Transl. Stroke Res. (2015) 6:88–97
DOI 10.1007/s12975-014-0375-5

REVIEW ARTICLE

The Single and Double Blood Injection Rabbit Subarachnoid Hemorrhage Model

Yuichiro Kikkawa · Ryota Kurogi · Tomio Sasaki

Received: 12 June 2014 / Revised: 25 September 2014 / Accepted: 22 October 2014 / Published online: 8 November 2014

Abstract Over the past 30 years, the rabbit subarachnoid hemorrhage model (SAH) has been used for investigating the post-hemorrhage pathology, especially with respect to understanding of the mechanisms of cerebral vasospasm. However, the molecular mechanisms of cerebral vasospasm remain to be elucidated. Furthermore, it is not clear whether the rabbit SAH model is suitable for the investigation of pathological conditions other than cerebral vasospasm, such as early brain injury. Therefore, the properties of the rabbit SAH model need to be validated, and the reasons for using the rabbit should be clarified. This review explores the settings and technical issues of establishing a rabbit cisterna magna single and double blood injection SAH model and discusses the characteristics and feasibilities of the models.

Keywords Rabbit · Subarachnoid hemorrhage · Cerebral vasospasm · Animal model · Cisterna magna

Methods

References for this review were identified by searches of PubMed database. Search terms were "rabbit" and "subarachnoid hemorrhage." Only papers published in English between 1969 and 2013 were included.

Y. Kikkawa (✉) · R. Kurogi · T. Sasaki
Department of Neurosurgery,
Graduate School of Medical Sciences, Kyushu University,
3-1-1 MaidashiHigashi-ku Fukuoka 812-8582, Japan
e-mail: ykikkawa@ns.med.kyushu-u.ac.jp

Y. Kikkawa
Department of Cerebrovascular surgery,
International Medical Center, Saitama Medical University,
1397-1 Yamane, Hidaka-city, Saitama 350-1298, Japan

Historical Background and Evolution

In 1969, Offerhaus and van Gool reported the first rabbit subarachnoid hemorrhage (SAH) model using a blood shunt method to investigate cardiac dysfunction after SAH [1]. In 1977, Svendgaard et al. reported an increased reactivity of the isolated basilar artery in the rabbit SAH model using a single blood injection method into the cisterna magna [2]. As far as we know, this is the first report of a rabbit SAH model using the cisterna magna blood injection method. In 1982, Edvinsson et al. first reported rabbit cerebral vasospasms after SAH using a single blood injection method into the chiasmatic cistern [3]. Since the early 1980s, the rabbit SAH model using a single blood injection method into cisterna magna has been used for the research of SAH or cerebral vasospasms (CVS) [4–7]. Since the late 1980s, the double blood injection method, which induces a more severe and prolonged vasospasm than the single blood injection method, and which is well established in rat and dog models [8], has been used for investigating CVS in rabbits [9, 10]. However, the double-injection method is not popular in rabbits, possibly because the enhancement of CVS is ineffective and carries a high mortality rate [11, 12]. Recently, Zhou et al. reported a lower mortality rate and significantly more pronounced CVS in the double blood injection method in comparison to the single blood injection method in the rabbit SAH model [13].

Rabbits Employed

The age of rabbit used for experimental SAH ranges from 80 days to 2 years, although few reports actually describe the age with any precision [14–16]. Nakajima et al. investigated the effect of aging on CVS in the rabbit single-injection model by comparing the time course of CVS and the vasodilating effect of papaverine among three groups: young (2–3 months),

adult (6–9 months), and old (20–40 months) [17]. With advancing age, the degree of CVS was augmented, while both the resolution of CVS after maximal constriction and the vasodilating effect of papaverine were impaired [17]. The weight of the rabbit used for the experimental SAH model ranges from 1.5 to 5 kg (depending on the age of rabbits used) [18–20], although most of the rabbits weigh about 2–4 kg (Table 1). As for the strain, the most popular rabbits for the SAH model are the New Zealand white rabbit and the Japanese white rabbit. Fauve de Bourgogne rabbits [21–23] and Burgundy rabbits [24, 25] have rarely been used for the rabbit SAH model. Male rabbits are often preferred to female rabbits [10, 26–28, 15] because of their general pathogenic susceptibility compared with the biologically resilient female [29]. However, the rationale for choosing the gender is not clearly described in the literature.

