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# Exploring cerebrovascular dynamics following cortical spreading depolarization in an autologous intracerebral hemorrhage porcine model

## Abstract

**Background:** Spreading Depolarization (SD) often emerges post-Intracerebral Hemorrhage (ICH). Autoregulation of cerebral blood flow and vascular reactivity can be impaired following SD. However, it is still unclear whether the association of SD and Cerebral Autoregulation (CA). We designed an exploratory study to investigate the dynamic changes in CA according to changes in cerebrovascular pressure and oxygen pressure reactivity during the early phase after SD in a porcine model of autologous ICH.

**Material and methods:** Nine craniotomized swine were monitored for Mean Arterial Pressure (MAP), Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), and partial pressure of brain tissue oxygen ($PbrO_2$). A subdural Electrocorticography (ECoG) recording strip was used to detect SD. ICH was induced by the injection of autologous arterial blood. The cerebrovascular Pressure Reactivity index (PRx) and a high-frequency $PbrO_2$ pressure reactivity index (H-ORx) were calculated, comparing measurements before and during SD development. Continuous multimodal monitoring enabled identification of transient cerebrovascular responses within short time windows (5–10 min) following each SD event.

**Results:** Following ICH, a total of 22 SDs occurred in 6 of 9 swine. Depolarizations recurred at intervals of 47 min on average, with a mean propagation velocity of 1.87±1.02 mm/min and a duration of 11.85±3.22 min. Both monitoring indices revealed transient impairment of autoregulation in the early phase of SD. For PRx, 9 SDs exhibited loss of CA 5 min after detection ($p=0.008$), whereas for H-ORx, all 22 SDs showed CA disruption 9.5 min after detection ($p=0.043$). These changes were accompanied by increases in ICP and $PbrO_2$ ($p<0.05$). The short-lived fluctuations in PRx and H-ORx coincided with moderate rises in ICP and $PbrO_2$, suggesting a brief loss of vasomotor reactivity rather than systemic hemodynamic alterations.

**Conclusion:** Autoregulatory changes observed during the early phase of SD can be monitored using continuous assessment of cerebrovascular and oxygen-pressure reactivity in a porcine model of autologous ICH. Disturbances of CA were found during SD occurrence. These findings suggest that SD may trigger transient vascular tone instability detectable by high-frequency CA monitoring, indicating a potential avenue for future translational research in neurocritical care.

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**Keywords:** Cerebral autoregulation; Cerebrovascular pressure reactivity; High-frequency oxygen pressure reactivity; Intracerebral hemorrhage; Intracranial pressure; Spreading depolarization.

**Abbreviations:** ARRIVE: Animal Research Reporting of In Vivo Experiments; CA: Cerebral Autoregulation; CBF: Cerebral Blood Flow; EcoG: Electrocorticography; H-Orx: High-Frequency Oxygen Pressure Reactivity Index; ICH: Intracerebral Hemorrhage; ICP: Intracranial Pressure; MAP: Mean Arterial Pressure; Orx: Oxygen Pressure Reactivity index; PbrO2: Partial Pressure of Brain Tissue Oxygen; PRx: Pressure Reactivity Index; SD: Spreading Depolarization; $SO_2$: Capillary Oxygen Saturation.

## Background

Spreading Depolarization (SD), characterized by waves of neuronal and glial depolarization, has emerged as a crucial factor in the pathophysiology of cerebrovascular diseases, notably Intracerebral Hemorrhage (ICH) [15]. Despite its significance, the debate surrounding the efficacy of surgical interventions [8] has limited the enrolment of ICH patients in clinical studies. Nevertheless, SD has been reported in a substantial proportion of ICH patients, with incidences exceeding 60% [11,12,15]. Experimental animal models have suggested the presence of impaired cerebrovascular reactivity and compromised neurovascular coupling during the occurrence or propagation of an SD [1]. This phenomenon may result from the ability of SD to induce alterations in resistance vessel tone, potentially leading to vasoconstriction and hypoperfusion in impaired tissue, while eliciting vasodilation and hyperperfusion in unaffected tissue [10].

