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Delayed Cerebral Ischemia After Subarachnoid Hemorrhage: Experimental-Clinical Disconnect and the Unmet Need

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Abstract

Background—Delayed cerebral ischemia (DCI) is among the most dreaded complications following aneurysmal subarachnoid hemorrhage (SAH). Despite advances in neurocritical care, DCI remains a significant cause of morbidity and mortality, prolonged intensive care unit and hospital stay, and high healthcare costs. Large artery vasospasm has classically been thought to lead to DCI. However, recent failure of clinical trials targeting vasospasm to improve outcomes has underscored the disconnect between large artery vasospasm and DCI. Therefore, interest has shifted onto other potential mechanisms such as microvascular dysfunction and spreading depolarizations. Animal models can be instrumental in dissecting pathophysiology, but clinical relevance can be difficult to establish.

Methods—Here, we performed a systematic review of the literature on animal models of SAH, focusing specifically on DCI and neurological deficits.

Results—We find that dog, rabbit and rodent models do not consistently lead to DCI, although some degree of delayed vascular dysfunction is common. Primate models reliably recapitulate delayed neurological deficits and ischemic brain injury; however, ethical issues and cost limit their translational utility.

Conclusions—To facilitate translation, clinically relevant animal models that reproduce the pathophysiology and cardinal features of DCI after SAH are urgently needed.

Keywords

Subarachnoid hemorrhage; Delayed cerebral ischemia; Animal models

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Authors' Contributions

FO collected, analyzed the data, and wrote manuscript; DYC analyzed the data and wrote manuscript; MS edited the manuscript; CA conceived the study, analyzed the data, and wrote the manuscript.

Compliance with Ethical Standards

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Introduction

Delayed cerebral ischemia (DCI) is one of the most feared complications of aneurysmal subarachnoid hemorrhage (SAH). It occurs in approximately 20% of survivors of initial aneurysmal rupture and is a major contributor to subsequent death, poor functional outcome, and prolonged intensive care unit (ICU) and hospital stay [1]. The calcium channel blocker nimodipine is the only drug that is the U.S. food and drug administration (FDA)-approved for the prevention of DCI. The Rho-associated, coiled-coil containing protein kinase (ROCK) inhibitor, fasudil, is also used as standard of care for the prevention of DCI in Japan. However, all other investigational therapies have failed in randomized controlled trials [2], including the endothelin receptor antagonist, clazosentan, which effectively reversed angiographic vasospasm in humans but failed to improve the overall clinical outcome [3]. Although clinical trial design and flawed preclinical studies may have played some role in the failure to translate preclinical findings [4], it is more likely that attention was misdirected on reducing large artery vasospasm instead of other potential causes of DCI such as microvascular dysfunction, inflammation, thromboembolism and spreading depolarizations [1, 5–7]. There are numerous models of experimental SAH, but it is unclear to what extent DCI is recapitulated in each model. This has been a limiting factor in the pathophysiological investigations and therapeutic testing. Here, we review the available animal models of SAH and their propensity to develop DCI, in search of pathophysiologically and clinically relevant experimental models.

Methods

We conducted a PubMed search inclusive of November 2017 using keywords “subarachnoid hemorrhage” AND “delayed cerebral ischemia” AND [“animal” OR “experimental”]. We excluded clinical studies and review articles, articles in a language other than English, studies that only assessed extracranial vasculature, and studies that employed hemolyzed blood or blood products other than whole blood. We also excluded one study that only used a transgenic animal model without a wild-type control [8], one study that did not assess any delayed endpoint relevant for DCI [9], one study that artificially induced spreading depolarizations [10], and one study that induced focal ischemia after induction of SAH [11]. Overall, our DCI-focused search strategy was representative of the rest of the literature on experimental SAH [12]. We recorded SAH outcomes only in control groups without any physiological, pharmacological, or genetic intervention. We defined DCI as a worsening in tissue perfusion over time after the recovery of the initial global ischemia at the time of SAH induction. Delayed neurological deficits (DND) were defined as sensory, motor or cognitive deterioration after a clearly discernible period of stability or improvement. Tissue injury was noted if cell death was confirmed using histological markers such as Fluoro-Jade staining or TdT-mediated dUTP nick end labeling, or reduced cell counts demonstrated histologically. Frank infarction was also recorded if examined histologically, or by computed tomography (CT) or magnetic resonance imaging (MRI). We used a general linear random intercept mixed effects model to construct a multivariable linear prediction model of vasospasm as measured by arterial diameter which incorporated species, SAH induction model, time of vessel measurement, artery measured, and measurement method.

Results

Overall Characteristics of Experimental SAH Models

The initial search strategy identified 324 studies. After applying the exclusion criteria outlined above, 119 studies describing a total of 121 experimental cohorts were analyzed (Table 1). Seven species were studied, most commonly rats (32%) and dogs (22%), followed by mice (17%), primates (16%), rabbits (12%), cats (1%), and pigs (1%). In two reports, two different species were used (dogs and primates, and rats and rabbits). SAH induction methods included prechiasmatic cistern, cisterna magna, or intrathecal blood injection (61%), endovascular perforation of the internal carotid terminus or external perforation of the basilar artery (24%), direct clot placement around an intracranial artery (14%), or transection of a subarachnoid vein (1%). Blood injection was used in all species, endovascular perforation was only used in rodents, and periarterial clot placement was only used in dogs and primates. Cisterna magna blood injection was repeated 2–3 times in some models (9 single, 7 double injection studies in rats; 11 single, 3 double injection studies in rabbits; 25 double, 1 triple injection studies in dogs). Large artery vasospasm was the most often studied endpoint (57%), particularly in larger animals. In contrast, microvascular abnormalities were assessed in only a small fraction of studies (8%), mostly in mice, and relatively recently. DND was assessed in less than half and tissue outcome in less than a fourth of all studies. Endpoint assessments were limited to the first week in most studies, although some continued for up to 48 days.