Anesthesia, Analgesia, Perioperative Care, and Monitoring

Ketamine is the most preferred drug for anesthesia (20 mg/kg [30, 31, 15], 25 mg/kg [32, 19, 33, 34, 13, 35], 30 mg/kg [20, 36–42], 35 mg/kg [43–47], 40 mg/kg [48–57], 50 mg/kg [58, 59, 14, 60, 61, 10, 62–67, 18, 68–71], 55 mg/kg [72, 73], 70 mg/kg [74], intramuscularly (i.m.); 3 mg/kg [75, 76], intravenously (i.v.)). Ketamine is used alone or in combination with xylazine (2.5 mg/kg [77], 5 mg/kg [43, 44, 30, 45, 74, 46, 31, 39, 41], 6 mg/kg [49, 52, 36–38, 40, 55, 42], 8 mg/kg [50, 51, 62, 53, 63, 56, 57], 9 mg/kg [72, 73], 10 mg/kg [58, 59, 61, 10, 66, 67, 18, 47, 69, 70], 15 mg/kg [19], i.m.), droperidol (1.0 mg/kg [32–34, 78, 13, 35], i.m.) or pentobarbital (20 mg/kg [65, 54, 68], 30 mg/kg [15], i.v.). Intravenous injection of pentobarbital is often used for anesthesia (20 mg/kg [4, 21, 12], 25 mg/kg [79–81], 30 mg/kg [82–84], 45 mg/kg [85, 5]). Acepromazine [21, 22, 31, 23], diazepam [75, 76], ethomidate [22], or alcuronium [24] are occasionally used in combination with other anesthesia. In a few cases, urethane has been used intraperitoneally [86] or intravenously [16, 87]. In intubated and ventilated cases, inhalation of isoflurane or halothane is often used for maintenance anesthesia [9, 88–91, 24]. During anesthesia, rabbits are often endotracheally intubated and ventilated, although spontaneous respiration without intubation has been achieved in many studies. In some intubated cases, rabbits were mechanically ventilated if necessary until spontaneous respiration resumed [50, 57, 42]. Tracheostomy was performed in a few cases [92, 93, 86]. Oxygen was supplied in some cases [79, 19, 24, 55]. In experiments requiring perfusion fixation, rabbits were often ventilated during anesthesia. The depth of anesthesia is usually evaluated by the presence of body movement during surgery, such as that following pain stimulation by a periodical toe-pinch [37]. Postoperative pain relief is

Table 1 Physiological parameters of rabbit

	BW (kg)	BT (°C)	MABP (mmHg)	ICP	pCO_2 (mmHg)	pO_2 (mmHg)	pH	BG (mg/dL)	Hct (%)	Angiographic diameter of BA (mm)	Thickness of the wall of BA (μm)	Cross-section area of BA
Parameters	1.5–5 (2–4 in most cases)	36–40	70–90	10 cmH_2O (V) [85], 1.8 mmHg (ND) [42], 1.67 mmHg (V) [25], 8 mmHg (IP) [94]	35–45	90–150	7.3–7.5	124±9	30–40	0.648–0.730 [37], 0.654 [56], 1.34 [10]	18.08±0.76 [13], 16.7±4 [47], 24.7±3.27 [74], 15.5±0.2 [106], 26±2 [43, 45], 19.6±6.3 [60]	98914.7±667 μm^2 [60], 211745.2±19158.4 μm^2 [33], 254266.4±12 μm^2 [43], 0.27±0.027 mm^2 [47], 0.294±0.0262 mm^2 [106], 310244.5±56697.34 μm^2 [74], 0.332 mm^2 [57], 0.377 mm^2 [67], 462127.9±74755.82 μm^2 [34], 614454 μm^2 [13], 0.78±0.2 mm^2 [24]
References	[19, 20, 18]	[106, 90, 47, 13]	[60, 74, 67, 25]	[85, 94, 25, 42]	[49, 60, 10, 36, 74, 67, 96, 90, 24, 56, 25, 87]		[60, 36, 74, 67, 96, 24, 56, 25, 87, 13]	[104]	[76]	[10, 37, 56]	[60, 43, 45, 106, 74, 47, 13]	[60, 43, 74, 67, 34, 24, 47, 57, 13]

BW body weight, *BT* body temperature, *MABP* mean arterial blood pressure, *ICP* intracranial pressure, *V* ventricle, *ND* not described, *IP* intraparenchymal, *BG* blood glucose, *Hct* hematocrit, *BA* basilar artery

managed by subcutaneous administration (0.1–0.2 mg/kg) or intramuscular injection (0.04 mg/kg) of buprenorphine [20, 77, 37, 38].

