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REVIEW ARTICLE

Systematic Review of In Vivo Animal Models of Subarachnoid Hemorrhage: Species, Standard Parameters, and Outcomes

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Abstract

In preclinical models, modification of experimental parameters associated with techniques of inducing subarachnoid hemorrhage (SAH) can greatly affect outcomes. To analyze how parameter choice affects the relevance and comparability of findings, we systematically reviewed 765 experimental studies of in vivo animal SAH models (2000–2014). During the last decade, we found marked increases in publications using smaller species and models for simulating acute events after SAH. Overall, the fewer types of species and models used did not correlate with an increased standardization in the experimental characteristics and procedures. However, by species, commonly applied, reliable parameters for each experimental SAH technique were identified in mouse, rat, rabbit, and dog models. Our findings can serve as a starting point for discussion toward a more uniform performance of SAH experiments, development of preclinical SAH common data elements, and establishment of standardized protocols for multicenter preclinical trials.

Keywords Subarachnoid hemorrhage · Animal · Model · Delayed cerebral vasospasm · Early brain injury

Introduction

Subarachnoid hemorrhage (SAH) caused by rupture of an intracranial aneurysm accounts for approximately 5% of all strokes, with an incidence of 5–10 per 100,000 in most populations [2]. This life-threatening condition primarily affects adults, often disrupting their productive lives with resulting severe disabilities. The disease has a significant socioeconomic impact and estimated lifetime costs are more than double that of an ischemic stroke [25]. Despite significant improvements in preclinical and clinical research, advanced treatment modalities, and modern neurologic critical care management, the rates of death and dependency 12 months after aneurysmal SAH remain unacceptably high [4].

The main culprit for dismal outcome in SAH patients was attributed to delayed cerebral vasospasm (DCVS) that leads to ischemia and delayed cerebral infarction. Although clinical attenuation of DCVS was achieved by successful translation of prior experimental animal studies using an endothelin-receptor antagonist, this application had no significant effects on functional outcome [23]. These results eroded the hypothesis of DCVS as the single main cause of poor outcome after SAH. Specifically, DCVS was not a clinically relevant outcome measure in experimental SAH. Rather, other mechanisms, such as early brain injury (EBI), might play a more important role than previously assumed [12].

The failure in translation of preclinical findings into clinical trials can be explained not only by differences in outcome measure but also by methodological shortcomings of animal

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SAH studies. Specifically, many traditional SAH animal models do not adequately mimic the acute human pathophysiology and have been criticized for missing delayed cerebral ischemia. Apart from challenges associated with the choice of endpoint, the study design and experimental execution carry great risks of methodological bias [3, 13]. Furthermore, in current SAH models, arbitrary use of experimental parameters can lead to results of uncertain relevance and complicate comparability of findings.

Clearly defined, more standardized use of parameters associated with SAH models would facilitate systematic reviews and meta-analyses of preclinical study publications that would ultimately aid in deciding whether to start a clinical trial in the first place. Therefore, our review of the literature aimed to identify and analyze the most commonly applied and reliable parameters for each experimental SAH technique. We propose that our findings will serve as a basis of discussion toward more standardized performance and harmonized reporting of in vivo SAH experiments.

Methods

Search Strategy

To identify animal studies of SAH, we searched the PubMed medical databases on January 31, 2015, using the keywords "murine," "rat," "rabbit," "canine," "primate," "cat," "pig," and "goat" in combination with "subarachnoid hemorrhage." The search was automatically restricted to animals by using the MEDLINE PubMed limit "animals." Two investigators (SM and CM) independently screened titles and abstracts for eligible studies and excluded duplicates. For any discrepancy in study selection by these two authors, a third author was consulted; if necessary, the full text was read to decide eligibility. The protocol of this systematic review and analysis was previously published September 1, 2014, on CAMARADES (http://www.dcn.ed.ac.uk/camarades/). Potential studies underwent full-text screening before inclusion to the data system of CAMARADES. The search algorithm was in accordance with PRISMA guidelines [16].

Eligibility Criteria

We considered in vivo experimental studies with mouse, rat, rabbit, cat, dog, pig, goat, and non-human primate species that investigated pathophysiological intracranial consequences of experimental SAH. Excluded were in vitro experiments, studies on extracranial vessels or organs other than the brain (e.g., the lung, the heart), studies on SAH methodology (e.g., technical refinements, evaluation of SAH models), review articles, and studies without SAH or with agents causing vasoconstriction or brain damage other than whole blood. Non-original research, conference papers, and research articles written in languages other than English were excluded.