Large Artery Spasm

Using our search criteria, large artery spasm was reported most often in primates (37% of all cohorts), followed by dogs (25%), rats (19%), rabbits (9%) and mice (8%) (Table 2). The most common SAH induction methods to examine large artery spasm were cisterna magna injection (46%), perivascular clot (35%) and endovascular puncture (11%) models. Vasospasm was examined in the basilar (52%), middle cerebral (19%), anterior cerebral (11%), and internal carotid arteries (10%). Although present in the majority of cohorts, the degree of vasospasm was generally mild, corresponding to a median of 70% (58–86% interquartile range) of control vessel diameters (i.e., only a 30% reduction) in the pooled dataset. A general linear random intercept mixed effects model showed that species [$F(4, 109) = 7.00$; $p < 0.0001$], SAH induction method [$F(3, 109) = 3.28$; $p = 0.0237$], time after SAH [$F(2, 109) = 6.71$; $p = 0.0018$], arteries involved [$F(4, 109) = 10.77$; $p < 0.0001$], and method of vasospasm assessment [$F(3, 109) = 2.77$; $p = 0.0449$] were independent predictors of the degree of vasospasm. Post hoc analyses suggested that vasospasm was most severe in dogs, followed in decreasing order by mice, rabbits and rats, and least severe in primates. Cisterna magna injection and perivascular clot placement led to the most severe large artery vasospasm, followed by endovascular puncture and prechiasmatic injection. Vasospasm tended to be more severe in middle cerebral arteries, followed by internal carotid and anterior cerebral arteries, and less severe in basilar and posterior cerebral arteries. Although the few studies examining multiple time points after SAH did not reveal a clear temporal progression of vasospasm, in the pooled dataset of all studies vasospasm was worse when measured 4–7 days after SAH compared with 1–3 days or 8–21 days. Data also

suggested that while some degree of large artery vasospasm was detectable in most cases, even in worst cases it appeared too mild to precipitate DCI, DND and infarction.

Microvascular Abnormalities

Given the disconnect between large artery spasm and clinical outcomes [3], attention in recent years has turned to microvascular abnormalities that may affect tissue perfusion and lead to DCI and DND (Table 3). Microvascular abnormalities in pial or parenchymal vessels were detected in all cohorts where this endpoint was examined, most often in mice, but also in dogs and rats. Microthrombi involving cerebral cortical, hippocampal and cerebellar parenchymal arterioles were commonly observed on routine histology and immunohistochemistry. However, absence of quantitative comparisons to sham controls in some studies made it difficult to assess the magnitude of this finding. Microthrombi peaked 2 days after SAH in mice in the only study that examined the time course. Reduced caliber of pial and parenchymal arterioles, and even capillaries, was also commonly observed on electron microscopy, optical microangiography, and two-photon microscopy. Smaller caliber vessels appeared to be more severely affected. The extent of constriction was sufficient to diminish perfusion when examined using two-photon microscopy, in vivo. There was also evidence of inflammation (e.g., increased P selectin). These microvascular abnormalities are all predicted to significantly increase cerebrovascular resistance and may be sufficient to cause tissue ischemia, especially when coupled to mild or moderate large artery spasm. However, in most cases, they were present at the first time point examined after SAH and did not worsen over time. Therefore, whether they are relevant for the development of DCI is unclear.

Perfusion Abnormalities

Cerebral blood flow (CBF) was examined in 17 studies within our search parameters. The species, SAH method, and the timing and techniques of perfusion assessment after SAH are summarized in Table 4. Although about half of all studies revealed perfusion abnormalities, hypoperfusion was only moderate (~ 40–80% of baseline), regardless of the cerebral blood flow (CBF) measurement technique. Moreover, only about half of the studies had more than 1 time point of assessment after SAH. Among those, worsening of perfusion (i.e., DCI) was detected in only three studies. One study in dogs found significantly lower cerebral, cerebellar and brain stem blood flow on day 8 (CBF ~ 60–70% of baseline) compared with day 1 using the microsphere technique after cisterna magna blood injection [13]. Interestingly, large artery spasm did not correlate with CBF in this study. In a more recent study, mice displayed worse perfusion on day 3 than day 1 after endovascular puncture of the intracranial carotid artery, when examined using optical coherence tomography [14]. However, the perfusion deficit was only mild (CBF 83% of controls). Finally, in a rat prechiasmatic blood injection model, hypoperfusion was significantly worse on day 2 compared with 1 h after SAH (CBF 40% of controls) [15]. Altogether, the data suggest that the majority of animal models of SAH do not faithfully reproduce DCI that is severe enough to cause infarction, regardless of the method and species.

Delayed Neurological Deficits

DND was detected in only ~ 20% of all studies where they were examined using grading systems or qualitatively based on consciousness, motor function and/or appetite (Table 5). DND was not detected in mice (0/9 cohorts) or dogs (0/8 cohorts) and was uncommon in rats (1/16 cohorts) and rabbits (1/5 cohorts). Signs of DND developed more commonly in primates (detected in 7/13 cohorts), albeit in only a small subset of animals in each cohort (10 out of 83 animals in total). Nevertheless, the proportion of animals that developed DND was similar to the incidence of DND in humans after aneurysmal SAH, and majority of these animals did develop ischemic infarcts demonstrated on imaging or histopathology. The most common signs of DND in primates were hemiparesis or reduced level of alertness observed between 3 and 8 days after SAH. Unfortunately, all but one primate study used perivascular clot placement, precluding any conclusion on the propensity of different SAH models for DND. These data show that, except for primates, animal models do not recapitulate the DND observed in aneurysmal SAH in humans.

