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Acute reaction of arterial blood vessels after experimental subarachnoid hemorrhage – An in vivo microscopic study

Thomas Westermaier*, Christian Stetter, Diana Koehler, Judith Weiland, Nadine Lilla

Department of Neurosurgery, University Hospital Wuerzburg, 97080 Wuerzburg, Germany

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ABSTRACT

Subarachnoid hemorrhage (SAH) results in a rapid decrease of cerebral perfusion. While cerebral perfusion pressure (CPP) may quickly recover, a sustained decrease of cerebral blood flow (CBF) has been observed. Acute vasospasm has been concluded from this mismatch. This study was conducted to visualize and investigate immediate vascular reactions during and after experimental SAH. Male Sprague-Dawley rats were subjected to SAH by the endovascular filament model (n = 7) or served as controls (n = 4). Videomicroscopy was performed via a cranial window. Regions of interest were defined in areas covered by videomicroscopy and arterial diameters measured at defined time-points from 15 min before until 3 h after SAH. Local CBF was monitored over the opposite hemisphere by laser-Doppler flowmetry.

Local CBF showed a typical decrease immediately after vessel perforation followed by an incomplete recovery in the 3 h thereafter. Videomicroscopy demonstrated a sharp decrease of the arterial diameter in the first minutes after SAH. In some animals, SAH was followed by a complete disappearance of arterial vessel filling. In the following minutes, arterial filling reappeared or improved, respectively. All animals subjected to SAH showed significant vasospasm in subarachnoid arteries.

This is the first study to visualize acute vascular reactions during and immediately after SAH. Although the cranial window technique only covers a part of the cerebral vasculature, it covers cerebral vessels rather distant from the site of endovascular perforation. Therefore, it is likely that acute vasospasm observed in the monitored areas reflects a global vascular reaction.

1. Introduction

Reduced diameters of intracranial arteries have previously been observed early after experimental subarachnoid hemorrhage (SAH). Brawley et al. found a narrowing of the internal carotid artery several minutes after experimental rupture of the anterior cerebral artery [1]. Echlin and coworkers demonstrated a rarefication of intracranial vessels by angiography in the first minutes after “forceful” injection of blood into the subarachnoid space of monkeys models [2]. In both studies, measurements of physiological parameters like intracranial pressure (ICP) and cerebral blood flow (CBF) had not been performed and the methodology suggests that the observed arterial vessel changes are, at least partly, the result of massive elevations of ICP in the first minutes after SAH. Using the endovascular filament model of SAH in rats and elaborate monitoring, Bederson et al. and Sehba et al. observed a discrepancy between cerebral perfusion pressure (CPP) and regional cerebral blood flow (rCBF) after experimental SAH in rats [3,4]. The authors concluded that this mismatch was due to early vasospasm after SAH and that this vasoconstriction may start much earlier than previously thought, perhaps immediately after the induction of SAH. To date, however, immediate or acute vasospasm has not been visually observed, nor has it been correlated with the decline and recovery of CBF. There are potential alternative explanations for a mismatch of CPP and CBF, namely a no-reflow phenomenon caused by microthrombosis or an edema-related rarefication of microvessels. This in-vivo microscopic study investigated the reaction of cerebral vessels before, during and for 3 h after the induction of SAH in rats.

2. Materials and methods

For the experiments, 13 male Sprague-Dawley rats (250–300 g body weight) were used. The animals were purchased from Harlan Winkelmann (Borchen, Germany). All experiments were approved by the regional authorities and the district government of Bavaria, Germany.

* Corresponding author at: Department of Neurosurgery, University Hospital Wuerzburg, Josef-Schneider-Str. 11, 97080 Wuerzburg, Germany.
E-mail address: westermaie_t@ukw.de (T. Westermaier).