Analyzed Features

For each eligible study, we recorded publication details (i.e., authors, journal, date, affiliation details), animal variables (i.e., sex, strain, weight, age, sample size), protocol details (i.e., temperature control, fasting before surgery, blood gas analysis), anesthetics, ventilation (mechanical or spontaneous), mortality and morbidity, SAH induction techniques (intracisternal blood injection, intracranial blood clot placement, endovascular vessel puncture, open cranium vessel puncture, closed cranium vessel puncture, closed cranium vessel rupture, blood shunting), and outcome measures (histology, angiography, cerebral blood flow measurement, direct vessel observation, neuronal cell death and degeneration, cortical spreading depolarization, SAH grading, neurological impairment, blood-brain barrier disruption, contractile vessel response, biochemical marker, cardiopulmonary responses) [15]. For blood injection techniques, we identified location, volume, injection time, and time between multiple injections. For endovascular perforation techniques, we recorded the filament size and volume of clot for the blood clot placement model. Focus on the study was identified as DCVS (morphological narrowing of large cerebral arteries) and/or EBI (any structural brain injury caused by mechanisms other than DCVS). Any discrepancies and uncertainties that arose during full-text data extraction (BG, SS, DC, JL, TR, BB, and CW) were discussed with the first author (SM).

Data Collection and Analysis

Data were extracted to the CAMARADES Microsoft Access 2003 data manager and analyzed using R version 3.4.3. Descriptive analyses by species and standard models are summarized in tables and figures; no hypothesis tests were performed. Standard models were defined as those used in at least 15% of the cases for one species. Analyses not explicitly determined for species or standard models were based on complete records. Distributions of blood volumes and injection times are shown in histograms with density estimates.

Results

Of 3415 items searched by title and abstract (or full-text screening if needed), 1832 articles were reviewed. Of these, 835 studies were included into the data system, and 765 underwent final analysis (Fig. 1).

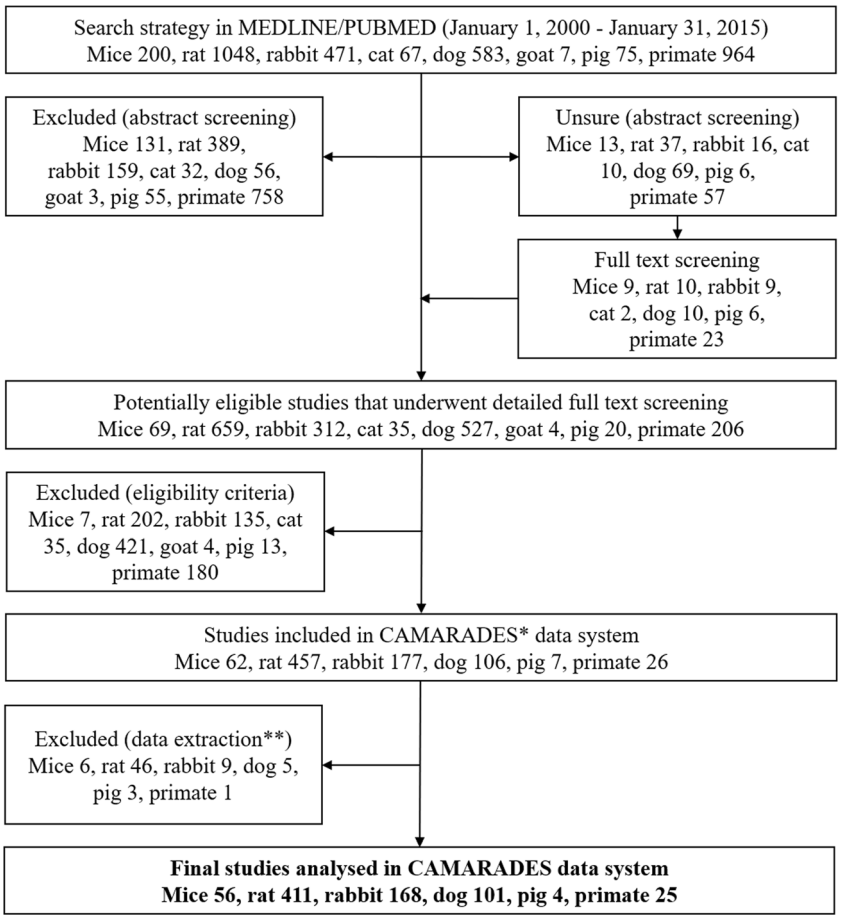

Fig. 1 Flowchart of study selection including search of 3415 titles, review of 1832 articles, and 765 in final analysis. * Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (http://www.dcn.ed.ac.uk/camarades); ** After full-text screening, few studies were excluded during data extraction