Tissue Injury

Scattered cell death was detected in 15 out of 18 cohorts where it was assessed, mostly in mice after cisterna magna or prechiasmatic blood injection, and in rats after endovascular puncture (Table 6). The small number of studies precluded any conclusions on the propensity of different species and SAH models to develop scattered cell death. Cortex and hippocampus were most commonly involved. Evidence for delayed injury, however, was sparse. In a mouse model of endovascular perforation, hippocampal neuronal counts appeared more severely reduced compared with cell death detected on day 1 (fluoro-Jade). In a rat model of cisterna magna blood injection, neuronal counts significantly decreased in both hippocampus and cortex at day 5 compared with day 3 [16]. Both studies detected large artery vasospasm (50% reduction in middle cerebral artery caliber), as well as DND. Other studies examined only a single time point or did not compare early and late time points side by side using the same readouts. For example, in a mouse endovascular puncture model hippocampal and cortical neuronal loss (NeuN staining) was more severe at 14 days compared to the histological evidence of cell death present on day 1 (fluoro-Jade staining) [17]. Such studies could not distinguish delayed cell death due to DCI from acute cell death triggered by the SAH induction method, such as global ischemia due to high intracranial pressure, or direct focal ischemia due to endovascular puncture. Indeed supporting the latter, cell death was often ipsilateral in endovascular puncture studies.

Frank infarction was assessed more often than scattered cell death (27 studies) and was detected in half of all cohorts, often using neuroimaging. It was most commonly observed in primate perivascular clot placement followed by mouse rodent puncture models (Table 7). The small number of studies again precluded any conclusions on the propensity of different species and SAH models to develop frank infarcts. As with DND, infarction appeared more common in primates (75%), in most cases involved the cortex ipsilateral to the SAH procedure, and was associated with DND in the same animal. Direct evidence for delayed emergence of infarcts using serial imaging, however, was once again missing. Using serial MRIs, four mouse studies from one lab and two rat studies from another reported infarcts 2–3 days after SAH [18–23]. All six studies employed the endovascular puncture model and

defined DCI as new infarcts that were either not present or smaller at the earliest time point of imaging. This definition, however, did not eliminate the possibility that infarcts developed or grew subacutely after the initial hours. Moreover, the distribution of infarcts was not described and might have been directly in the territory of the punctured artery. Hence, the data did not provide incontrovertible evidence that infarcts were caused by DCI after SAH, rather than the endovascular puncture procedure itself disrupting the structural integrity of the artery.

Mortality

Nearly 80% of all studies captured by our search strategy reported mortality, ranging between 0 and 67% among all species and SAH methods. It was generally higher in rodents and after endovascular perforation, possibly reflecting inadvertent direct morbidity associated with the procedure.

Discussion

This focused literature review suggests that animal models, with the exception of primates, do not fully recapitulate the progression and outcome of aneurysmal SAH in patients. The disconnect stems from large artery vasospasm, microvascular, and perfusion abnormalities that are too mild in most animal models, and from the lack of delayed emergence of cerebral ischemia, neurological deficits, and infarction. The latter is one of the most feared subacute consequences of SAH in surviving patients, and one that should be most amenable to treatment by virtue of the delayed therapeutic window of opportunity, in contrast to the global or focal ischemic injury suffered at the time of rupture. Therefore, there is an unmet need to develop new animal models of SAH, or improve upon existing models, by optimizing the choice of species, SAH induction method, experimental design and clinically relevant readouts.

Failure to recapitulate DCI after SAH in animal models in part stems from species differences. Brain size and morphology, white matter content, vascular anatomy and physiology all differ between human brain and other species. Notably, the clearance rate of subarachnoid blood varies among species [24] and is especially rapid in rodents after cisterna magna and to a lesser extent prechiasmatic injections. Indeed, rapid clearance of subarachnoid blood is the rationale for double injections in many models of SAH in rats as well as in dogs. Furthermore, abundant collaterals in animal brain may compensate for any regional vascular dysfunction [25]. Consequently, other delayed processes that may be important in human pathophysiology, such as cortical spreading depolarizations, microthrombosis, and microembolism [2, 5, 26] might not develop or have the same impact in experimental animals. Alternatively, DCI and DND may have been missed in studies without longitudinal examinations in the same animal, or reporting bias may have led to underrepresentation of experimental studies showing the absence of DND or DCI. Hence, the true incidence of DND and DCI in experimental SAH is difficult to discern from the literature.

Non-human primate models are attractive in SAH research due to phylogenetic, anatomic, and morphologic similarities to humans, as well as relatively well-established behavioral

outcomes. In most primate studies, SAH was induced by perivascular clot placement, which likely leads to lasting presence of blood and breakdown products in subarachnoid space and is critical for DCI [27]. However, perivascular clot placement does not reproduce the sharp increase in intracranial pressure (ICP) and resulting transient global ischemia at the time of aneurysm rupture, or the acute exposure to fresh arterial blood, both of which may also contribute to DCI in humans [1]. Although DND and DCI were more common in primates than other species tested, ethical issues, cost and low throughput make non-human primate research prohibitive except in a few specialized facilities [25]. Therefore, it is not realistic to utilize nonhuman primates as the main species in SAH research, but perhaps as the gateway to a clinical trial. It should be acknowledged, however, that there is no evidence supporting that therapeutic efficacy in non-human primates are more predictive than phylogenetically lower species for therapeutic efficacy in human, no matter how intuitive it sounds.