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2.1. Animal preparation and monitoring

The animals were anesthetized with 4% Isoflurane, orally intubated and mechanically ventilated with an air/oxygen mixture to maintain normal arterial blood gases. After induction of anesthesia, Isoflurane was reduced to 2.5% for surgical procedures and to 2% from 30 min prior to SAH until the end of the monitoring period. Temporalis muscle and rectal probes were used to monitor temperature throughout the experiment. A thermostatically regulated, feedback-controlled heating lamp was used to maintain temporalis muscle and rectal temperature at 37.5 °C. The tail artery was cannulated for continuous measurement of mean arterial blood pressure (MABP) and for blood sampling. Arterial blood gases were measured 30 min and 5 min before and in hourly intervals after induction of SAH.

2.2. Laser doppler flowmetry and in vivo microscopy

A two-channel laser Doppler flowmeter (LDF) (MBF3D; Moor Instruments, Axminster, England) was used for continuous monitoring of local cerebral blood flow (LCBF) in the area of the cerebral cortex supplied by the middle cerebral artery (MCA). To place the LDF probe, a burr hole was drilled 5 mm lateral and 1 mm posterior to the bregma on the left side without injury to the dura mater. For in vivo microscopy, a cranial window was made over the right hemisphere. Using a diamond drill, the skull bone was thinned. The remaining inner layer of the bone was then carefully removed without damage to the dura mater (Fig. 1).

The animals were then placed in a supine position with their head fixed in a stereotactic frame using non-perforating earbars. A rectangularly bent laser-Doppler probe was positioned in the burr hole using a micromanipulator. The video microscope (Veho VMS-004 D USB microscope) was positioned below the animal to cover the cranial window and visualize branches of the MCA (Fig. 2a). Animals with an accidental injury of the dura mater were excluded from further analysis (Fig. 2b). Prior to video recordings and photo shots, the dura mater within the cranial window was humidified with saline using a bent catheter. Photos were taken 15 min and immediately before induction of SAH and 1, 5, 15, 30 min after SAH and then in 30-minute intervals. Video recordings were made during the advancement of the filament and vessel perforation and immediately thereafter.

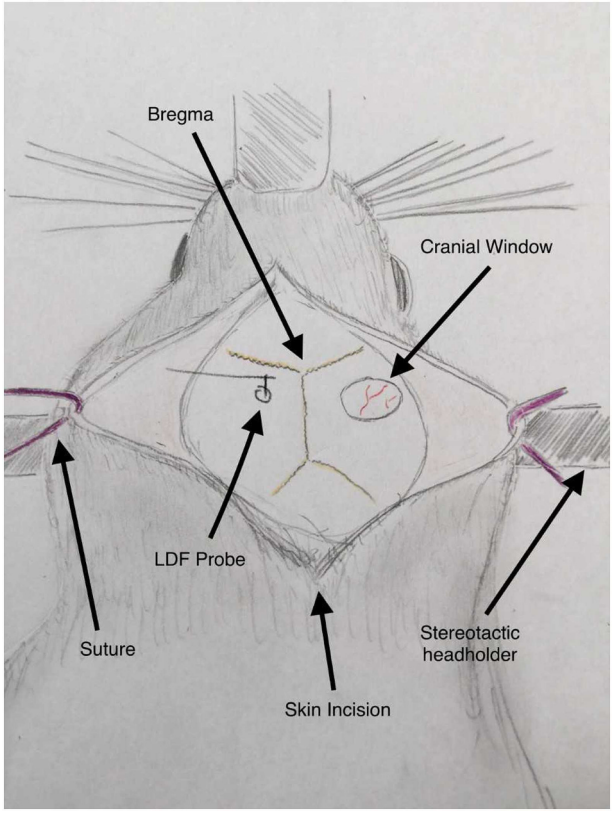

Fig. 1. Schematic drawing of the rat's skull after preparation of the cranial window for videomicroscopy and of the burr hole for LCBF monitoring. The cranial window was located on the right side of the skull behind the coronar suture to cover distal branches of the MCA ipsilateral to the side of vessel perforation. The burr hole was located on the left side to record contralateral laser-Doppler flow, thus obtaining a parameter for global changes of cerebral blood flow (LDF = laser-Doppler flowmetry).