After blood injection, the intracranial pressure (ICP) and the blood pressure transiently increase before gradually recovering. Using the ICP-controlled extra-intracranial blood shunt model, Marbacher et al. reported that within 1–2 min after SAH induction, the ICP rose to a peak (about 8-fold higher than the baseline value), and within 5–10 min, the ICP returned to a steady state that was significantly higher than the baseline [94]. In the single blood injection model, a 2-fold increase of ICP was seen after SAH, even following 1 mL of autologous blood injection [25]. Marbacher et al. also reported that the mean arterial blood pressure (MABP) increased steadily from 70 to 90 mmHg until reaching the ICP peak and then slowly decreased toward the baseline under subcutaneous injection of ketamine (30 mg/kg), xylazine (6 mg/kg), and continuous intravenous anesthesia [94]. Further, in the single blood injection model, 4 mL of autologous blood produced a 1.3-fold increase of the MABP (from 89 to 115 mmHg) within the first minute following SAH, which returned to the baseline 15 min after SAH under anesthesia (intramuscular injection of ketamine (50 mg/kg) and xylazine (5 mg/kg)) [67]. In the same model, 1 mL of autologous blood has been shown to induce a 1.3-fold increase of MABP (from 65 to 85 mmHg) after SAH while under intravenous anesthesia using urethane (8 mg/kg) [87]. These results suggest that the amount of clot influences ICP, but not MABP.

The mortality of the single blood injection model is comparatively low (0–8 %) [61, 43, 36, 37, 46, 84, 13], with very few exceptions [53, 90] (Table 2). In the double blood injection model, the mortality is comparatively high (5.56 % [13], 16.7 % [78], 20 % [12], 25.8 % [9], and 30 % [95]) (Table 2). In the triple blood injection model, Black et al. reported a mortality rate of 46 % [85]. Rabbits often die owing to acute respiratory distress after the subarachnoidal injection of blood [12], angiographic procedure [12], or brain stem injury during cisternal injection [85]. Above all, respiratory arrest after blood injection is the most important cause of the death after SAH. Zhou et al. reported that respiratory arrest occurred immediately or within 5 min of blood injection with intervals between 8 s to 1 min in 13 % of rabbits in the single blood injection model and 22 % of rabbits in the double blood injection model [13]. Spallone et al. reported that apnea was observed in 50 % of rabbits in the double-injection model with intervals between 8 and 30 s [12]. In the double blood injection model, death tends to occur immediately after the second injection of blood [78, 13]. Therefore, the volume of blood in the second injection has often been reduced to about 60 % of the first injection [10, 52, 30, 64, 31, 39, 16].

Regardless of the presence or absence of respiratory support, $PaCO_2$ and PaO_2 are generally maintained around 35–45 and 90–150 mmHg, respectively [49, 60, 10, 36, 74, 67, 96, 90, 24, 56, 25, 87] (Table 1). In spontaneous respiration, body temperature and pH are maintained between 38 and 40 °C and between 7.3 and 7.5 [49, 60, 36, 74, 67, 96, 90, 38, 24, 56, 25], respectively (Table 1). There is great variability in reported heart rates: 140–300 beats per minute (bpm) [74, 67, 37, 24, 25].

The neurobehavior of the rabbit following SAH has been evaluated using grading systems by Endo et al. [10, 53, 92, 70], Strong et al. [90, 76, 16, 97], and Zhou et al. [13] (Table 2). A few reports have performed neurobehavioral scoring of rabbits using a system commonly employed for scoring dogs [61, 98, 99, 35]. Using the grading system by Strong et al., Song et al. reported that the neurobehavioral score gradually deteriorated after the second blood injection in the double blood injection model, which peaked at day 5 postinjection [16]. After the first blood injection, rabbits presented with an apathetic mood, reduced locomotor activity and sleepiness, decreased feeding and drinking, and occasional neck stiffness [95]. These signs were significantly aggravated after the second blood injection [95]. Spallone et al. and Tang et al. reported that hemiparesis was observed in 5 and 40 % of SAH rabbits with the double blood injection model, respectively [12, 70].