Experimental models of SAH, as in most other disease models, range from holistic to mechanistic (i.e., reductionist). Holistic approaches try to approximate all aspects of human aneurysmal SAH with the intent of, for example, examining clinically relevant outcomes for therapeutic testing. Mechanistic models, on the other hand, mimic one particular aspect to better understand the pathophysiology. Clearly, none of the existing SAH models achieve a truly holistic representation of human aneurysmal SAH. The endovascular puncture model is practical, acutely introduces oxygenated arterial blood into the subarachnoid space, and raises intracranial pressure. However, it is also associated with a high rate of acute focal cerebral ischemia and infarcts from destruction of arterial continuity by the endovascular filament, and likely by gross endothelial injury in extended segments of the carotid artery during filament insertion. If acute tissue injury is not examined by a sensitive technique in the endovascular puncture model (e.g., MRI < 24 h after the procedure), any ischemic injury detected subsequently can be erroneously attributed to DCI. As discussed above in the context of primates, perivascular clot placement ensures dense presence of blood and breakdown products for extended periods of time, but the model does not reproduce fresh arterial blood exposure or the intracranial pressure spike at the time of rupture. Conversely, direct prechiasmatic or cisterna magna blood injection models reproduce the oxygenated arterial blood exposure and the intracranial pressure spike, but injected blood is often rapidly cleared without recreating the dense presence of blood and breakdown products for extended periods of time. To the extent that these processes are relevant for DCI and DND, perivascular clot placement and direct subarachnoid blood injection models remain more mechanistic than holistic. A holistic model to examine DCI and DND in rodents is the elastase-hypertension model [28–31]. Aneurysms are induced by subarachnoid elastase injection on a hypertensive background via mechanisms involving inflammation and focal vessel wall weakening that are implicated in human aneurysm formation as well. The model faithfully recreates spontaneous aneurysmal rupture and SAH with a natural range of severities mimicking human aneurysmal SAH [32, 33]. Mechanistically, however, the unpredictable timing of spontaneous aneurysmal rupture (5–14 days) blurs the timing of DCI and DND, and elastase-induced changes in arterial morphology may, in theory, affect the vascular mechanisms of DCI and DND. Despite these caveats, we believe the elastase-hypertension model is valuable to examine therapeutic interventions on SAH outcomes, when administered after the spontaneous rupture, which is marked by an acute neurological

worsening in this model. Therefore, we believe preclinical efficacy screening would benefit from this holistic SAH model.

Outcome endpoints can also be more holistic or more mechanistic. A holistic approach to quantify DND as a clinically relevant (i.e., functional) outcome measure after experimental SAH is not easy due to the poor sensitivity of neurocognitive testing in most species. Moreover, unlike in models of focal ischemia, the severity and distribution of ischemia in SAH models can be highly variable even within a single model and species. As a result, the tissue and neurocognitive outcomes of each SAH model have not been well defined [34], and as noted above, most studies have indeed failed to detect DND using available tests. There may also be differences in the definition of what constitutes DND. Moreover, immediate or early deficits directly caused by SAH induction method may be severe enough to mask subsequent DND. More mechanistic readouts are easier to define. After the realization that large artery spasm is not a good predictor of DCI or DND [27] and that its successful treatment has not improved the outcomes, the focus on large artery spasm as the primary endpoint has shifted to microvascular dysfunction, inflammation, thromboembolism and spreading depolarizations [1, 5, 6]. However, these more mechanistic endpoints have not yet been proven to be a critical contributor or predictor of DCI and DND. Therefore, more studies are needed to establish causality.

Longitudinal outcome assessments, preferably in the same animal, are critical to ascertain whether any ischemia or neurocognitive deficit develops in a delayed manner, to qualify as DCI and DND. This important study design principle, unfortunately, has been missing in all but a handful of experimental SAH studies examining DCI and DND, as summarized above. Moreover, it is important to examine the spatiotemporal correspondence among various endpoints (e.g., CBF, infarction, neurocognitive deficits) to establish causation. This has also been missing except for a few studies. Longitudinal assessments in the same animal, and establishing correlations among various readouts, can best be established using advanced neuroimaging techniques to measure supply–demand mismatch and injury [35]. Finally, it is worth noting that when prioritizing investigational therapies for clinical trials, we must take into account the limitations of preclinical models, and perhaps more importantly the strength of preclinical data, such as proper experimental design and independent replication.

Although developing guidelines on preclinical SAH models for novel therapeutic intervention screening requires an expert consortium, we here offer some recommendations that we feel are critical to enhance the reproducibility and congruity among studies targeting DCI or DND, as well as their predictive value toward clinical translation. Most importantly, DCI must be distinguished from acute ischemia, and DND from acute deficits directly caused at the time of SAH induction. This requires longitudinal examination of the same animal, preferably for more than 7 days. Ideally, neuroimaging should be used to quantify injury and CBF within the first 24 h of SAH induction as a reference point for subsequent changes. Of course, availability and high cost are significant barriers for routine use of these tools. Neurological examination should document acute deficits within the first 24 h of SAH induction, and serial exams should seek evidence for worsening deficits over time. Importantly, severe deficits at onset may mask subsequent DND. For example, certain models that are known to induce a concurrent large vessel ischemic stroke, such as