2.3. Induction of SAH

SAH was induced using the endovascular filament method as described by Bederson and coworkers [3]. After surgical exposure of the right cervical carotid bifurcation, temporary aneurysm clips were placed on the common and internal carotid artery. A 3–0 Prolene© filament (Ethicon, Inc., Somerville, NJ) was inserted into the external carotid artery and fixed with a silk ligature and the temporary clips were removed. After a recovery period of 30 min, the filament was advanced into the internal carotid artery (ICA) for intracranial vessel perforation. The suture was then quickly withdrawn into the external carotid artery to ascertain reperfusion and development of SAH.

2.4. Experimental groups

The rats were randomly assigned to one of two groups:

1) Sham-operated animals (n = 4). The filament was advanced into the internal carotid artery without perforation of the vessel and then withdrawn.
2) SAH animals (n = 7). The filament was advanced into the ICA causing vessel perforation.

A variety of studies using the same highly standardized experimental model in the same animal species has previously been conducted in our laboratory. In all studies, no change of physiological parameters and CBF and no histological damage were recorded in sham operated animals [5–7]. On the basis of this previous data, no marked vessel reaction was expected in animals not subjected to SAH. Therefore, the number of animals in the sham operated group was reduced to 4 as compared to 7 animals in the SAH group.

2.5. Termination of the experiment

180 min after SAH or sham-procedure, respectively, the animals were transcardially perfused with 4% paraformaldehyde under deep isoflurane anesthesia. After perfusion fixation, the brains were removed and the amount of subarachnoid blood was determined using a semi-quantitative scale as follows: 0) No blood visible; 1) traces of blood visible, no blood clot: 2) unilateral clot; 3) generalized bilateral basal blood clot; 4) intracerebral hematoma with or without subarachnoid blood.

2.6. Measurement of vasoconstriction

Images were stored as JPEG files (600 dpi, 10.0 cm × 7.5 cm) and transferred to GIMP 2 graphical software (Version 2.8.10). Using the image taken immediately before induction of SAH, 3 regions of interest (ROI) were defined, each containing a subarachnoid artery and the vessel diameter in this ROI measured (Fig. 2c). Subsequently, the diameter of the vessels in the predefined ROI was measured in the images taken at the other time-points by a blinded investigator.

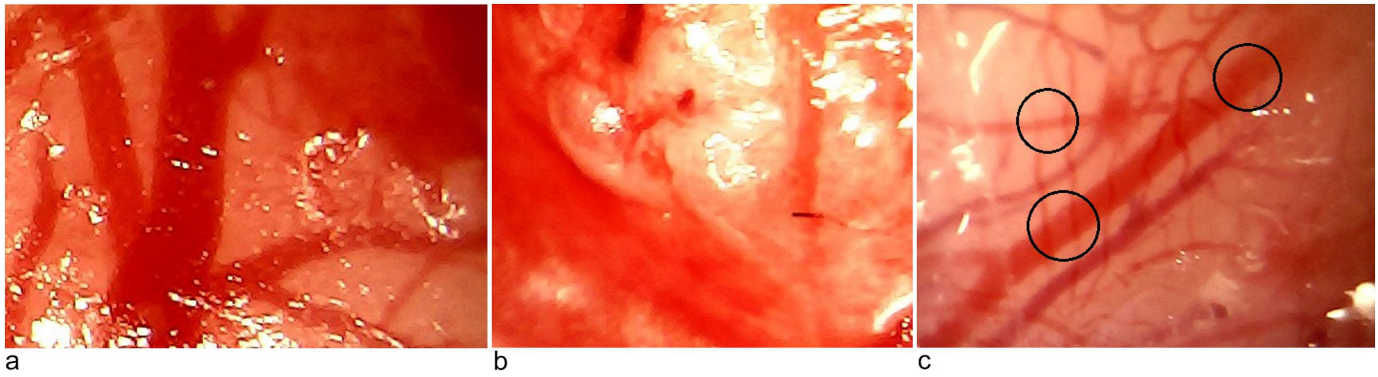

Fig. 2. a-c: In vivo microscopy of subarachnoid vessels through a cranial window over the right hemisphere. Mirror artifacts are caused by the continuously lubricated intact dura mater (a). In case of injury to the dura mater during surgical preparations, the experiment was terminated (b). For digital measurements, regions of interest were predefined on the image which was obtained immediately before vessel perforation and served as baseline for subsequent measurement (c).