Autoregulation of Cerebral Blood Flow (CBF) can be defined as the ability of brain arteries to vasodilate or constrict in response to blood pressure changes to maintain a stable CBF; this is essential to provide the brain with oxygen and energy substrates [16]. It is known that changes in arterial blood pressure usually elicit a response in Intracranial Pressure (ICP), thus describing cerebrovascular pressure reactivity, defined as the capacity of vascular smooth muscle in the wall of cerebral arteries and arterioles to respond to changes in transmural pressure [5,6]. This means that in a healthy brain, increases in MAP will tend to cause cerebral vasoconstriction with a subsequent decrease of ICP and cerebral blood volume. In cases of impaired cerebrovascular reactivity, increases in MAP will tend to lead to an increase of ICP due to a passive vasomotor response of the cerebral resistance vessels [1,5,6].

Direct CBF measurements provide the most comprehensive assessment of Cerebral Autoregulation (CA); however, they are not always feasible, particularly in experimental animal models. Indices of cerebrovascular reactivity have therefore been developed from the need for continuous CA monitoring. The cerebrovascular Pressure Reactivity index (PRx) [7] and oxygen pressure reactivity index (ORx) [14] provide information about Cerebral Blood Flow (CBF) fluctuations and have been used as predictors for neurological outcome [7,14,21].

PRx permits a continuous estimation of cerebrovascular reactivity as a surrogate marker for CA, thereby reflecting the capacity of cerebral resistance vessels to modify their diameter in response to perfusion pressure changes [4-7]. PRx is derived from the correlation between Intracranial Pressure (ICP) and mean arterial pressure (MAP), serving as an indicator of the brain's pressure reactivity. A positive PRx suggests impaired autoregulation, where MAP alterations are passively mirrored by ICP, signifying a compromised vascular response. Conversely, a negative PRx denotes active and robust autoregulation, with cerebral vessels responding to uphold stable CBF [4-7]. ORx measures the correlation between the partial pressure of brain tissue oxygen ($PbrO_2$) and Cerebral Perfusion Pressure (CPP). Since $PbrO_2$ is intimately associated with cerebral blood volume and flow, ORx acts as an indirect marker for shifts in cerebral oxygenation in response to changes in perfusion pressure. A positive ORx value implies that perturbations in CPP are mirrored by changes in $PbrO_2$, indicating potential autoregulatory dysfunction [14]. Both PRx and ORx are continuous, non-invasive indices that furnish instantaneous insights into cerebrovascular responsiveness. These indices adeptly monitor cerebrovascular reactivity to perturbations in perfusion pressure and thereby indirectly indicate variations in CBF.

However, the absence of continuous CA monitoring during SDs in a gyrencephalic animal model presents a knowledge gap in current research. To address this gap, this exploratory study aims to investigate the feasibility of monitoring cerebrovascular and oxygen-pressure reactivity during the early phase following or accompanying SD onset within a porcine model of autologous ICH.

## Materials and methods

All procedures were conducted in accordance with the European Directive 2010/63/EU for animal experiments and approved by the institutional ethics committee. The study design and reporting adhered to the ARRIVE 2.0 guidelines [19].

### Animal preparation

Male swine (*n*=9) with an average mean weight of 32 kg (range: 29 to 36 kg) were included in the study. A standardized animal preparation setup was followed as previously described [22]. Animals were anesthetized with midazolam (5 mg/kg) and azaperone (40 mg/kg) administered intramuscularly. A 2 to 3 mg IV application of propofol was administered for sedation whenever necessary. They were orally intubated and mechanically ventilated ($F_iO_2$=0.3). Anesthesia was maintained using isoflurane (1.0 to 1.8%). A venous line was placed in the right ear vein, and capillary oxygen Saturation ($SO_2$) was continuously monitored from the left ear. After surgical exposure of the right femoral artery, a 4-French catheter was inserted for continuous monitoring of mean arterial pressure (MAP) (Raumedic AG, Helmbrechts, Germany).