endovascular perforation, should be interpreted with additional caution. Sensorimotor tests can be performed during acute to subacute stages. However, cognitive tests (e.g., learning and memory) are often confounded by acute systemic disturbances and sensorimotor deficits and are thus suitable in later stages. In principle, therapeutic interventions should be tested in more than one species in a stratified manner. For practical reasons one can start with smaller, high-throughput species (e.g., rodents), and escalate to larger and preferably gyrencephalic species (e.g., pigs) if the results are promising. Similarly, interventions should be tested in more than one experimental model. All models have advantages and disadvantages, and none has been shown to be more predictive than the others, precluding an algorithmic approach. When selecting models, one has to keep in mind their strengths and caveats, as well as the relevance of model readouts for the targeted mechanism. Although initial screening in high-throughput models may be justified, we advocate a multimodal approach to provide information about tissue and neurological outcomes. Physiological (e.g., CBF), neurological (e.g., sensorimotor or cognitive deficits) and tissue (e.g., neuroimaging or histological) readouts should be collected and reconciled in each animal as much as possible. Furthermore, rigor and reproducibility are indispensible. Experiments should adhere to principles of good laboratory practice, including randomization and blinding, and predetermined exclusion criteria (or adopting intention-to-treat), primary and secondary endpoints, and sample sizes for sufficient statistical power. We recommend including equal numbers of male and female animals in the initial cohort, but powering the study for the pooled sample size with sex as an independent variable. If a trend for sex differences is observed in outcomes of this initial cohort, sample size can be increased for within-sex comparisons. While knowing the estrus cycle stage of the females is of scientific and biological significance, it is not a relevant parameter for clinical translation, since clinical trials do not include or stratify women based on their estrus cycle stage at the time of the event.

In conclusion, there are important limitations to each animal model of SAH that contribute to the difficulty in translating preclinical findings to effective therapies. We have also learned that mechanistic readouts such as vasospasm cannot substitute for readouts with direct clinical relevance such as tissue and functional outcomes. In order to enhance clinical relevance and predictive value for DCI and DND, we should dedicate more time and effort to develop better experimental models, rather than continue using previously published models without modification. We must better define the characteristics of existing models in multiple species and perhaps develop a battery of models representing different aspects of aneurysmal SAH as testing grounds. Finally, we must adhere to good study design and reporting principles to enhance the collective effort [36].

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Table 1

Overall characteristics of experimental SAH cohorts focusing on delayed cerebral ischemia and neurological deficits

Species	SAH method	Number of cohorts	Study duration (days) range (median)	Large artery spasm		Microvascular abnormalities		Perfusion abnormalities		Delayed neurological deficits		Scattered cell death		Infarction		Mortality		References
				Examined	Present	Examined	Present	Examined	Present	Examined	Present	Examined	Present	Examined	Present	Examined	Median (range)	
Mouse	CMI	2	7 (7)	0 (0%)	–	2 (100%)	2(100%)	0 (0%)	–	0 (0%)	–	2 (100%)	2 (100%)	0 (0%)	–	1 (50%)	7.1%	[37, 38]
	PCI	5	2 (2)	1 (20%)	1 (100%)	3 (60%)	3 (100%)	1 (20%)	1 (100%)	1 (20%)	0 (0%)	4 (80%)	4 (100%)	0 (0%)	–	2 (40%)	0%	[39–43]
	EVP	12	2–28 (3)	4 (33%)	4 (100%)	2 (17%)	2 (100%)	4 (33%)	4 (100%)	7 (58%)	0 (0%)	1 (8%)	1 (100%)	5 (42%)	4 (80%)	8 (67%)	26% (6–33%)	[14, 17–21, 44–49]
	VT	1	34	1 (100%)	1 (100%)	0 (0%)	–	0 (0%)	–	1 (100%)	0 (0%)	0 (0%)	–	0 (0%)	–	0 (0%)	–	[50]
Rat	CMI	16	2–14 (6)	7 (44%)	7 (100%)	0 (0%)	–	4 (25%)	2 (50%)	7 (44%)	1 (14%)	2 (13%)	1 (50%)	3 (19%)	0 (0%)	11 (69%)	0 (0–41%)	[16, 51–65]
	PCI	7	2–7 (4)	1 (14%)	1 (100%)	1 (14%)	1 (100%)	1 (14%)	1 (100%)	6 (86%)	0 (0%)	1 (14%)	1 (100%)	0 (0%)	–	7 (100%)	20% (12–33%)	[15, 66–71]
	EVP	14	1–9 (2.5)	2 (14%)	2 (100%)	0 (0%)	–	0 (0%)	–	3 (21%)	0 (0%)	4 (29%)	4 (100%)	4 (29%)	2 (50%)	9 (64%)	25% (13–67%)	[22, 23, 72–83]
	EP	2	2–4 (3)	1 (50%)	1 (100%)	0 (0%)	–	0 (0%)	–	0 (0%)	–	0 (0%)	–	0 (0%)	–	2 (100%)	20% (5%, 36%)	[84, 85]
Rabbit	CMI	13	2–10 (3)	8 (62%)	8 (100%)	0 (0%)	–	2 (15%)	2 (100%)	5 (39%)	1 (20%)	2 (15%)	1 (50%)	1 (8%)	0 (0%)	10 (77%)	0% (0–37%)	[70, 86–97]
	EP	1	5	1 (100%)	1 (100%)	0 (0%)	–	0 (0%)	–	0 (0%)	–	0 (0%)	–	0 (0%)	–	1 (100%)	0%	[98]
Cat	CMI	1	10	1 (100%)	1 (100%)	0 (0%)	–	0 (0%)	–	1 (100%)	1 (100%)	0 (0%)	–	0 (0%)	–	1 (100%)	19%	[99]
Dog	CMI	26	1–48 (7)	22 (85%)	21 (96%)	2 (8%)	2 (100%)	3 (12%)	2 (67%)	7 (27%)	0 (0%)	1 (4%)	0 (0%)	4 (15%)	1 (25%)	26 (100%)	0% (0–18%)	[13, 100–124]
	PVC	1	7	1 (100%)	1 (100%)	0 (0%)	–	0 (0%)	–	1 (100%)	0 (0%)	0 (0%)	–	0 (0%)	–	1 (100%)	7%	[125]
Pig	IT	1	14	1 (100%)	1 (100%)	0 (0%)	–	0 (0%)	–	1 (100%)	1 (100%)	0 (0%)	–	0 (0%)	–	0 (0%)	–	[126]
Primate	PVC	16	7–28 (7)	15 (94%)	15 (100%)	0 (0%)	–	3 (19%)	1 (33%)	10 (63%)	6 (60%)	0 (0%)	–	8 (50%)	6 (75%)	14 (88%)	0% (0–13%)	[122, 127–141]