2.7. Correlation of LCBF and vessel diameters

For the calculation of correlation between vessel diameters and the LCBF-value, the mean value of the 3 ROI of each animal was calculated. Using the above mentioned time-points, the area under the curve (AUC) of vessel diameters and LCBF was calculated using GraphPad Prism 4 statistical software from the course of microvasospasm and LCBF with “minutes after SAH” on the x-axis and “% of baseline” on the y-axis.

2.8. Statistical analysis

Statistical analysis was performed with GraphPad Prism 4 statistical software (GraphPad Software, La Jolla, CA). Physiological data for each time point, LCBF and vessel diameters in predefined ROIs were analyzed for normal distribution using a Shapiro-Wilk normality test. Normally distributed data was analyzed by an unpaired *t*-test. Due to the relatively small groups, alternative statistical calculations were done using a Mann-Whitney test which, however, did not differ in terms of whether differences were significant or not. Correlation was determined calculating Pearson's r. A p-value of < 0.05 was considered significant. Results are presented as mean ± standard deviation (SD).

3. Results

One animal assigned to the control group died during the induction of anesthesia and one animal assigned to receive vessel perforation was removed from the analysis and replaced due to an accidental injury to the dura mater during the preparation of the cranial window (Fig. 2b).

3.1. Mean arterial blood pressure and physiological parameters

Arterial blood gases were maintained in the physiological range throughout the experiments. In sham-operated controls, MABP was 77 ± 14 mmHg at baseline and slightly increased to 79 ± 18 and 83 ± 13 mmHg after 60 and 180 min, respectively. In animals subjected to SAH, MABP was 75 ± 14 mmHg at baseline, increased to a maximum of 95 ± 21 mmHg 10 min after SAH and declined to 87 ± 15 mmHg after 60 min and 85 ± 20 mmHg after 180 min. The difference of MABP between the two groups was not statistically significant at any time-point after induction of SAH (Fig. 3a).

3.2. Local cerebral blood flow

In the control group, the contralateral LCBF (left hemisphere) was 105 ± 4% of baseline 60 min after SAH and 100 ± 2% of baseline after 180 min. In the SAH group, LCBF declined to a minimum of 19 ± 10% of baseline five minutes after SAH and recovered to 61 ± 25% after 60 min and increased further to 86 ± 19% of baseline at the end of the observation period. The differences were significant from 1 to 120 min after SAH (Fig. 3b).

3.3. Extent of hemorrhage

No sham-operated animal showed signs of subarachnoid or other intracranial hemorrhage. In the SAH group, all animals had significant subarachnoid blood clots. According to the semiquantitative score, 4 animals were classified as grade 2 and 3 animals as grade 3. No animal in this series had subdural or intracerebral hemorrhage. Although it cannot be systematically evaluated by the equipment used in this study, we observed at least traces of blood in all animals subjected to SAH after endovascular perforation.

3.4. Vessel diameter in regions of Interest

In sham-operated animals, no signs of vasoconstriction was observed or measured. The vessel diameter was 107 ± 5% of baseline after 60 min and 101 ± 2% of baseline after 180 min. In the SAH-group, vessel diameter was reduced to 58 ± 34% of baseline one minute after vessel perforation, to 65 ± 20% of baseline after 60 min and to 72 ± 23% of baseline after 180 min. The differences were significant from 5 min to 180 min after induction of SAH (Fig. 4).