SAH Induction

The most commonly used site for blood injection is the cisterna magna. The lateral prepontine cistern has rarely been used as a blood injection site (using a silastic tube) [100, 71]. Typically in the prone position, cerebrospinal fluid (CSF) is aspirated percutaneously or through a surgically opened wound from the cisterna magna using a needle, and autologous arterial blood is injected into the cistern magna. For head fixation, a stereotactic head frame has been used in some cases [85, 63, 100, 5, 12, 42]. The occipital protuberance is commonly used as a palpable landmark to identify the injection site [90]. Autologous blood from the central ear artery (auricular artery) was used in most cases, while that from the femoral artery was used in some cases [101, 27, 21, 44, 102, 66, 103, 15, 84, 104]. Rarely, venous autologous blood was used for this model [91, 87]. Autologous blood is rarely heparinized before injection [4, 23]. Usually, the blood injection is performed manually without using any pumping device. The injection pressure depends on the time period of the blood injection. The most popular blood volumes have been 1.0 mL/kg in a weight-adapted volume injection and 1.0, 1.5, 2.0, 2.5, and 3.0 mL in a fixed volume injection, while a wide range of weight-adapted (0.3 mL/kg [95], 0.5 mL/kg [82, 91], 0.9 mL/kg [19, 92], 1.25 mL/kg [4], 1.5 mL/kg [90, 76]) and fixed (0.5 mL [101, 86], 4.0 mL [49, 36, 67], and 5.0 mL [48, 50, 62, 53, 36, 40, 55, 56, 69]) volumes of blood have been used in the cisterna magna blood injection model. As

Table 2 Pathophysiological parameters of rabbit to be expected

	Acute change of (value before SAH)				Mortality (%)		Neurological deficit	Peak of DCVS		Thickness of the wall (% control)	Cross-section area of BA (% control)	Scoring system of outcome evaluation	
	MABP (mmHg)	ICP (mmHg)	HR (bpm)	CBF reduction (% baseline)	SBIM	DBIM		SBIM	DBIM			Neurobehavioral	Clot formation
Parameters	114.8±6.5 (88.6±3.1) [67], 82.0±6.6 (90.0±3) [42],. 69±4 (94±5) [24],	120±7.1 (1.8±0.3) [42], 82.5±18.8 (6.5±1.8) [61]	279±8 (304±11) [24], 146.7±29.8 (169.7±22.4) [67]	19±9 % (just after BI)[a][94], 71±7 % (5 min after BI)[a] [94], 86 % (1 day after BI) [16]	0 % [61, 43, 46, 84, 13], 8 % [36], 25 % [53], 42 % [90]	5.56 % [13], 16.7 % [78], 20 % [12], 25.8 % [9], 30 % [73]	opisthotonos, neck stiffness, horizontal nystag-mus, apathy, sleepiness, drowsiness reduced locomotor activity limb weakness, hemiparesis seizure appetite loss .	Day 3	Day 4–5	128 % – 180 %	29 %–83.4 %	Scoring system by Endo et al. (1988) [10], Strong et al. (1991) [97], Ahmad et al. (1996) [79], Zhou et al. (2007) [13]	Scoring system by Kaneko et al. (2005) [66], Zhou et al. (2007) [13]
References	[67, 24, 42]	[61, 42]	[67, 24]	[94, 16]	[61, 43, 53, 36, 90, 46, 84, 13]	[9, 73, 78, 12, 13]	[51, 90, 95, 46, 16, 12, 70]	[79, 4, 100, 6, 71, 42]	[9, 10, 95, 12, 70]	[59, 43, 106, 74, 47]	[43, 53, 45, 106, 74, 67, 72, 34, 73, 107, 47, 55, 57]	[10, 53, 96, 90, 76, 92, 16, 97, 70, 13]	[66, 13]

MABP mean arterial blood pressure, *ICP* intracranial pressure, *HR* heart rate, *CBF* cerebral blood flow, *BI* blood injection, *DCVS* delayed cerebral vasospasm, *SBIM* single blood injection model, *DBIM* double blood injection model, *BA* basilar artery