Trends in SAH Research

With a steady increase in the number of publications in the field of SAH research, contemporary animal models were most often mouse, rat, and rabbit species and least often dog, pig, and primate species (Fig. 2). During the study period, no cats or goats were used.

Induction of experimental SAH was typically by intracisternal blood injection (95% of rabbit and 63% of rat studies) and endovascular vessel perforation (59% of mouse studies) (Fig. 3; Supplementary Fig. 1 and Supplementary Table 1). Standard models and their associated parameters were identified (Table 1), and distributions of applied blood volume and injection time for each model are shown (Fig. 4). The most popular models were single-blood injection and endovascular filament model; both were in rats (Supplementary Fig. 2).

During the review period, the percentage of studies that addressed research questions other than DCVS increased steadily. Compared with the early period, more than twice as many studies today now include EBI as primary outcome/endpoint (Fig. 5). Research communities were most active in the USA, Europe, China, and Japan (Supplementary Fig. 3 and Supplementary Table 2).

The average number of animals per study slightly increased in mouse and rat models but remained stable in larger species (Supplementary Fig. 4). Overall, basic characteristics of the animals (sex, age, weight), animal history (temperature control, fasting before surgery, blood gas analysis, ventilation mechanisms), and morbidity/mortality were poorly reported (Supplementary Table 3). Delayed cerebral vasospasm was the most prominent outcome measure in rabbit, dog, and pig SAH models using the blood injection technique and in primate models of craniotomy and blood clot placement. Neurological impairment was not routinely monitored (range 20–30%) but was more often noted in the acute SAH models in mouse (55%) and rat (58%) endovascular filament models. Outcome parameters identified in these models are detailed in Supplementary Fig. 5 and Supplementary Table 4.

Trends in SAH Models by Species

Mouse In 56 mouse studies, 33 (59%) and 18 (32%) used the endovascular filament model and single infra- (44% in cisterna magna) or supratentorial (56% prechiasmatic) blood injection, respectively. Injection volumes (μl) of autologous venous or arterial fix ranged from 30 to 100 μl (with or without cerebrospinal fluid aspiration) with injection times

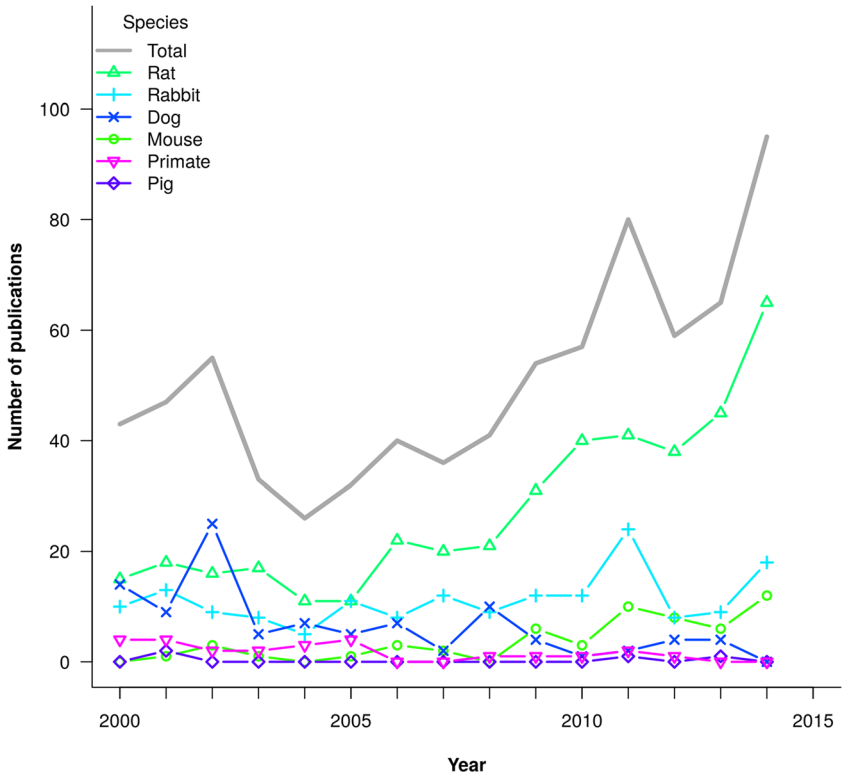

Fig. 2 Number of experimental SAH studies published per year by species between 2000 and 2014. Trends were for a marked increase in publications using smaller species (mouse and rats), a significant decline in larger animals (dogs and primates), and the rat became by far the most popular species in preclinical SAH research