3.5. Correlation of LCBF and vessel diameter

The course of LCBF and vessel diameters in the predefined ROIs showed a concurrent course after the induction of SAH. Comparing AUCs, the correlation was significant ($p = 0.044$) with a Pearson's R of 0.61.

4. Discussion

The phenomenon of cerebral arterial vasoconstriction was described early after the existence of the disease aneurysmal SAH had been noticed and established. Ecker and Riemenschneider characterized delayed cerebral vasospasm after SAH by cerebral angiography [8] and, soon thereafter, a correlation with delayed neurological worsening was suggested. As clinical and experimental research proceeded, the occurrence of an early vasoconstriction after SAH was suggested. However, the experimental studies this observation originated from were based on artificial arterial rupture of a large cerebral artery or “forceful” injection of blood into the subarachnoid space [9,10]. In spite of these rather violent experimental procedures to induce SAH, ICP and CBF were not been monitored. Changes of arterial diameters, in turn, were only minor so that it cannot be ruled out that the authors observed vessel changes that were the result of a massively elevated ICP.

Bederson et al. were the first to record a mismatch of cerebral

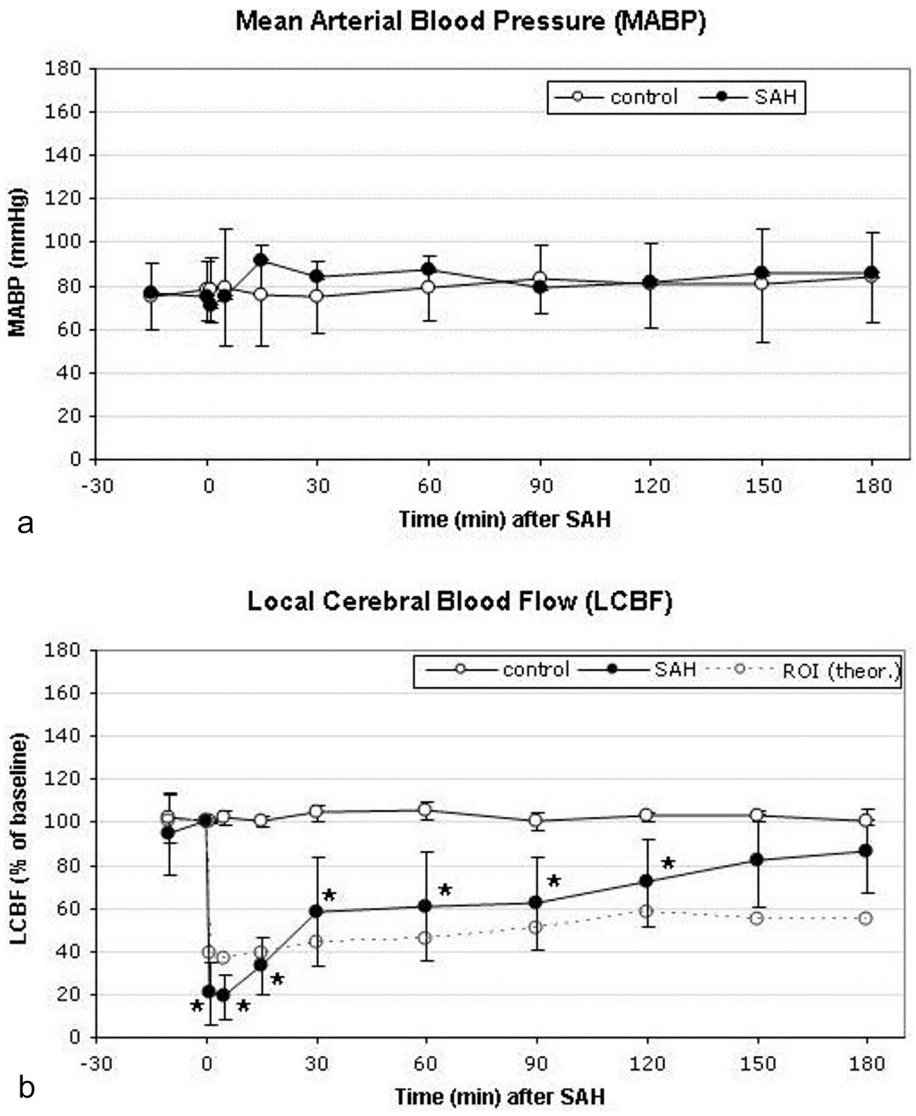

Fig. 3. a and b: Courses of mean arterial blood pressure (MABP) and local cerebral blood flow (LCBF), measured by laser-Doppler flowmetry (LDF), continuously monitored from 30 min before until 180 min after induction of SAH by the endovascular filament model. LCBF was significantly reduced starting immediately after induction of hemorrhage until 2 h thereafter (mean ± SD, *$p < 0.05$). The broken line indicates the theoretical value obtained by calculating the expected CBF from the decline of vessel diameters (see Fig. 4) for each timepoint by to the Hagen-Poissuille equation.

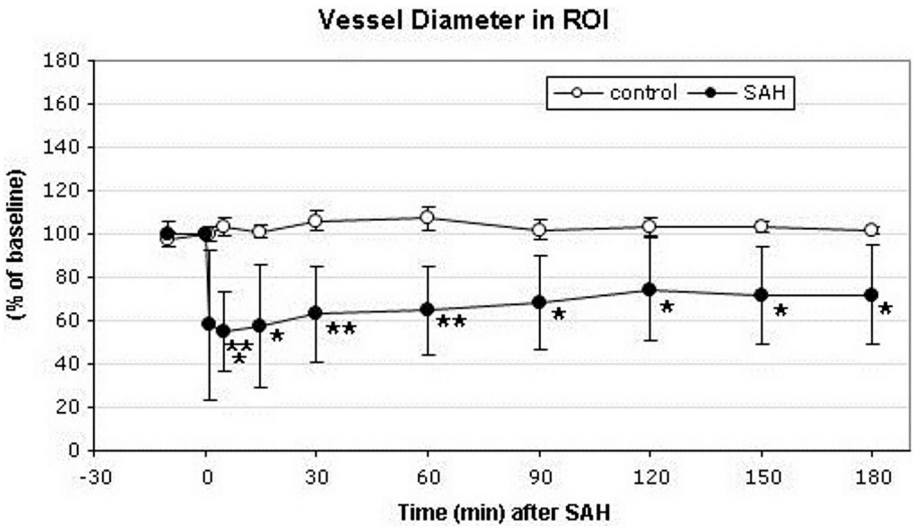

Fig. 4. Course of arterial reaction in animals subjected to SAH from 15 min before until 3 h after vessel perforation. (a) 15 min and (b) 1 min before, and (c) 1 min, (d) 5 min, (c) 30 min, (d) 60 min, (e) 90 min, (f) 120 min, (g) 150 min, (h) 180 min after SAH. Vessel diameters were significantly smaller in animals subjected to SAH from 5 min after induction of hemorrhage until the end of the monitoring period (mean ± SD, *$p < 0.05$).

perfusion pressure and CBF in the first 60 min after induction of SAH and concluded that there may be an acute vasospasm in the early period of SAH [11]. This discrepancy has been confirmed by several other experimental studies since then [12,13]. However, acute vasoconstriction has not been visualized in the period immediately after SAH. Alternative explanations for a mismatch of CPP and CBF could be microthrombosis after a cerebral circulatory arrest, an incomplete reperfusion ("no-reflow") after initial ischemia or a relative decrease of blood vessel density and longer diffusion distance due to an increased brain water content. It seems important, though, to know the reason for the observed CPP/CBF-mismatch as potential forms of treatment would be completely different. Uhl and coworkers first used orthogonal polarization spectral (OPS) imaging to visualize microvessels during surgical aneurysm repair and reported microvasospasm several hours after SAH [14]. Using the same imaging modality, Pennings et al. systematically compared microvessels and their reactivity upon hyperventilation. The authors found that during early surgery, i.e. within 48 h after aneurysm rupture, the contractile response of cerebral arterioles was more pronounced if clots of subarachnoid blood were present. They concluded that increased contractility might be due to the presence of subarachnoid blood and may result in a greater susceptibility to ischemia [15]. These studies as well as reports about early angiographic vasospasm in humans and animals [10] started their observation time several hours after SAH not covering the first minutes and hours after aneurysm rupture. Early microcirculatory vasospasm has been detected by 2-photon microscopy as early as 60 min after experimental SAH [16]. Using videomicroscopy through a cranial window, Sun et al. investigated the change of pial vessel diameters in a cisternal injection model of SAH in rats. The authors found a marked change starting at the first measurement point 5 min after blood injection without recovery over the following 2 h [17]. In contrast to that study, we used a closed cranial window without injury to the dura mater not exposing the cerebral cortex, and an endovascular perforation model, thus ruling out that external influences may have affected the superficial vessels. Furthermore, we measured the contralateral LCBF as a parameter of global cerebral perfusion rather than local blood flow in spastic vessel segments in order to correlate it with the reduction of vessel parameters.

The above mentioned literature concludes rather unequivocally that the presence of blood may be the decisive factor of the early vessel contraction. In accordance, we found at least traces of blood after vessel perforation in the region monitored by videomicroscopy. An immediate reaction to extravasated blood is more likely than other possible factors for the reduction of CBF and vessel contraction, respectively. A slight initial shift of the optical focus through the videomicroscope was observed in some animals after induction of SAH but recovered within some seconds or few minutes. Herniation of the brain through the cranial window, which could have influenced the vessel diameter by an up- or downstream obstruction of the vessel continuity, was not observed as the dura had been kept closed during preparation. Accidental injury to the dura mater during surgical preparation occurred, but those animals were excluded from the analysis (Fig. 2b).

In previous studies we had repeatedly observed that ICP sharply increases immediately after induction of SAH but shows a relatively rapid decrease within the following minutes. The initial disappearance of subarachnoid arteries as shown in the Supplementary Video 1 may be due to increased ICP. Their re-appearance after less than a minute, though, is in accordance with our previous findings of an early decrease of ICP and recovery of CPP [18,19].

Our findings suggest that there is an immediate vasoconstriction after the induction of SAH by endovascular vessel perforation. The area covered by in-vivo microscopy was rather distant from the point of vessel damage and, therefore, it is likely that we observed a global vascular reaction. This is further substantiated by the correlation of AUCs of vessel diameters and CBF as the latter was recorded over the opposite hemisphere. According to the Hagen-Poissuille law, vessel diameters and CBF should react concordantly. While segmental stenoses represent a certain increase of resistance, they do not one to one result in a decreased flow volume. In addition, there are various other factors that influence CBF apart from the vessel diameter and that may explain why a parallel course of CBF and vessel diameter was not the case in the present study (Fig. 3a). In the first minutes, the decline of CBF was more pronounced than the decrease of vessel diameters. Considering the findings of previous studies, this is most likely due to the increase of ICP and subsequent decrease of CPP which has been reported to largely recover within the first 30 min. Between 30 and 90 min after SAH, the course of CBF and vessel diameters are nearly parallel. While vessel diameters remain constant after 2 h, CBF further recovers the reason for which cannot be finally concluded from the results of these experiments. At the end of the monitoring period, arterial blood pressure increased slightly. That may be one expression of an increased cardiac output and result in an increased flow velocity, thus compensating for a decreased vessel caliber. Alternatively or additionally, microvasospasms located downstream from the part of the vasculature, which could not be monitored by the equipment used in this study, may already start to resolve in this period. Friedrich and coworkers observed such microvasospasms using 2-Photon microscopy. They reported an increase of the diameter of spastic microvessels between 3 and 6 h after experimental SAH [20]. As 3 h was the earliest time of monitoring in that study, it cannot be concluded from the data whether the resolution of microvasospasm may start even earlier or not. If this was the case, this could be another explanation of an increase of CBF in spite of a consistent vasospasm in the observed subarachnoid vessels. If other factors contributing to the course of CBF after SAH gain importance over time, this might imply that the strong correlation of the AUCs of CBF and vessel diameters which we found in the present experiments, could become weaker at a later point of observation.