Species	SAH method	Number of cohorts	Study duration (days) range (median)	Large artery spasm		Microvascular abnormalities		Perfusion abnormalities		Delayed neurological deficits		Scattered cell death		Infarction		Mortality		References
				Examined	Present	Examined	Present	Examined	Present	Examined	Present	Examined	Present	Examined	Present	Examined	Median (range)	
	CMI	1	10	1 (100%)	1 (100%)	0 (0%)	–	0 (0%)	–	1 (100%)	0%	0 (0%)	–	0 (0%)	–	1 (100%)	0%	[142]
	PCI	2	7–21 (14)	2 (100%)	1 (50%)	0 (0%)	–	2 (100%)	0 (0%)	2 (100%)	1 (50%)	1 (50%)	1 (100%)	2 (100%)	0 (0%)	2 (100%)	20% (15%, 28%)	[143, 144]
All		121		69 (57%)	68 (99%)	10 (8%)	10 (100%)	20 (17%)	13 (65%)	53 (44%)	11 (21%)	18 (15%)	15 (83%)	27 (22%)	13 (48%)	96 (79%)	–	

Cohorts are sorted by species followed by SAH method. Two reports included more than one species, shown in the table as separate cohorts. “Examined” column shows the percentage of all cohorts where the endpoint was assessed and reported. “Present” column indicates the percentage of cohorts among those examined in which the outcome was detected

CMI cisterna magna blood injection ×1–3, *EP* external perforation of basilar artery, *EVP* endovascular perforation of internal carotid artery terminus, *IT*, intrathecal blood injection, *PCI* prechiasmatic blood injection, *PVC* perivascular clot placement, *SAH* subarachnoid hemorrhage, *VT* transection of subarachnoid vein

Table 2

Cohorts in which large artery spasm was examined after SAH

Species	SAH method	Time after SAH (days)	# Cohorts	Artery	Median diameter (% of control) [IQR][a]	Refs.
Mouse	EVP	2–3	9	MCA, ACA, BA, ICA	70 [70–100]	[12, 44–46]
Mouse	PCI	2	1	MCA	57	[41]
Mouse	VT	6	1	MCA	66	[50]
Rat	CMI	1–3	8	BA	89 [75–93]	[16, 54, 55, 57, 64]
Rat	CMI	4–7	9	BA	80 [73–85]	[16, 57, 61, 62, 64]
Rat	EP	4	1	BA	66	[85]
Rat	EVP	2	6	MCA, ACA, BA, ICA	94 [74–100]	[22, 81]
Rat	PCI	7	2	MCA, ACA	70, 77	[66]
Rabbit	CMI	1–3	8	BA	70 [64–81]	[86, 89–91, 93, 94, 96]
Rabbit	CMI	4–7	2	BA	68, 89	[90, 92]
Rabbit	CMI	8–14	2	BA	90, 91	[90]
Rabbit	EP	5	1	BA	32	[98]
Dog	CMI	1–3	4	BA	83 [81–85]	[100, 101, 105]
Dog	CMI	4–7	23	BA	58 [52–66]	[13, 101–103, 105–113, 115, 117–120, 122–124]
Dog	CMI	8–14	4	BA	66 [54–83]	[105, 109, 122, 124]
Dog	PVC	7	3	MCA, ACA, ICA	44 [42–49]	[126
Pig	CMI	7	2	ACA, ICA	86, 89	[126]
Pig	CMI	12	2	ACA, ICA	69, 81	[126]
Primate	CMI	7	3	MCA, ACA, ICA	71 [66–72]	[142]
Primate	PCI	2	1	?	86	[144]
Primate	PCI	7	2	?	56, 100	[143, 144]
Primate	PCI	14–21	2	?	69, 74	[144]
Primate	PVC	7	39	MCA, ACA, P, BA, ICA, ?	68 [55–86]	[122, 127–132, 134–140]
Primate	PVC	14	5	MCA, ACA, ICA, ?	87 [86–89]	[127, 136]
Pooled					70 [58–86]	

Cohorts are sorted by species followed by SAH method and time after SAH (grouped into days 1–3, 4–7 and 8–21).

[a]Individual data points are given when only 1 or 2 cohorts were present

ACA anterior cerebral artery, *BA* basilar artery, *CMI* cisterna magna blood injection ×1–3, *EP* external perforation of basilar artery, *EVP* endovascular perforation of internal carotid artery terminus, *ICA* internal carotid artery, *MCA* middle cerebral artery, *PCA* posterior cerebral artery, *PCI* prechiasmatic blood injection, *PVC* perivascular clot placement, *SAH* subarachnoid hemorrhage, *VT* transection of subarachnoid vein, *?* not specified