[a] Cisterna magna blood shunt model

discussed above, the blood volume in the second injection was often reduced compared with the first injection volume (2.5 mL+1.5 mL [10], 5 mL+3 mL [30, 31, 39], 1.5 mL/kg+1.0 mL/kg [16], 0.8 mL/kg+0.5 mL/kg [64]). While the most popular injection devices are 23- and 25-gauge butterfly needles, others include 16-gauge [49, 60], 21-gauge [9, 85, 66], 22-gauge [101, 24], 24-gauge [68], and 27-gauge needles [79, 19, 44, 12, 83]. Lumber puncture needles [34], silicone tubes [26, 100, 71], polyethylene catheters [25], trocar needles [16] are among the other devices used for injection. Blood injection is performed over a period of time, which is commonly within several minutes, to avoid respiratory arrest (for 10 s [27, 70], 20 s [60, 34, 12], 30–45 s [77, 23], 30–90 s [22], 1 min [22], 2 min [74, 47], 2–3 min [21, 87], 3–5 min [90, 76], and 4 h [71]; over 10 s [51, 40, 56, 57], 20 s [4, 91], 20–30 s [62], 30 s [36], 1 min [101, 61, 82, 15, 78], 2 min [59, 64, 24, 42], and 30–45 min [77]). After blood injection, the rabbit is kept in a prone position with the head tilted down (30° [79, 9, 59, 61, 33, 77, 82, 36, 54, 67, 90, 34, 95, 76, 15, 78, 83, 104, 13, 42], 45° [102, 88, 26, 25, 41], 65° [20, 37]) (Fig. 1) for some time (3 min [44], 5 min [21, 22, 102, 12], 10 min [85, 19, 20, 95, 37, 91, 92, 23], 15 min [79, 48, 58, 27, 4, 43, 52, 45, 82, 72, 73, 55, 56, 83, 41, 42], 20 min [50, 51, 60, 66, 70], 30 min [59, 32, 77, 65, 88, 74, 54, 89, 18, 15, 68, 16, 13, 35], 40 min [84], 45 min [46], 60 min [105, 104]). To spread the blood across the cranium, it is important to place the head in a downward position. In the double blood injection model, the second blood injection is usually performed following a 24- or 48-h interval [82, 12].

Technical Considerations

For accurate puncture, the neck should be flexed as much as possible to maximize the craniocervical junction. Furthermore, touching the inion and C2 spinous process is important for the accurate puncturing of cisterna magna (Fig. 2a). For improved visualization, the posterior neck of the rabbit should be sprayed with alcohol (Fig. 2b), or the hair of the posterior neck should be trimmed. To avoid puncture failure, the following factors may be important: (1) having an appropriate posture for injection, (2) not evacuating too much CSF, and (3) directing the needle slightly rostrally and puncturing as the tip of a needle runs through under the foramen magnum. During manual blood injection, the size of the syringe is important, because the resistance of the ICP can be felt through the appropriate-sized syringe, such as 2.5 cc. After the injection of blood, the respiratory condition of the rabbits should be observed for around 10 min, because respiratory arrest mostly occurs in the first few minutes after blood injection. Accidental movement of the needle tip induced by body movement during puncture causes the erroneous injection of blood into a space other than the subarachnoid space. To avoid body movement, appropriate control of the depth of anesthesia is important. Immediate withdrawal of the needle after injection causes leakage of injected blood with CSF from a dural pinhole.

The most common method of sacrificing rabbits is by perfusion fixation. In some cases, rabbits have been sacrificed by bolus injection of sodium thiopenthal (40 mg/kg [37], 20 mg/kg [19]), intravenous injection of potassium chloride [36, 46], intraperitoneal injection of sodium pentobarbital (200 mg/kg) [18], intracardiac injection of 15 mL of alcohol [44], exsanguination under intravenous injection of sodium pentobarbital (120 mg/kg [54], 60 mg/kg [89], 25 mg/kg [81]) and decapitation [21]. Perfusion fixation is commenced with 200–500 mL of flushing solution (physiological saline solution [43, 45, 36, 66, 74, 31, 15, 47, 83] which is occasionally heparinized [15, 83], Hank's balanced salt solution [50, 58, 59, 67, 72, 39, 56, 41, 57], or physiological phosphate buffer solution [78, 13]) under an appropriate perfusion pressure (100 cm H_2O [58, 59, 74, 39], 120 cm H_2O [60, 32, 43, 33, 45, 78, 47, 55, 57, 13, 35], 75 mmHg [50, 56, 83, 41], 100 mmHg [85]) followed by 200–1000 mL of fixative