ranging from 10 s to several minutes. Details regarding ventilation were not reported in 89% of single-injection studies. In all blood injection studies (100%), a fixed 60-μl volume was manually injected over 15 s, with blunt or sharpened filaments varied in suture sizes from 4-0, 5-0, or 6-0. In endovascular perforation methods, size 5–0 was used in 85% of studies. Anesthesia was typically a combination of ketamine with xylazine (85%) and/or isoflurane (42%) in single blood injection and endovascular filament models (Supplementary Table 5). The most popular mouse strain was C57/Bl6 (33%) (Supplementary Fig. 6). Age ranged averaged from 10 weeks minimum to 15 weeks maximum; weight averaged 23 to 30 g.

Rat In 411 rat studies, SAH was induced by intracisternal blood injection in 259 (63%) rats (46% single, 17% double) and by endovascular filaments in 173 (33%) rats. Volumes ranged from 50 to 1000 μl and from 100 to 400 μl/kg of fix (single 97%, double 89%); weight-adapted volumes (single 3%, double 11%) with or without previous withdrawal of cerebrospinal fluid (CSF) were injected in single- and double-injection models. Injections were administered in supratentorial (59%), infratentorial (40%), or transclival (1%) locations in single-injection models and mainly infratentorial (92%) in double-injection models. Although injection times varied greatly from 12 s to 30 min, most were 20 and 120 s in the single-injection ($n = 13$) and double-injection ($n = 10$) models, respectively. In cases of double injections, times between injections were 24 (20%), 28 (1%), 48 (72%), or 72 (7%) h. Two suture sizes of 3-0 (31%) and 4-0 (69%) were used. Although a large proportion of animals were spontaneously breathing during SAH induced by double injection (49% spontaneous; 3% mechanical; 48% not reported), most animals during endovascular vessel perforation (58% mechanical; 13% spontaneous; 29% not reported) were mechanically ventilated. In the blood injection rat model, anesthesia was typically a combination of chloral hydrate, pentobarbital, or ketamine with xylazine (irrespective of the experimental SAH induction technique) (Supplementary Table 6) in strains of Sprague Dawley (75%; 80%; 81%, respectively) and Wistar (24%; 18%; 19%) rats; this finding was irrespective of single- or double-injection or endovascular filament models. Age ranged averaged from 21 weeks minimum to 26 weeks maximum; weight averaged 287 to 346 g.

Rabbit In 168 rabbit studies, SAH was induced by a single (71%) or double (23%) blood injection. In both single-and double-injection models, respectively, the blood was almost exclusively (99% and 97%) injected into the cisterna magna (transclival in 1% and 3%). Injection volumes ranged from fix 0.3 to 4 ml and weight-adapted 0.5–1.5 ml/kg, and injection times varied from 10 s to 5 min. Most researchers applied fixed (69% and 75%) instead of weight-adapted blood amounts in single- and double-injection methods. Variations in blood volumes and injection times were identified: 16 different volumes (range 300 μl to 5 ml) and 11 injection times in

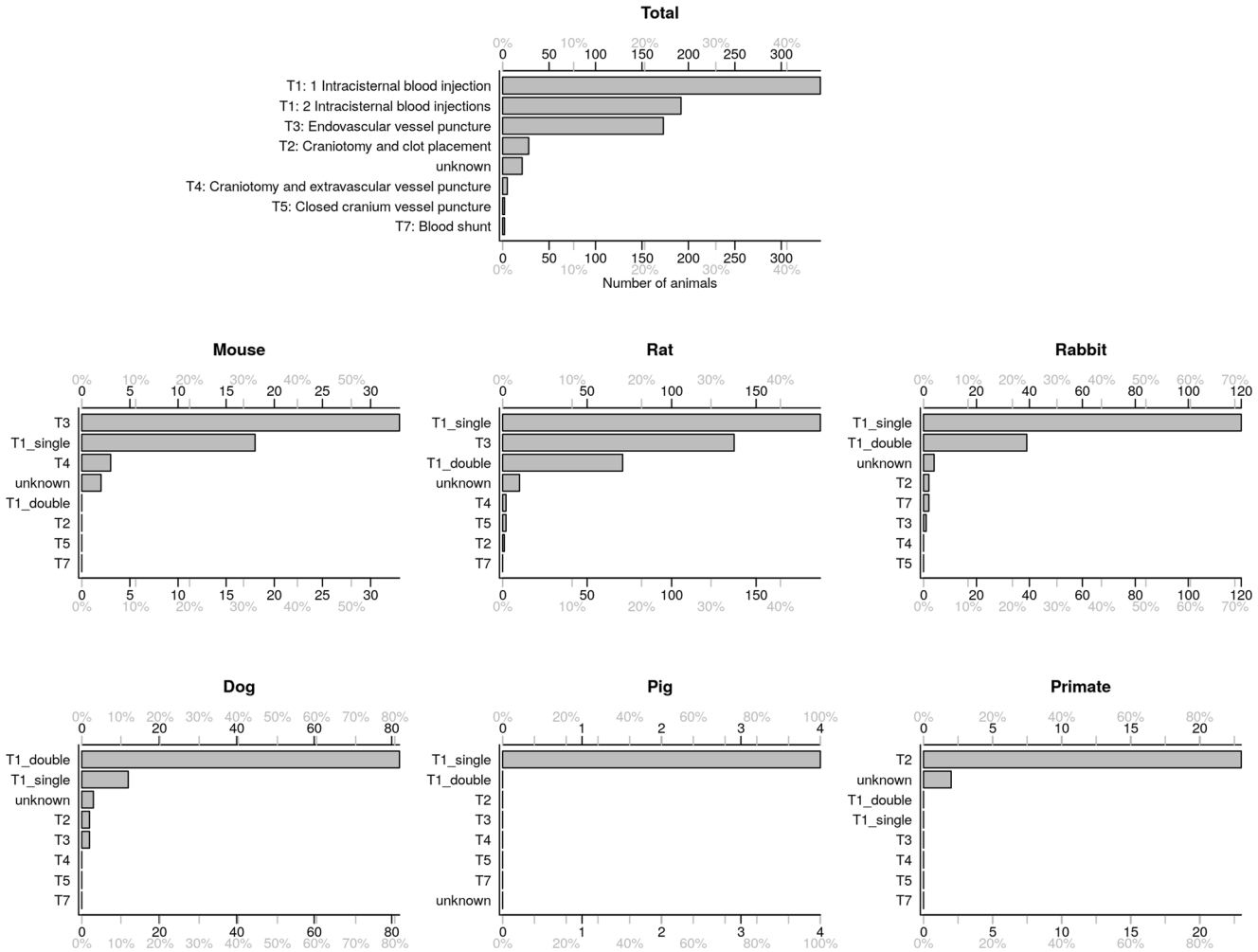

Fig. 3 Distribution of popular SAH techniques, overall and by species. A single or double intracisternal blood injection was the most common procedure to induce experimental SAH overall and in species of rat, rabbit, and dog. Endovascular perforation of an intracranial artery was the most common technique in the mouse and the second most common method in rats. Craniotomy and clot placement were typical in primates. T1, intracisternal blood injection; T2, intracranial blood clot placement; T3, endovascular vessel puncture; T4, open cranium vessel puncture; T5, closed cranium vessel puncture; T6, closed cranium vessel rupture; T7, blood shunting

single-injection models and 8 volumes and 7 injection times in double-injection models. Injection speeds were typically 60 s. Fixed and weight-adapted blood volumes of 1 ml (1 ml/kg) and 1.5 ml (1.5 ml/kg) were the most often applied parameters

Table 1 Standard animal models and associated parameters

Animal	SAH technique	Injection location	Blood volume	Injection time (s)	Delay between injections (h)
Mouse	Single blood injection	Infra- and supratentorial	0.06 ml	15	na
	Endovascular perforation	Supratentorial	5-0 suture	na	na
Rat	Single blood injection	Infra- and supratentorial	0.3 ml or 0.1 ml/kg	20	na
	Double blood injection	Infratentorial	0.3 ml or 0.1 ml/kg	120	48
	Endovascular perforation	Supratentorial	4-0 suture	na	na
Rabbit	Single blood injection	Infratentorial	1 ml or 1 ml/kg	60	na
	Double blood injection	Infratentorial	1.5 ml or 1.5 ml/kg	60	48
Dog	Double blood injection	Infratentorial	0.5 ml or 0.5 ml/kg	60	48
Primate	Craniotomy and clot placement	Supratentorial	5 ml	na	na

na not applicable

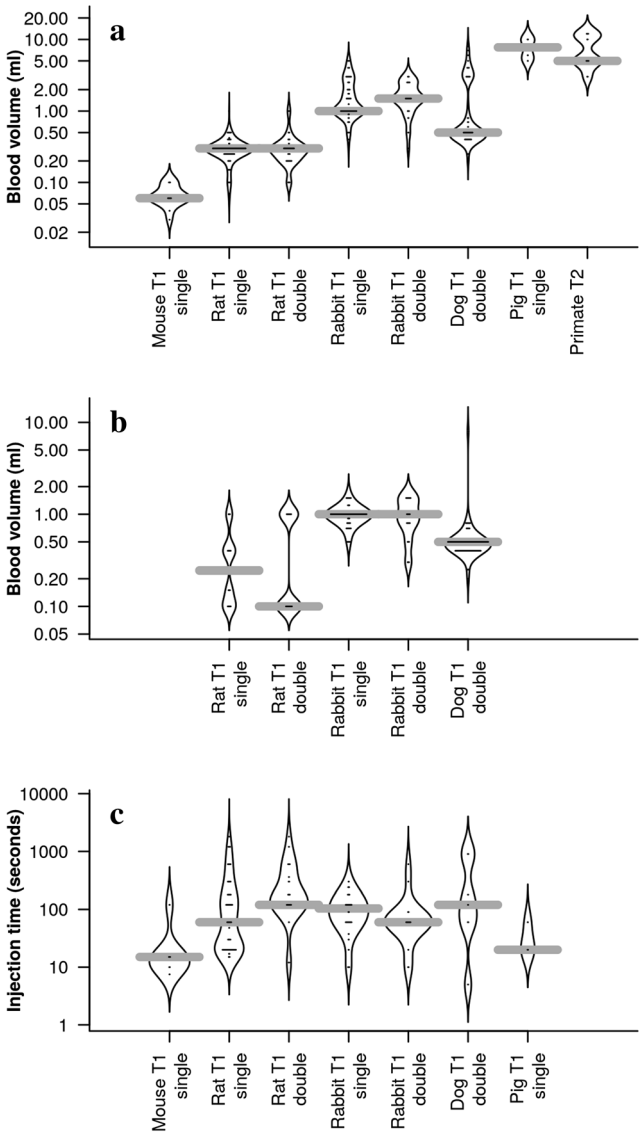

Fig. 4 Distribution by violin plots of fixed (**a**) and weight-adapted (**b**) blood volumes and injection times (**c**) for standard models. Thick black horizontal lines represent standard model medians whereas thin gray lines show number of cases (length) for each volume and injection time (longest thick horizontal line as most common). Vertical axis is log scale

in the single- and double-injection models, respectively. Of 39 studies using a double-injection model, time between the two injections was 48 h in 92% and 24 h in 8%. Animals were predominantly spontaneously breathing during the experiment irrespective of SAH technique (73% single injection, 85% double injection). Anesthetics were most often varied combinations ketamine, xylazine, droperidol, or pentobarbital (Supplementary Table 7). Nearly all studies used New Zealand or Japanese white rabbits for the single-injection (89% and 10%) and double-injection (57% and 43%) techniques, respectively. Age ranged averaged from 18 weeks minimum to 43 weeks maximum; weight averaged 2.5 to 3.3 kg.

Dog In 101 dog model studies, SAH was induced by a single (82%) or double (12%) blood injection into the cisterna magna (100% and 98%), with 6 injection times that varied from 5 s to 15 min (mostly 60 s). Of 15 different volumes reported for fixed (32%) and weight-adapted (68%) injections, range varied from 200 μl to 8 ml (most were 0.5 ml fix or weight-adapted). Time between injections was typically 48 h (68%) followed by 72 h (16%), 24 h (9%), 86 h (2%), 96 h (2%), and 168 h (2%). In the double-injection model, 79% of dogs were mechanically ventilated and anesthetized with thiopental (32%) and pentobarbital (27%) during SAH (Supplementary Table 8). Dogs were mongrels (79%) and Beagles (19%) that ranged from 10 to 25 weeks old and weighed 4.29–5.86 kg.