Table 3

Cohorts in which microvascular abnormalities were examined after SAH

	Species	SAH method	Time after SAH (days)	Microvascular abnormality	Tissue assessment	Distribution	Refs.
Microthrombi	Mouse	PCI	2	Fibrinogen (+) arterioles[a]	IHC	Cortex, hippocampus	[42]
	Mouse	PCI	2	Fibrinogen (+) parenchymal microvessels[a]	IHC	Cortex, hippocampus	[41]
	Mouse	PCI	2	Fibrinogen (+) parenchymal microvessel	IHC	Cortex, hippocampus	[39]
	Mouse	EVP	1, 2, 3, 4	Antithrombin (+) parenchymal microvessels	IHC	Cortex	[47]
	Rat	PCI	7	Fibrinogen (+) parenchymal microvessels, microclot on H&E	H&E	Cortex, cerebellum	[66]
	Dog	CMI	14	Fibrinogen (+) parenchymal microvessels[a]	IHC	Cortex	[122]
Constriction	Mouse	PCI	2	Parenchymal arteriole diameter 35% smaller than controls	EM	Cortex	[39]
	Mouse	EVP	1, 3	Pial arteriole diameter 10% smaller than controls at both time points	OCT	Cortex	[14]
	Mouse	CMI	6 h	Pial artery diameter 15–20% smaller than controls Parenchymal arteriole diameter 28–42% smaller than controls	2P	Cortex	[37]
	Mouse	CMI	2	Pial arteriole diameter 14% smaller than controls	2P	Cortex	[38]
	Dog	CMI	3, 7, 14	Parenchymal arteriole diameter 40% smaller than controls on days 3, 7	EM, EVG	Cortex	[116]

Cohorts are sorted by microvascular abnormality, followed by species and SAH method

[a]No comparison to a sham control group

CMI cisterna magna blood injection ×1–3, *EM* electron microscopy, *EVG* elastic van Gieson stain, *EVP* endovascular perforation of internal carotid artery terminus, *H&E* hematoxylin–eosin staining, *IHC* immunohistochemistry, *OCT* optical coherence tomography-based microangiography, *PCI* prechiasmatic blood injection, *SAH* subarachnoid hemorrhage, *2P* two-photon microscopy

Table 4

Cohorts in which blood flow was examined after SAH

Species	SAH method	Time after SAH	Measurement technique	Regions examined	Lowest perfusion (% of control)	Worsening over time	Refs.
Mouse	PCI	2 days	LSF, MRI	MCA territory (LSF); forebrain, midbrain, hindbrain (MRI)	77% in MCA territory 46% in forebrain	–	[43]
Mouse	EVP	1–3 days	OCT	Cerebral cortex	83% on day 3 in MCA territory	Yes	[14]
Rat	CMI	3–5 days	PW-MRI	?	56% on day 5	No	[16]
Rat	CMI	3 min–5 days	H_2 clearance	Parietal, occipital, cerebellar cortex	60% on day 0 globally	No	[53]
Rat	CMI	3 h–14 days	^{14}C autoradiography	Whole brain, frontal and parieto-occipital cortex, diencephalon, brainstem, cerebellum	No hypoperfusion[a]	No	[52]
Rat	PCI	1 h–4 days	^{14}C autoradiography	Cerebral cortex	40% on day 2	Yes	[15]
Rat	PCI	3 days	^{14}C autoradiography	Cerebral cortex	50%	–	[69]
Rat	EVP	1 h–9 days	MRI	Single slice 0.5 cm anterior to bregma	88% on day 2 ipsilateral to EVP[a]	No	[22]
Rabbit	CMI	6 days	H_2 clearance	Cerebral cortex (bilateral frontal and parietal)	130%[a]	–	[87]
Dog	CMI	1–8 days	Microspheres	Cerebral cortex, cerebellum, pons, medulla	75% on day 8 in pons and medulla[a]	Yes	[13]
Dog	CMI	7 days	H_2 clearance	Cerebral (occipital) cortex	57%	–	[108]
Dog	CMI	5 days	Microspheres	Cerebral cortex, cerebellum, brain stem	No hypoperfusion[a]	–	[109]
Dog	CMI	8 days	Microspheres	Cerebral cortex, cerebellum, brain stem	No hypoperfusion[a]	–	[109]
Primate	PVC	7 days	H_2 clearance	Cerebral cortex	44% in frontal lobe[b]	–	[134]
Primate	PVC	7 days	^{133}Xe clearance	Cerebral cortex	88% in right hemisphere[b]	–	[128]
Primate	PVC	7–14 days	^{133}Xe clearance	Cerebral cortex	No hypoperfusion[b]	No	[127]
Primate	PCI	0–21 days	^{133}Xe clearance	Cerebral cortex	No hypoperfusion[b]	No	[144]
Primate	PCI	7 days	^{133}Xe clearance	Cerebral cortex	No hypoperfusion[b]	–	[143]

Cohorts are sorted by species followed by SAH method. Region with lowest perfusion is also indicated when specified in the report

[a]No statistical difference compared with sham

[b]No comparison with sham

CMI cisterna magna blood injection ×1–3, *EVP* endovascular perforation of internal carotid artery terminus, *LSF* laser speckle flowmetry, *MRI* magnetic resonance imaging, *OCT* optical coherence tomography-based microangiography, *PCI* prechiasmatic blood injection, *PVC* perivascular clot placement, *PW-MRI* perfusion weighted magnetic resonance imaging using masseter muscle to calculate relative regional CBF and CBV, *SAH* subarachnoid hemorrhage, *?* not specified, ^{133}Xe intraarterial ^{133}Xenon clearance

Table 5

Cohorts in which delayed neurological deficits were examined after experimental SAH

Species	SAH method	Neurological assessment method	DND rate	Onset of DND (days after SAH)	Neurological signs	Refs.
Rat	CMI	Grade based on motor function	?	3–5	Average grade worsened	[16]
Rabbit	CMI	Grade based on consciousness and activity	2/7 (29%)	4, 6	Average grade worsened	[90]
Cat	CMI	Grade based on consciousness and activity	6/21 (29%)	3–5	Average grade worsened	[99]
Pig	CMI	Qualitative based on motor function, consciousness and activity	4/8 (50%)	3–4	Unable to walk ($n = 2$), paraparesis ($n = 1$), loss of appetite followed by forelimb paresis ($n = 1$)	[126]
Primate	PVC	Qualitative based on consciousness	1/8 (13%)	8	Reduced level of consciousness, death	[140]
Primate	PVC	Qualitative based on consciousness and activity	2/7 (29%)	5–6	Decreased activity ($n = 1$), reduced level of consciousness ($n = 1$)	[134]
Primate	PVC	Qualitative based on motor deficit	1/8 (13%)	5	Hemiparesis	[131]
Primate	PVC	Qualitative based on motor deficit	1/12 (8%)	5	Hemiparesis	[130]
Primate	PVC	Qualitative based on motor deficit	2/8 (25%)	3, 5	Ataxia, death ($n = 1$), hemiparesis followed by contralateral monoparesis ($n = 1$)	[129]
Primate	PVC	Qualitative based on motor deficit	1/15 (7%)	4	Hemiparesis	[127]
Primate	PCI	Qualitative based on motor deficit, consciousness and activity	2/25 (8%)	Days 4 and 17	Unsteadiness and drowsiness ($n = 1$), apathy ($n = 1$)	[144]

Cohorts are sorted by species followed by SAH method. DND rate indicates % of animals in the cohort that developed DND

CMI cisterna magna blood injection ×1–3, *DND* delayed neurological deficits, *PCI* prechiasmatic blood injection, *PVC* perivascular clot placement, *SAH* subarachnoid hemorrhage, *?* not reported

Table 6

Cohorts in which scattered cell death was detected after experimental SAH

Species	SAH method	Time of assessment (days)	Histological method to show cell death	Region	Refs.
Mouse	PCI	2	FJ, TUNEL, caspase 3	C	[43]
Mouse	PCI	2	FJ	C, H	[41]
Mouse	PCI	2	TUNEL	C, SC, H	[40]
Mouse	PCI	2	TUNEL	C, SC, H	[39]
Mouse	CMI	7	NeuN	C	[37]
Mouse	CMI	7	Nissl	C, H	[38]
Mouse	EVP	1, 14	FJ (day 1), NeuN (day 14)	C, H	[17]
Rat	PCI	1, 3	Caspase 3 & TUNEL (day 1), Nissl (day 3)	C	[70]
Rat	CMI	3, 5	H&E	C, H	[16]
Rat	EVP	7	Cresyl violet	H	[80]
Rat	EVP	2–7	Cresyl violet, FJ, TUNEL	H	[77]
Rat	EVP	5	Cresyl violet	H	[72]
Rat	EVP	1	FJ, TUNEL	C	[83]
Rabbit	CMI	1	TUNEL and Nissl	C	[70]
Primate	PVC	7	Cresyl violet	C	[143]

Studies are sorted by species and SAH method

C cortex, *CMI* cisterna magna blood injection ×1–3, *EVP* endovascular perforation of internal carotid artery terminus, *FJ* fluoro-Jade staining, *H* hippocampus, *H&E* hematoxylin–eosin staining, *PCI* prechiasmatic blood injection, *PVC* perivascular clot placement, *SAH* subarachnoid hemorrhage, *SC* subcortex, *TUNEL* terminal deoxynucleotidyl transferase dUTP nick end labeling

Table 7

Characteristics of cohorts that showed frank infarction after experimental SAH

Species	SAH method	Time of assessment	Method of assessment	Findings	Region	Refs.
Mouse	EVP	2 h, 3 days	MRI	New or larger infarct on day 3 in 33% (5/15) of animals	C	[18]
Mouse	EVP	3 h, 3 days	MRI	New or larger infarct on day 3 in 30% (3/10) of animals	C	[19]
Mouse	EVP	1, 3 days	MRI	New or larger infarct on day 3 in 50% (4/8) of animals	C	[20]
Mouse	EVP	1, 3 days	MRI	New or larger infarct on day 3 in 50% (5/10) of animals	C	[21]
Rat	EVP	1 h, 2, 9 days	MRI	Average infarct volume doubled on day 2	C	[22]
Rat	EVP	1, 3 days	MRI	Average infarct volume increased by 29 mm^3 on day 3	C, SC, H	[23]
Dog	CMI	?	H&E	Infarct in 29% (4/14) of animals	CBL	[120]
Primate	PVC	7 days	MRI	Infarct in 100% (2/2) of animals	C, SC	[122]
Primate	PVC	8 days	Autopsy	Infarct in 13% (1/8) of animals	C	[140]
Primate	PVC	5 days	CT	Infarct in 13% (1/8) of animals	C	[131]
Primate	PVC	5 days	MRI	Infarct in 8% (1/12) of animals	C	[130]
Primate	PVC	5, 7 days	MRI, CT, autopsy	Infarct in 25% (2/8) of animals on day 5 or 7	C, CBL	[129]
Primate	PVC	7 days	CT	Infarct in 7% (1/15) of animals	C	[127]

Studies are sorted based on type of injury, followed by species and subarachnoid hemorrhage method

C cortex, *CBL* cerebellum, *CMI* cisterna magna blood injection ×1–3, *CT* computed tomography, *EVP* endovascular perforation of internal carotid artery terminus, *FJ* fluoro-Jade staining, *H* hippocampus, *MRI* magnetic resonance imaging, *PCI* prechiasmatic blood injection, *PVC* perivascular clot placement, *SAH* subarachnoid hemorrhage, *SC* subcortex