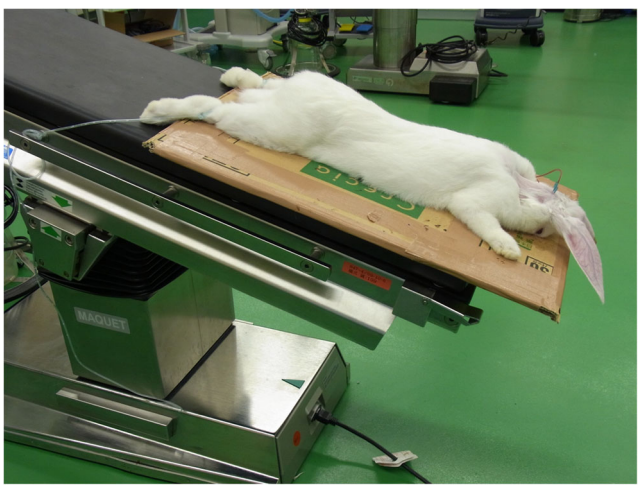

Fig. 1 Prone position with the head in downward. Tilting the head 30° down on an adjustable bed with the feet of the rabbit strapped to the bed frame using silicone tubes

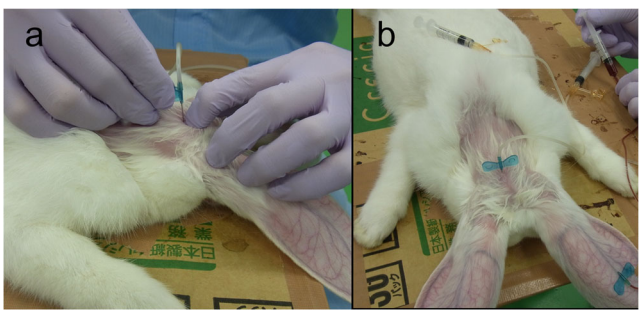

Fig. 2 Improvement of visibility of rabbit neck and identifying the landmark for puncturing. **a** Touching the inion and spinous process of C2 for identifying the puncturing point. **b** For improved visualization, the posterior neck of the rabbit was sprayed with alcohol

solution (3 % [49, 60, 47] or 4 % [82, 66, 18, 15, 68, 83] paraformaldehyde, 2.5 % glutaraldehyde [85, 5], 10 % formaldehyde [33, 74, 28, 34, 78, 13, 35, 42], or a mixture of paraformaldehyde and glutaraldehyde (2 %+2.5 % [59, 36, 67, 72, 73, 31], 2 %+2 % [58], 2 %+1.5 % [39], 1 %+1.5 % [50, 41]).

Discussion

Table 3 summarizes the advantages and disadvantages/limitations of the rabbit cisterna magna blood injection SAH model. Compared with large animals such as pigs, dogs, and monkeys, the size of rabbit can be easily handled in addition to its inexpensiveness and docile nature. The size of rabbit is large enough to perform angiography unlike small-size animals such as rat or mouse. Therefore, rabbit SAH model allows us to evaluate the chronological change of the arterial diameter by repetitive angiography in the same animal. Furthermore, the size of rabbit basilar artery is easy to handle, and the amount of the tissue of basilar artery is sufficient for performing gene or protein expression analysis. For these reasons, rabbit SAH model seems to be appropriate for the study of delayed CVS. In addition, rabbit has safe, less invasive, and highly reliable vascular access in the ear, central auricular artery, and marginal auricular vein. This is one of the most important advantages in surgical procedure of SAH induction. On the other hand, using rabbit for SAH model seems to have limitation in the research using molecular biological approach because of the less availability of useful antibodies or genetically modified animals in rabbit.

Currently, there is no evidence confirming the appropriateness of rabbit cisterna magna blood injection SAH model in the study of early brain injury. In volume-controlled blood injection method, ICP elevation seems to be insufficient. Rapid increase in ICP followed by decreased cerebral perfusion pressure (CPP) is one of the most important factor causing early brain injury. Therefore, pressure-controlled blood injection method, such as endovascular perforation, appears to be more appropriate than volume-controlled blood injection method for the study of early brain injury. Recently, Marbacher et al. demonstrated that the rabbit blood shunt model can be used for the study of early brain injury after SAH. In their rabbit ICP-controlled blood shunt model, the bleeding provoked rapid ICP increase, causing CPP decrease to almost zero, and consistent early damage to the hippocampus, basal cortex, and cerebral vasculature [94]. Therefore, the rabbit ICP-controlled blood shunt model might be better than the cisterna blood injection model to study early brain injury. However, there is insufficient accumulation of research knowledge regarding early brain injury using rabbit single or double blood injection model. Further study using rabbit blood injection method is needed to evaluate the suitability of this model in the study of early brain injury.

Table 3 Advantage and disadvantage of using rabbit for SAH model

Advantage	Disadvantage/limitation
-Inexpensiveness	-Limitation in molecular biological research
-Appropriate body size for handling	Less availability of useful antibodies for rabbits
Not too small compared to rat, mouse etc.	Limited availability of genetically modified rabbits
Not too large compared to dog, monkey, pig etc.	(transgenic, knockout, knock-in, etc.)
-Docile nature	-Insufficient accumulation of research knowledge regarding EBI using rabbit
-Applicability of BA for research	
Easiness to handle	
Suitability for vascular research	
(measurement of contractile response or $[Ca^{2+}]_i$ etc.)	
Sufficient amount of BA tissue for protein or gene research	
-Safeness, less invasiveness and high reliability of vascular access	
Central auricular artery	
Marginal auricular vein	
-Easiness of evaluating narrowing of BA	
Angiography, perfusion-fixation	
-Accumulation of a wide body of research knowledge regarding DCVS using rabbit BA	

BA basilar artery, *DCVS* delayed cerebral vasospasm, *EBI* early brain injury

Conclusion

In this review, detailed features of animals used, detailed methods and settings of SAH induction and various physiological and pathological parameters of rabbit cisterna magna single and double blood injection model were demonstrated, and technical issues of making models as well as the advantages, disadvantages, and limitations of using this model were discussed. This review might deepen the understanding of rabbit cisterna magna blood injection model and be helpful for choosing the appropriate animal model in accordance with each investigation for various pathological conditions after SAH.

Acknowledgments This research was supported by JSPS KAKENHI (Grant Numbers 24791510, 25670624, and 26462164).

Compliance with Ethics Requirements All institutional and national guidelines for the care of laboratory animals were followed.

Conflict of Interest Yuichiro Kikkawa, Ryota Kurogi, and Tomio Sasaki declare that they have no conflict of interest.

References

1. Offerhaus L, van Gool J. Electrocardiographic changes and tissue catecholamines in experimental subarachnoid haemorrhage. Cardiovasc Res. 1969;3(4):433–40.
2. Svendgaard NA, Edvinsson L, Owman C, Sahlin C. Increased sensitivity of the basilar artery to norepinephrine and 5-hydroxytryptamine following experimental subarachnoid hemorrhage. Surg Neurol. 1977;8(3):191–5.
3. Edvinsson L, Egund N, Owman C, Sahlin C, Svendgaard NA. Reduced noradrenaline uptake and retention in cerebrovascular nerves associated with angiographically visible vasoconstriction following experimental subarachnoid hemorrhage in rabbits. Brain Res Bull. 1982;9(1–6):799–805.
4. Chan RC, Durity FA, Thompson GB, Nugent RA, Kendall M. The role of the prostacyclin-thromboxane system in cerebral vasospasm following induced subarachnoid hemorrhage in the rabbit. J Neurosurg. 1984;61(6):1120–8. doi:10.3171/jns.1984.61.6.1120.
5. Liszczak TM, Black PM, Tzouras A, Foley L, Zervas NT. Morphological changes of the basilar artery, ventricles, and choroid plexus after experimental SAH. J Neurosurg. 1984;61(3):486–93. doi:10.3171/jns.1984.61.3.0486.
6. Nakano Y, Rumbaugh CL, Wang AM, Zamani AA, Colucci V. Experimental treatment of cerebral vascular spasm secondary to subarachnoid hemorrhage. Radiat Med. 1983;1(4):299–304.
7. Svendgaard NA, Edvinsson L, Owman C. Changes in sensitivity of cerebral vessels to noradrenaline and 5-hydroxytryptamine in the presence of subarachnoid blood. Acta Physiol Scand Suppl. 1977;452:73–5.
8. Gules I, Satoh M, Clower BR, Nanda A, Zhang JH. Comparison of three rat models of cerebral vasospasm. Am J Physiol Heart Circ Physiol. 2002;283(6):H2551–9. doi:10.1152/ajpheart.00616.2002.
9. Baker KF, Zervas NT, Pile-Spellman J, Vacanti FX, Miller D. Angiographic evidence of basilar artery constriction in the rabbit: a new model of vasospasm. Surg Neurol. 1987;27(2):107–12.
10. Endo S, Branson PJ, Alksne JF. Experimental model of symptomatic vasospasm in rabbits. Stroke. 1988;19(11):1420–5.
11. Marbacher S, Fandino J, Kitchen ND. Standard intracranial in vivo animal models of delayed cerebral vasospasm. Br J Neurosurg. 2010;24(4):415–34. doi:10.3109/02688691003746274.
12. Spallone A, Pastore FS. Cerebral vasospasm in a double-injection model in rabbit. Surg Neurol. 1989;32(6):408–17.
13. Zhou ML, Shi JX, Zhu JQ, Hang CH, Mao L, Chen KF, et al. Comparison between one- and two-hemorrhage models of cerebral vasospasm in rabbits. J Neurosci Methods. 2007;159(2):318–24. doi:10.1016/j.jneumeth.2006.07.026.
14. Bunc G, Kovacic S, Strnad S. Attenuation of cerebral vasospasm in rabbits using clonidine hydrochloride, a central adrenergic agonist. Auton Neurosci. 2003;105(1):71–6. doi:10.1016/S1566-0702(03)00003-1.
15. Naraoka M, Munakata A, Matsuda N, Shimamura N, Ohkuma H. Suppression of the Rho/Rho-Kinase pathway and prevention of cerebral vasospasm by combination treatment with statin and fasudil after subarachnoid hemorrhage in rabbit. Transl Stroke Res. 2013;4(3):368–74. doi:10.1007/s12975-012-0247-9.
16. Song JN, Chen H, Zhang M, Zhao YL, Ma XD. Dynamic change in cerebral microcirculation and focal cerebral metabolism in experimental subarachnoid hemorrhage in rabbits. Metab Brain Dis. 2013;28(1):33–43. doi:10.1007/s11011-012-9369-8.
17. Nakajima M, Date I, Takahashi K, Ninomiya Y, Asari S, Ohmoto T. Effects of aging on cerebral vasospasm after subarachnoid hemorrhage in rabbits. Stroke. 2001;32(3):620–8.
18. McGirt MJ, Pradilla G, Legnani FG, Thai QA, Recinos PF, Tamargo RJ, et al. Systemic administration of simvastatin after the onset of experimental subarachnoid hemorrhage attenuates cerebral vasospasm. Neurosurgery. 2006;58(5):945–51. doi:10.1227/01.NEU.0000210262.67628.7E. discussion −51.
19. Cosar M, Eser O, Fidan H, Sahin O, Buyukbas S, Ela Y, et al. The neuroprotective effect of dexmedetomidine in the hippocampus of rabbits after subarachnoid hemorrhage. Surg Neurol. 2009;71(1):54–9. doi:10.1016/j.surneu.2007.08.020. discussion 9.
20. Fathi AR, Marbacher S, Graupner T, Wehrli F, Jakob SM, Schroth G, et al. Continuous intrathecal glyceryl trinitrate prevents delayed cerebral vasospasm in the single-SAH rabbit model in vivo. Acta Neurochir (Wien). 2011;153(8):1669–75. doi:10.1007/s00701-011-1049-7. discussion 75.
21. Debdi M, Seylaz J, Sercombe R. Early changes in rabbit cerebral artery reactivity after subarachnoid hemorrhage. Stroke. 1992;23(8):1154–62.
22. Gomis P, Tran-Dinh YR, Sercombe C, Sercombe R. Dexamethasone preventing contractile and cytoskeletal protein changes in the rabbit basilar artery after subarachnoid hemorrhage. J Neurosurg. 2005;102(4):715–20. doi:10.3171/jns.2005.102.4.0715.
23. Tran Dinh YR, Jomaa A, Callebert J, Reynier-Rebuffel AM, Tedgui A, Savarit A, et al. Overexpression of cyclooxygenase-2 in rabbit basilar artery endothelial cells after subarachnoid hemorrhage. Neurosurgery. 2001;48(3):626–33. discussion 33–5.
24. Roux S, Clozel M, Wolfgang R, Sprecher U, Clozel JP. Comparative evaluation of acute cerebral vasospasm by the microsphere and the angiography techniques. J Neurosci Methods. 1995;59(2):245–52.
25. Visocchi M, Di Rocco F, Ciampini A, Di Muro L. A new animal model for monitoring the early cerebral vasospasm after subarachnoid haemorrhage. J Neurosurg Sci. 2006;50(4):89–94.
26. Kawada S, