean lesion size was 20.3 ± 6.6 mm3. In four animals a noticeably smaller lesion was demonstrated, measuring between 6 and 14 mm3. In these animals LDF and PtiO2 (29.7 ± 7 mm Hg compared with 23.3 ± 8 mm Hg) revealed a trend toward higher values. On EEG studies recovery was nearly (two animals) or fully (one animal) restored in three of these animals. After completion of monitoring and removal of the balloon device, a non-space-occupying epidural blood film was found between the dura mater and the balloon at the level of the trephination. No relevant SDH was found on the brain surface, but compressed and obliterated pial and cortical vessels and a thin subarachnoidal blood film were common findings. Maximum balloon inflation was accompanied by brain swelling, which was pronounced on the side of the lesion, a midline shift, and mild signs of a supracallosal, un-
cal, and central herniation. Around the balloon device, we observed an ischemic lesion with early signs of necrosis; massive swelling of astrocytes in the cortex, basal ganglia, and corpus callosum; small tissue ruptures; and sites of bleeding (Fig. 5). Morphometric analysis illustrated a clearly demarcated ischemic area; the maximum portion of the lesion was found at the coordinate bregma -6 mm (Fig. 6). Sham-operated animals were not found to have ischemic damages or intracerebral bleeding.

Discussion

The main goal of the present study was to verify a new model of an epidural mass lesion in rodents so that we may study pathophysiological changes during primary and secondary traumatic brain damage. The choice of rodents is convenient because inbreeding of this species allows more stable experimental conditions and, therefore, unbiased results.19 The reproducibility of this model could be confirmed by parameters that are commonly used in clinical multimodal neurophysiological monitoring. Evaluation or determination of methodological thresholds for critical brain homeostasis was possible. In addition, the lesion was characterized by postmortem histological and MR imaging studies. The neuroimaging characterization of the model is presented in more detail in Part II of this report, in which we describe the in vivo MR imaging experiments.3

Because of the bony tentorium structure in rodents, pathoanatomical conditions and subsequent clinical courses are similar to those previously encountered with established mass lesion models involving large animal species.15,16,20,24 In most animals the only developments were a temporary anisocoria and a Cushing response with a mild vasomotor component, bradycardia, and respiratory dysfunction during maximum brain compression. The evidence of an isoelectric EEG tracing, a demarcated lesion on MR imaging, and no proof of bulbar paralysis determined the time point of maximum balloon expansion in our series. The capability of varying the extents and time courses of the balloon expansion and reperfusion easily is a considerable advantage of this model. In contrast with SDH16,69 and intracerebral hematoma31,46 models, determination of the influence of blood substances on ischemia and brain edema is not feasible; however, this is only of minor interest because a direct toxic effect of blood within 72 hours after subdural blood injection is under debate.13

Multimodal Neurological Monitoring

Neurophysiological monitoring was applied in sham-operated animals to ensure that all parameters were reliable in this rodent model. Intracranial pressure was stable throughout the whole observation time. The PtiO2 measurements ranged between 20 and 25 mm Hg, corresponding to experimental and clinical findings.5,8,11,25,31,46,47,56,65,66 The PtiO2 reached normal values with a delay of 60 to 90 minutes; this was most likely caused by the trauma of probe insertion, accompanied by temporary local swelling and bleeding.15 In contrast the LDF value was immediately stable and re-

![Image](image.jpg)

**Fig. 4.** Coronal T2-weighted images through lesions in decapitated, paraformaldehyde-fixed rodent heads 3 hours after a period of ischemia–reperfusion (Group B). Hyperintense areas (surrounded by notched lines) illustrate the lesion with sites of bleeding between the cortex and cingulum (arrowheads) and swelling accompanied by a distinct midline shift (arrow).
mained so for the entire 240-minute experiment, with less than a 20% diversion from mean values. The EEG visual inspection score allowed a simplified assessment of EEG findings\textsuperscript{10} and showed EEG alpha waves in sham-operated animals.

The most sensitive method used to register the mass effect during balloon expansion was ICP monitoring, the focus of which was the greatest distance from the balloon. This method was followed by LDF, in which the probe was located rostral to the lesion and very close to it, and subsequently by PtiO\textsubscript{2} monitoring. Electroencephalographic activity was altered first when the CPP was reduced to 57 mm Hg, the CBF to 66%, and the PtiO\textsubscript{2} to 12 mm Hg, which corresponds to the results of other authors who used a fluid-percussion injury model.\textsuperscript{10} Moreover, these results are in accordance with those of clinical studies in which the identical method of PtiO\textsubscript{2} measurement was applied and 10 mm Hg was reported as a critical threshold for the development of hypoxia and an unfavorable clinical outcome.\textsuperscript{2,11,32,66} Shalit and Cotev\textsuperscript{59} reported that ICP values greater than 50 to 60 mm Hg were able to alter EEG activity, despite a sufficient CPP between 60 and 70 mm Hg.

At the maximum ICP elevation, a critical intracranial lesion volume of 6 to 7%\textsuperscript{3,52,70,71} triggered a mild Cushing response in most animals, followed by systemic hypotonia during sustained inflation. Most likely this was caused by reduced blood flow in the brainstem.\textsuperscript{15,16} Simultaneously the ICP decreased in response to a reduction in intracranial blood volume, a shift of cerebrospinal fluid to the spinal compartment, and a brain shift toward the tentorium.\textsuperscript{35,37,42,67} Nevertheless, hypotonia caused a maximum decrease in CPP with isoelectric EEG findings and progressive declines in the PtiO\textsubscript{2} and LDF values at the end of a prolonged compression.

After reperfusion ICP again increased to above the normal range, as reported for former balloon models\textsuperscript{29,57} and remained elevated throughout the entire observation time. In

![Figure 5](image1.png)

**Fig. 5.** Histological findings. A: Paraformaldehyde-fixed coronal slice through the maximum area of the lesion (asterisk) with sites of bleeding and brain swelling, generally pronounced on the side of the lesion, combined with a midline shift (arrowhead) and mild signs of supracallosal, uncal, and central herniation. B: Photomicrograph obtained beyond the balloon device in an animal in Group B showing an ischemic lesion (arrowheads) with necrosis; sites of bleeding; massive swelling of astrocytes in the cortex, basal ganglia, and corpus callosum; and small tissue ruptures. H & E, original magnification × 40. C: Photomicrograph of the cortex showing direct microvascular cortical occlusion and thrombosis (arrowheads). H & E, original magnification × 400.

![Figure 6](image2.png)

**Fig. 6.** Graph demonstrating cortical–subcortical infarct lesion areas in animals in Group B 3 hours after ischemia–reperfusion plotted as a function of the anteroposterior stereotactic coordinate. Values are represented as means ± SDs.
particular, the duration and extension of brain compression seem to be related to the grade of the secondary rise in ICP.29 The LDF monitoring revealed an incomplete cortical reperfusion close to the lesion, compared with a complete reperfusion, which was illustrated by a more frontally placed PtO2, measurement in this study. This finding supports the theory that ischemia and brain edema seem to be consequences of local elevated tissue pressure with a severe reduction in CPP, direct kinking of vessels, and microvascular cortical occlusion, as well as excitotoxic mechanisms.3,15 Incomplete recovery of EEG activity in this study additionally confirms this theory because the reperfusion of cortical microvessels was correlated with EEG-confirmed recovery.28 Miller and associates,48 applying the SDH model, reported similar results, but speculated that ischemia was primarily caused by a direct toxic effect on the overlying cortical blood layer.

The selected extent of maximum balloon expansion and the time course of prolonged ischemia in this study provoked severe pathophysiological changes and histological alterations. This may contradict common clinical sense in the treatment of epidural hematomas, but these results are in line with those reported by other authors who have demonstrated a highly increased rate of mortality in cases of concomitant arterial hypotonia, brain edema, and clinical signs of brainstem alteration.39,40 Disruption of the blood–brain barrier and disturbances of autoregulation during ischemia were not tested in this study, but may have contributed to the increase in ICP and secondary brain damage in this model.

Magnetic Resonance Imaging and Histological Analysis

The T2-weighted MR images demonstrated lesion volumes that were comparable to those demonstrated in histological specimens in studies of focal cerebral ischemia, regardless of whether MR imaging was performed in vitro or in vivo. In this study the mean lesion volume was 20.3 ± 6.6 mm3, as determined using T2-weighted sequences. The lesions were clearly demarcated after 180 minutes of reperfusion, as reported in the literature.1,2,22 Other authors consider the severity of trauma or ischemia to be a crucial factor in the development of a lesion on T2-weighted images.22 After regular balloon inflation in four animals significantly smaller lesions were identified on MR images and histological slides. The neurophysiological parameters in these animals resembled the data obtained in nonlesioned animals. This may be the consequence of an improved vascular collateralization that prevents an extension of the lesion.50 In vivo MR imaging characterization of the lesion will be discussed in detail in Part II of this publication.4

Compared with experiments in cats and dogs,20,13 similar histological signs of transfalcine and uncal herniations with petechial bleeding in the tectum and tegmentum were observed.

According to the SDH model48 histological analysis revealed a cortical and also a subcortical ischemia and an ipsilateral brain swelling below the level of the balloon, depending on the inflation volume and prolongation of brain compression. Cortical bleeding, tissue tearing, and sites of bleeding between the cingulum and capsula externa and the cortex were typical histological alterations. Morphometric analyses based on anatomical stereotactic coordinates showed a maximum extension of the lesion at the coordinate bregma −6 mm. Because of shrinking artifacts on photomicrographs, no comparison of absolute lesion volumes was performed.

Conclusions

The presented model of extraaxial balloon expansion is feasible in rodents with a high level of reproducibility and closely resembles the clinical dynamics of an extraaxial hematoma. Ischemia and brain swelling are the main sequelae during extraaxial brain compression. Identification of critical thresholds of neurophysiological parameters by multimodal monitoring in rodents may enable a better understanding of the underlying pathophysiology and eventually lead to improved outcomes of patients with severe head injury. Characterization of the lesion by using MR imaging should be integrated whenever an animal model has to be validated.

Acknowledgments

We express our grateful appreciation to our coauthor A. Marma-rou, Ph.D., Division of Neurosurgery, Medical College of Virgini, Richmond, VA, whose energy and support aided the first author in the further development of the balloon trauma model. We thank a former research technician, Mrs. Doris Evans (Alpharetta, GA), and Mrs. Brünner, Department of Neurology, University of Würzburg, for their technical help and advice. We also thank M. Poeschold, M.D., and A. L. Pina, Ph.D., Department of Neurosurgery, University of Regensburg, for their useful commentaries on this paper.

M. D., and A. L. Pina, Ph.D., Department of Neurosurgery, Universit

References


Epidural mass lesion model in rodents


52. Nakatani S, Ommaya AK: A critical rate of cerebral compression, in Brock M, Dietz H (eds): Intracranial Pressure: Experi...
58. Seyde WD, Longnecker DE: Cerebral oxygen tension in rats during deliberate hypotension with sodium nitroprusside, 2-chloroadenosine, or deep isoflurane anesthesia. Anesthesiology 64:480–485, 1986

Manuscript received January 7, 2002.
Accepted in final form August 7, 2002.
Address reprint requests to: Ralf Burger, M.D., Department of Neurosurgery, University of Regensburg, Franz-Josef-Strausse-Allee 11, 93053 Regensburg, Germany. email: RBurger@t-online.de.