Primate All 25 experiments performed used the supratentorial craniotomy and blood clot placement technique in animals weighing 2.4 to 5.4 kg. Five different blood clot volumes (range 3 to 12 ml) were placed around the great cerebral vessels. All animals underwent mechanical ventilation and received ketamine (59%) or isoflurane (29%) as anesthetics.

Pig In our review, this was the least often used species in preclinical SAH research. In all four pig studies, a single blood injection (75% supratentorial and 25% infratentorial) was given to mimic SAH in mechanically ventilated or spontaneous breathing scenarios. Male animals (domestic and mini pigs) weighing 10 to 15 kg were injected with blood volume ranging from 5 to 10 ml (Supplementary Table 6).

Discussion

Our systematic review of 765 studies during a 15-year period identified in vivo animal research that investigated pathophysiological intracranial consequences of experimental SAH. Our findings demonstrated trends during the last decade for decreased use of larger species and animal models to explore the nature of DCVS. In parallel, there was increasing use of acute SAH models that focused on findings associated with EBI. Despite the overall fewer types of models and SAH induction techniques, the arbitrary choice of experimental parameters lies far from standardization. Although overall variability was great, our study defined the most often used standard parameters and consistent SAH techniques by specific animal models, that is, mouse, rat, rabbit, dog, and primate species (Table 1).

The translational roadblock from bench to bedside became apparent particularly in general stroke research. Numerous potential treatment approaches failed to translate the preclinical success into effective clinical therapy. Preclinical treatment success was often only measured by the degree of vasospasm or brain injury and was independent from improved clinical outcome. Our review confirmed that clinical impairment is