This study, however, has several clear limitations. The extent of monitoring had to be reduced due to a lack of space. We chose to keep CBF-monitoring and to refrain from ICP monitoring because it was our primary target to analyze the correlation of CBF and microvasospasm. Moreover, we had observed a largely uniform course of ICP and CPP in a number of experiments using the same animal model including continuous ICP/CPP- and bilateral LCBF-monitoring. In these previous studies, we consistently found a rapid elevation of ICP followed by a rather quick and then gradual but imcomplete recovery and a rapid decrease of CPP with a near complete recovery after less than an hour. The decrease of CBF was more pronounced and sustained than the decrease of CPP [18,19,21]. Due to the lack of ICP and CPP monitoring, alternative explanations for a CBF-decrease, such as a continuously elevated ICP cannot be ruled out with complete certainty for this particular series of animals. However, previous and very consistent findings of our and various other groups observing a clear discrepancy between the course of ICP/CPP and CBF make it rather unlikely that the reduction of CPP should have significantly contributed to the reduced filling of the imaged vessels and the reduced LCBF in this present study.

Second and most obvious, the image quality is only moderate. The endovascular filament model of SAH in rats is highly established in our laboratory including anesthesia with mechanical ventilation, arterial blood gas analysis and multimodal monitoring [5,22], and so is the cranial window technique [23]. However, the specific tools for measurement of vessel diameters are not specific medical or research devices. Vessels were observed with a commercially available USB-videomicroscope and vessel diameters were measured using freely available software. Planning this study, it became clear that, if the first seconds an minutes after SAH are to be monitored, a videomicroscope had to be placed underneath the animal that is already fixed in a supine position in order to be able to advance the filament in the carotid artery. Hence, the prerequisite for the videomicroscope was that it had to be small and mobile to place it into the limited space between the stereotactic frame and the animal's head. None of the available professional devices fulfils these criteria. Most are stationary and too large

for this purpose. Mobile devices with high resolution imaging and the possibility to attach a polarization filter for absorbing mirror-like artifacts are too large for this purpose, too. As a consequence, we had to accept a limited image quality. We believe, however, that the devices used in this study served the purpose to confirm that arterial vasoconstriction occurs immediately after SAH and is responsible for the reduction of CBF in this period.

Measurements of vessel diameters were made using graphical software. This implicates that no absolute values can be measured as the analysis is pixel-based and only values relative to the baseline value can be calculated. This form of analysis does not answer the question if vessels of different diameter show different reactions after SAH. Finally, this is an animal study. Although it is more than likely that this kind of vasoreaction is highly conserved in mammals, we do not know whether conductive subarachnoid vessels, which are larger in humans, react in the same way and similar extent as observed in our experiments in rats. Alternatively, the responsiveness in this phase of SAH may depend on the vessel's diameter and wall thickness and may, in humans, be located in different position such as the pia mater or superficial cerebral cortex. If this was the case, this may be an explanation of early spot-like ischemic areas in humans after SAH [24].

5. Conclusion

The idea that the acute stage is the most crucial period in SAH is not entirely new [12], but it has been focused on after the Endothelin-antagonist Clazosentan has shown a positive effect on delayed cerebral vasospasm but failed to prevent infarction and improve outcome [25,26]. Our findings suggest that this early vascular reaction may, at least partly, be the cause of early hypoperfusion and may have a decisive impact on early brain injury. Considering the correlation with a decrease of LCBF might make it the target of choice for emergency treatment of SAH patients.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2018.11.007.

Conflict of interest

None of the authors has a conflict of interest to report.

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