### Operative procedure

A craniotomy with dura dissection was performed to expose the right cerebral hemisphere. A linear, subdural 8-contact platinum electrocorticography (ECoG) recording strip (Wyler, 10/5 mm, Ad-tech, Racine, USA) was placed on the surface of the cerebral cortex (Figure 1a). In addition, an intracranial pressure (ICP) probe (Neurovent-P®, Raumedic AG, Helmbrechts, Germany) and a partial pressure of brain tissue oxygen ($P_{br}O_2$) probe (Neurovent-TO®, Raumedic AG, Helmbrechts, Germany) were inserted into the parietal white matter in proximity to each other (distance <10 mm). The distance between the ECoG strip and the ICP and $P_{br}O_2$ probe was between 10 and 20 mm. The center of the hematoma was located approximately 10–15 mm from the ICP and $PbrO_2$ probes and 10–20 mm from the nearest ECoG contacts. Finally, an autologous intracerebral hematoma with 3 ml arterial blood from the femoral artery was injected manually using a 22-gauge needle to a depth of ~3 mm below the dura, 0.5 cm anterior to the coronal suture in the right frontal cortex. Injection was performed slowly over ~5 minutes to allow gradual volume expansion and to minimize tissue trauma, following previous descriptions [17,22], and the bone flap was replaced (Figure 1b).

### Monitoring

Continuous monitoring of MAP, ICP, cerebral perfusion pressure (CPP=MAP-ICP), $P_{br}O_2$, and ECoG was conducted for 180 min. Analogue data of MAP, ICP, CPP, and $P_{br}O_2$ were collected and stored using the ICU Pilot™ software (CMA Microdialysis AB, Solna, Sweden). ECoG electrodes were connected sequentially in a monopolar configuration. Sampling frequency was set at 1,000 Hz using a DC amplifier Powerlab 16/SP analogue-todigital converter. SD duration was defined on ECoG as the interval from the onset of the negative DC shift to the recovery to baseline (or near-baseline) potential across the recording contact. Propagation velocity was calculated as the inter-electrode distance divided by the latency of SD arrival between consecutive ECoG contacts along the linear strip. ECoG registration and analysis were performed with LabChart7 (AD Instruments, Bella Vista, Australia).

**Autoregulatory indices calculation**

PRx was calculated as a moving linear (Pearson's) correlation coefficient between 30 past consecutive 10s averages of MAP and ICP, resulting in a time window of 5 min as described previously [4,5,7]. Due to the amount of monitoring time of 180 min, a modification of ORx [14] was applied to obtain more detailed information about changes in $P_{br}O_2$ and CPP. Therefore, a high-frequency ORx (H-ORx) was calculated as a moving linear (Pearson's) correlation coefficient between 30 past consecutive 10s averages of $P_{br}O_2$ and CPP, resulting in a time window of 5 min. The window was repeated every 10 s for both indices, generating an overlapping index.

Cerebral autoregulatory changes were assessed by comparing the resulting indices at the time point following SD detection and evaluating for 30 minutes thereafter. Both indices yielded values with ranges of -1 to 1. Negative values were considered indicative of preserved autoregulation, while positive values implied a loss of cerebral autoregulation. As shown by various studies, we consider a value greater than 0.2 as a cut-off value for CA disruption. Clinical studies indicate that sustained values >0.20 are associated with unfavorable outcomes in neurological conditions [4,5,7,23].

**Statistical analysis**

Continuous variables were tested for normality using histograms and the Shapiro–Wilk test. Parametric and non-parametric tests were used according to variable distribution. Given the exploratory design and the limited number of planned comparisons, no formal multiple-testing correction was applied; $p<0.05$ was considered nominal significance and statistically significant. Statistical analyses were performed using the SPSS 20.0 software (SPSS, Chicago, Illinois, USA).