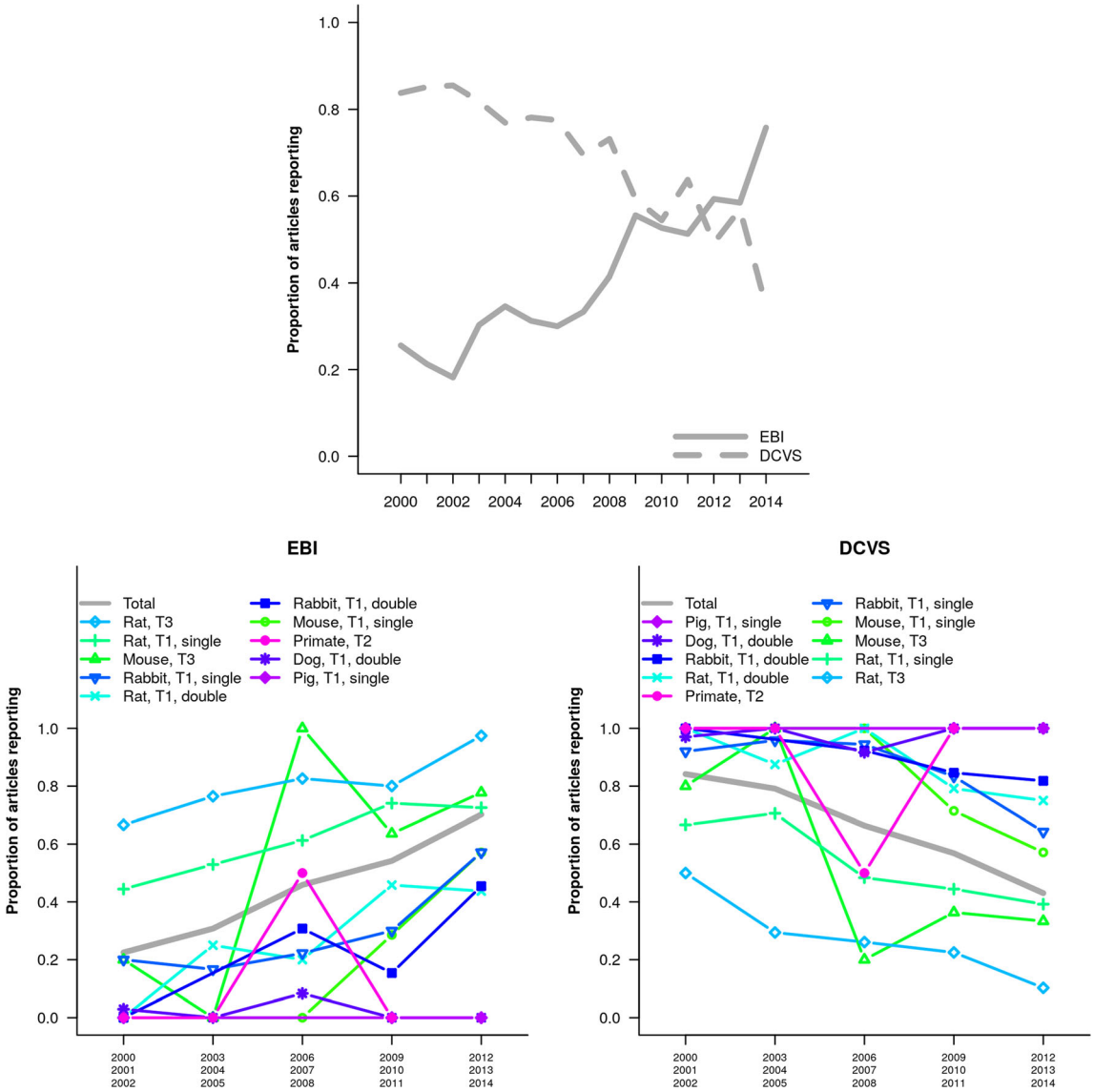

Fig. 5 Proportion of studies reporting delayed cerebral vasospasm (DCVS) or early brain injury (EBI). Top panel depicts changing proportion of EBI (solid line) and DCVS (dashed line) as primary endpoint (average per year). Bottom panels depict proportion of EBI and DCVS studies by standard species models (average based per 3-year periods). Thick gray lines show trends across all species. T1, intracisternal blood injection; T2, intracranial blood clot placement; T3, endovascular vessel puncture

rarely reported. Implementation of adequate outcome measures including robust neurological and neurobehavioral endpoints could be powerful tools to increase translational success [7]. Clearly, the need exists for more translational models that reflect human SAH pathophysiology and clinical outcome [10, 22]. Preclinical researchers also learned how boundary conditions, including comorbidities, sex, age, and strain-related differences, and anesthetics strongly influenced the outcomes measured. In SAH research, factors, such as age [17], genetic background [1], and anesthetics [6], strongly impacted outcome.

The disease course is affected not only by these experimental conditions but also by the SAH induction procedure and its associated parameters. In preclinical research, modification of the SAH induction technique strongly affected outcome measures. For example, in the blood injection model, volumes directly influenced severity and time course of DCVS whereas injection speed affected intracranial pressure change, cerebral perfusion pressure, and brain autoregulation during the acute phase of SAH [15, 20]. In the endovascular filament model, variations in filament size from 4-0 to 3-0 resulted in significant differences in distribution and amount of extravasated blood and changed the course of intracranial and mean arterial blood pressures during the acute phase and for at least 1 h after SAH [21].

During the last decade, immense progress has been made to support basic science in stroke research, namely, specific and general tools that have improved the quality of preclinical

studies [14]. Checklists and guidelines help to design, perform, analyze, and report animal experiments [8, 9, 18]. However, there remains a lack of guidance in the performance and modeling of experimental SAH. Standardization in performance of preclinical SAH studies would improve data quality, give opportunities to compare results among different laboratories, and facilitate systematic reviews for evaluation of target therapies that might qualify for a clinical trial. Importantly, the performance and report of standard models and associated parameters should not impede exploratory studies from investigating a narrow research question under highly specific conditions. In fact, experiments performed under highly standardized conditions may result in data with little external validity (poor reproducibility) [19].

Our systematic appraisal of contemporary preclinical SAH research may serve as a basis for discussion toward a more harmonized performance of SAH experiments. Our results may also help to define common data elements for inclusion in future data collection and reporting of SAH studies, such as those already established for preclinical traumatic brain injury or epilepsy research [5, 24]. Common data elements could further simplify data sharing and enhance rigor, transparency, and reproducibility of SAH research. A common language and definition of a standard set of SAH models and associated parameters in various species could pave the way for a coordinated approach of multicenter preclinical trials. The first preclinical randomized controlled trial proved the utmost importance in establishing clear animal characteristics and standardized protocols among the participating research centers [11].

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Compliance with Ethical Standards

Conflict of Interest The authors declare that there is no conflict of interest.

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