## Results

Continuous multimodal monitoring enabled the evaluation of cerebrovascular and oxygen-pressure dynamics during the experimental period. Table 1 presents the mean values of physiological parameters and autoregulatory indices observed during monitoring. Following ICH, two-thirds (6/9) of the animals exhibited the development of 22 spontaneous and recurrent SDs. Notably, alterations in the ECoG were consistent with brain tissue depolarization, originating from channels nearest to the hematoma foci. The occurrences of SDs manifested at intervals averaging 47 min (range: 1 to 170 min), with a mean frequency of 1.38±0.46 SDs per hour. The average propagation velocity measured 1.87±1.02 mm/min, with a duration spanning 11.85±3.22 min.

Among the observed SDs, 40.90% (9/22) displayed dynamic fluctuations in PRx, transitioning from preserved to impaired autoregulation and subsequently normalizing within 30 minutes post-SD detection. Notably, PRx reached its peak value, denoting impaired autoregulation at 0.38 (range: 0.10 to 0.55) after 5 min ($p$=0.008) (Figure 2a). This change in PRx occurred together with an increase in ICP by 15.43%, escalating from 9.59±0.09 mmHg to 11.07±0.29 mmHg within the initial 10 min following SD initiation ($p$=0.005) (Figure 2c). No significant MAP changes were found during the 30-minute post-SD.

Furthermore, in over 86.36% (19/22) of the recorded SD events, the H-ORx exhibited oscillations between preserved and impaired autoregulation subsequent to SD occurrences. The peak of impaired autoregulation for H-ORx measured 0.26 (range: 0.05 to 0.46) after 9.5 min ($p$=0.043) (Figure 2b). In parallel, a transient increase in partial pressure of brain $P_{br}O_2$ was noted, rising by 10.90% from 18.52±0.82 mmHg to 20.54±0.39 mmHg within the initial 10 min post-SD detection ($p$=0.005) (Figure 2d). Ten to twenty minutes after SD occurrence, CPP slightly increased from 76.48±0.52 mm Hg to 79.55±0.57 mm Hg, which was found statistically significant ($p$=0.0005).

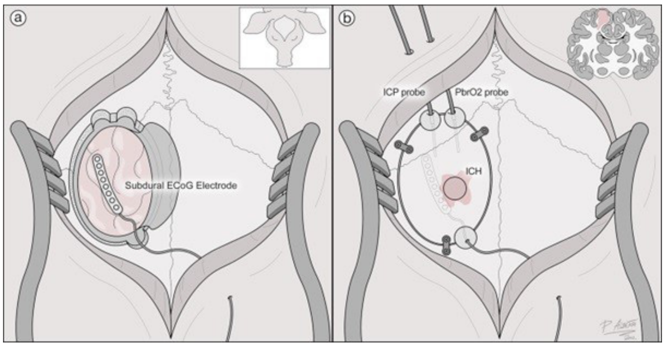


**Figure 1:** Schematic illustration of the experimental setup and probe placement in relation to the autologous Intracerebral Hemorrhage (ICH). (A) Subdural 8-contact Electrocorticography (ECoG) strip positioned over the right cerebral hemisphere. (B) Placement of the Intracranial Pressure (ICP) Probe, Brain tissue Oxygen partial pressure ($PbrO_2$) probe, and the autologous hematoma within the right frontal cortex.

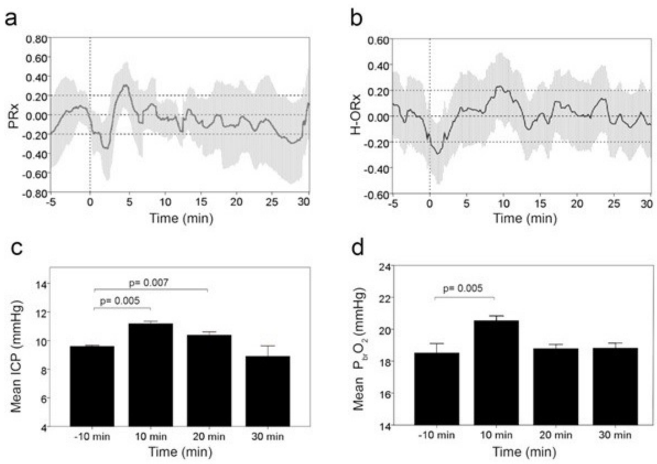


**Figure 2:** Cerebral autoregulation indices and physiological responses associated with SD**. (A)** Line plot of the Pressure Reactivity index (PRx) and **(B)** High-frequency Oxygen pressure reactivity index (H-ORx) from 5 minutes before to 30 minutes after SD onset. **(C)** Bar plot of mean Intracranial Pressure (ICP) and (**D)** bar plot of mean brain tissue oxygen partial pressure ($PbrO_2$) from 10 minutes before to 10-, 20-, and 30-minutes relative to SD onset. Values are presented as mean±95% confidence intervals. Statistical significance was defined as $p$<0.05.

**Table 1:** Mean physiological parameters and cerebral autoregulation indices during continuous multimodal monitoring in the porcine Intracerebral Hemorrhage (ICH) model. Values represent mean ± SD for all animals (n=9), animals without spreading depolarization (SD) (n=3), and animals with SD (n=6). Physiological variables include Mean Arterial Pressure (MAP), Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), and brain tissue oxygen partial pressure ($PbrO_2$). Autoregulation indices include the pressure reactivity index (PRx) and High-frequency Oxygen pressure reactivity index (H-ORx). p-values refer to comparisons between animals with and without SD.

| Parameter | Total (n=9) | Animals without Spreading Depolarization (n=3) | Animals with Spreading Depolarization (n=6) | p-value |
|---|---|---|---|---|
| **Physiological parameters** | | | | |
| Mean arterial pressure (MAP) | 83.3±9.8 | 83.2±16.4 | 83.4±8.2 | p=0.985 |
| Intracranial pressure (ICP) | 8.2±2.9 | 8.7±4.0 | 7.8±2.9 | p=0.606 |
| Cerebral perfusion pressure (CPP) | 74.5±10.3 | 74.5±15.3 | 75.6±9.8 | p=0.796 |
| Partial pressure of brain tissue Oxygen (PbrO2) | 21.5±8.7 | 18.7±6.4 | 22.8±9.1 | p=0.439 |
| **Cerebral autoregulation (CA)** | | | | |
| Pressure reactivity index (PRx) | 0.01±0.14 | -0.07±0.11 | 0.06±0.13 | p<0.001 |
| High-frequency Oxygen pressure reactivity index (H-ORx) | 0.09±0.14 | 0.05±0.08 | 0.11±0.17 | p<0.001 |

## Discussion

This preliminary study aimed to assess the feasibility of continuous CA monitoring during SD in an experimental gyrencephalic swine model of autologous ICH. The findings show a transient alteration in cerebrovascular reactivity during the early phase of SD development. Notably, indices of PRx and H-ORx displayed values exceeding 0.2 within 5-10 minutes post-SD onset, which may reflect a transient loss of CA. These fluctuations were temporally associated with increases in ICP and partial $P_{br}O_2$ during the early stages of SD detection.

CA signifies the inherent capability of cerebral vessels to regulate CBF in response to changes in blood pressure. Understanding CA has become increasingly crucial in the evolution and management of cerebrovascular diseases [6]. Various indices, reflecting autoregulatory changes, have demonstrated that impaired CA contributes to vascular deterioration and heightened mortality. These indices offer insights into CBF fluctuations, with the loss of autoregulation indicated by positive plateau waves in intracranial pressure, accompanied by maximal cerebrovascular dilation [6,7]. Studies on CA have underscored that impaired cerebrovascular reactivity post-ICH contributes to subsequent injury and poor outcomes, as elucidated by PRx and ORx indices [21,22]. PRx, a monitoring index, indicates impaired pressure reactivity when cerebral blood volume increments are not compensated, causing passive responses in ICP following cerebral perfusion pressure variations [5,7]. Leveraging ORx, $P_{br}O_2$ serves as a surrogate indicator of CBF [14]. In our experiment, we adopted a similar index, H-ORx, focusing on a narrower time window encompassing $P_{br}O_2$ and CPP.

In this translational model of ICH, the observation of regular spontaneous SDs, akin to occurrences in the human brain, is notable. SD is recognized for inducing alterations in cerebral resistance vessels. Typically, under physiological conditions and in most species, SD triggers a characteristic hemodynamic response, spreading hyperemia, marked by a substantial increase in CBF ranging from 35% to 250%. This response is accompanied by pial artery dilation of 25% to 120%, persisting up to 3 min [1,10,15]. However, in pathological scenarios, the typical response to SD may be disrupted and reversed, leading to hypoperfusion and ischemia due to pronounced vasoconstriction [1,10]. Hence, SD following ICH may be associated with disturbances in vascular tone, potentially contributing to autoregulatory impairment.

Yet, establishing a direct causal relationship between SD and CA impairment remains unresolved. Our hypothesis posits that the transient autoregulatory disruption detected by both PRx and H-ORx could represent a hemodynamic response during SD expansion, possibly reflecting the impact of SD on ICP and $P_{br}O_2$ within the initial 5-10 min post-detection. This phenomenon might be linked to temporary impairment in vascular reactivity, as indicated by the observed changes in PRx and H-ORx. The finding that only 40% of SDs were associated with PRx alterations may correspond to previous reports showing that clusters of SD, rather than isolated events, are more frequently accompanied by ICP elevations [9,20].

This supports the interpretation that temporally close SD developments, rather than isolated occurrences, may influence ICP. Furthermore, the greater number of SDs disrupting autoregulation in H-ORx might indicate hyperoxic responses to SD due to increases in CPP. Notably, H-ORx relies on $P_{br}O_2$ fluctuations in response to changes in CPP. Studies have indicated a high spatiotemporal association between SD and $P_{br}O_2$, reaching up to 90% [3]. Hence, it is plausible that both the insult from ICH and hemodynamic responses to SD collectively contribute to transient impairment in dilatory limits and autoregulatory mechanisms. This interaction between the ICH insult and the physiological responses to SD could significantly impact cerebral hemodynamics and autoregulation in the early stages post-ICH.

### Study limitations

The present study carries several limitations warranting cautious interpretation of the results. First, no sham group was included in this preliminary study, as the main goal was to evaluate the feasibility of continuous autoregulation monitoring during SD rather than to compare normal and pathological conditions. Long-term dynamics of cerebrovascular reactivity were not evaluated, as this study focused on the early phase after ICH. Baseline recordings before ICH induction served as internal references, thereby reducing the number of animals used in accordance with the 3R principle (Replacement, Reduction, and Refinement).

Isoflurane was chosen because of its favorable anesthetic profile and its widespread use in experimental neurophysiology. It is a potent cerebral vasodilator with dose-dependent effects on cerebrovascular autoregulation: low-dose isoflurane delays dynamic autoregulatory responses but leaves static autoregulation largely intact, whereas at 1.5 MAC, both dynamic and static cerebral autoregulation are abolished [24]. A minor influence on vascular tone cannot be entirely excluded, but identical anesthetic conditions across animals minimize potential bias. A further caveat is the potential impact of the craniotomy and experimental positioning on ICP, which should be taken into account when interpreting early ICP changes.

Additionally, the exploratory use of H-ORx derived from ORx represents another limitation. The relatively short monitoring duration of 3 hours led to a reduced time window of 5 minutes, compared to the original 1-hour window used in ORx calculations. Although our results show a temporal association between spreading depolarizations and transient disturbances in cerebrovascular autoregulation, the study design does not permit causal inference. Therefore, the observed fluctuations in PRx and H-ORx should be interpreted as correlates of SD-related hemodynamic changes rather than direct effects. Future translational studies with extended monitoring periods could overcome this limitation and provide more robust data on long-term autoregulatory trends.

The exploratory nature of the investigation primarily aimed to examine CA fluctuations during SD development in a translational animal model. Notably, similar temporal associations between SDs and alterations in CA indices have been reported in clinical studies following subarachnoid hemorrhage and traumatic brain injury [13,18,20,25]. A further important consideration arises from the potential coexistence of CA dysfunction and SD post-ICH. Establishing whether one phenomenon precedes or influences the other was beyond the scope of this study. The causal relationship between these processes, therefore, remains undetermined. It also remains speculative whether CA deficits might predispose tissue to spreading ischemia in response to SD, or whether SD itself could be linked to transient autoregulatory impairment and subsequent CBF reduction [2,13,25]. Addressing this question and exploring their dynamic interaction will require further experimental studies with dedicated designs.

## Conclusions

In this exploratory translational study, continuous assessment of cerebrovascular and oxygen-pressure reactivity in an autologous ICH model revealed transient fluctuations in CA parameters following early SD development. These changes were temporally associated with increases in intracranial and oxygen pressure. Taken together, these observations suggest a potential interplay between SD-related hemodynamic dynamics and cerebrovascular reactivity, which warrants further investigation. Future studies with larger samples and extended monitoring durations will be essential to confirm these associations and clarify their physiological significance.

## Declarations

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**Competing interests:** The authors declare that they have no conflicts of interest.

**Ethics approval:** All procedures involving animals were conducted in accordance with the European Directive 2010/63/EU and were approved by the Regierungspräsidium Karlsruhe, Referat 35 – Tierschutz und Tierarzneimittel. The study design and reporting adhered to the ARRIVE 2.0 guidelines.

**Data availability:** The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

**Authors' contributions:** RSP designed the project, performed the experiments, analysed the data, and wrote the manuscript. FLRC performed experiments, analysed data, prepared the graphics, and revised the manuscript. MK performed experiments and analysed data. PAP analysed data and prepared the figures. APL, MASG, JW and ES provided scientific support and revised the manuscript. BY analysed data, provided scientific support, and revised the manuscript. All authors read and approved the final version of the manuscript and fulfill the authorship criteria of the International Committee of Medical Journal Editors (ICMJE).

## References

1. Ayata C, Lauritzen M. Spreading depression, spreading depolarizations, and the cerebral vasculature. Physiol Rev. 2015; 95: 953–93.

2. Bere Z, Obrenovitch TP, Kozák G, Bari F, Farkas E. Imaging reveals the focal area of spreading depolarizations and a variety of hemodynamic responses in a rat microembolic stroke model. J Cereb Blood Flow Metab. 2014; 34: 1695–705.

3. Bosche B, Graf R, Ernestus RI, Dohmen C, Reithmeier T, Brinker G, et al. Recurrent spreading depolarizations after subarachnoid hemorrhage decreases oxygen availability in human cerebral cortex. Ann Neurol. 2010; 67: 607–17.

4. Budohoski KP, Czosnyka M, de Riva N, Smielewski P, Pickard JD, Menon DK, et al. The relationship between cerebral blood flow autoregulation and cerebrovascular pressure reactivity after traumatic brain injury. Neurosurgery. 2012; 71: 652–61.

5. Czosnyka M, Smielewski P, Kirkpatrick P, Laing RJF, Menon D, Pickard JD. Continuous assessment of the cerebral vasomotor reactivity in head injury. Neurosurgery. 1997; 41: 11–19.

6. Czosnyka M, Brady K, Reinhard M, Smielewski P, Steiner LA. Monitoring of cerebrovascular autoregulation: facts, myths, and missing links. Neurocrit Care. 2009; 10: 373–86.

7. Czosnyka M, Czosnyka Z, Smielewski P. Pressure reactivity index: journey through the past 20 years. Acta Neurochir. 2017; 159: 2063–65.

8. de Oliveira Manoel AL. Surgery for spontaneous intracerebral hemorrhage. Crit Care. 2020; 24: 45.

9. Dreier JP, Major S, Manning A, Woitzik J, Drenckhahn C, Steinbrink J, et al. Cortical spreading ischaemia is a novel process involved in ischaemic damage in aneurysmal subarachnoid haemorrhage. Brain. 2009; 132: 1866–81.

10. Dreier JP. The role of spreading depression, spreading depolarization and spreading ischemia in neurological disease. Nat Med. 2011; 17: 439–47.

11. Fabricius M, Fuhr S, Bhatia R, Boutelle M, Hashemi P, Strong AJ, et al. Cortical spreading depression and peri-infarct depolarization in acutely injured human cerebral cortex. Brain. 2006; 129: 778–

90.

12. Helbok R, Schiefecker AJ, Friberg C, Beer R, Kofler M, Rhomberg P, et al. Spreading depolarizations in patients with spontaneous intracerebral hemorrhage: association with perihematomal edema progression. J Cereb Blood Flow Metab. 2017; 37: 1871–82.

13. Hinzman JM, Andaluz N, Shutter LA, Okonkwo DO, Pahl C, Strong AJ, et al. Inverse neurovascular coupling to cortical spreading depolarizations in severe brain trauma. Brain. 2014; 137: 2960–72.

14. Jaeger M, Schuhmann MU, Soehle M, Meixensberger J. Continuous assessment of cerebrovascular autoregulation after traumatic brain injury using brain tissue oxygen pressure reactivity. Crit Care Med. 2006; 34: 1783–88.

15. Lauritzen M, Dreier JP, Fabricius M, Hartings JA, Graf R, Strong AJ. Clinical relevance of cortical spreading depression in neurological disorders: migraine, malignant stroke, subarachnoid and intracranial hemorrhage, and traumatic brain injury. J Cereb Blood Flow Metab. 2011; 31: 17–35.

16. Meng L, Wang Y, Zhang L, McDonagh DL. Heterogeneity and variability in pressure autoregulation of organ blood flow: lessons learned over 100+ years. Crit Care Med. 2019; 47: 436–48.

17. Orakcioglu B, Kentar M, Uozumi Y, Santos E, Schiebel P, Unterberg A, et al. Multiparametric characterisation of the perihemorrhagic zone in a porcine model of lobar intracerebral hemorrhage. Acta Neurochir Suppl. 2011; 111: 19–23.

18. Owen B, Vangala A, Fritch C, Alsarah AA, Jones T, Davis H, et al. Cerebral autoregulation correlation with outcomes and spreading depolarization in aneurysmal subarachnoid hemorrhage. Stroke. 2022; 53: 1975–83.

19. Percie du Sert N, Ahluwalia A, Alam S, Avey MT, Baker M, Browne WJ, et al. Reporting animal research: explanation and elaboration for the ARRIVE guidelines 2.0. PLoS Biol. 2020; 18: e3000411.

20. Sanchez-Porras R, Ramírez-Cuapio FL, Hecht N, Seule M, Díaz-Peregrino R, Unterberg A, et al. Cerebrovascular pressure reactivity according to long-pressure reactivity index during spreading depolarizations in aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2023; 39: 135–44.

21. Santos E, Diedler J, Sykora M, Orakcioglu B, Kentar M, Czosnyka M, et al. Low-frequency sampling for PRx calculation does not reduce prognostication and produces similar CPPopt in intracerebral haemorrhage patients. Acta Neurochir. 2011; 153: 2189–95.

22. Santos E, Orakcioglu B, Kentar MM, Diedler J, Uozumi Y, Schöll M, et al. Pressure reactivity index correlates with metabolic dysfunction in a porcine model of intracerebral hemorrhage. Acta Neurochir Suppl. 2012; 114: 363–67.

23. Steiner LA, Coles JP, Johnston AJ, Chatfield DA, Smielewski P, Fryer TD, et al. Assessment of cerebrovascular autoregulation in head-injured patients: a validation study. Stroke. 2003; 34: 2404–09.

24. Strebel S, Lam AM, Matta B, Mayberg TS, Aaslid R, Newell DW. Dynamic and static cerebral autoregulation during isoflurane, desflurane, and propofol anesthesia. Anesthesiology. 1995; 83: 66–76.

25. Sugimoto K, Shirao S, Koizumi H, Inoue T, Oka F, Maruta Y, et al. Continuous monitoring of spreading depolarization and cerebrovascular autoregulation after aneurysmal subarachnoid hemorrhage. J Stroke Cerebrovasc Dis. 2016; 25: e171–77.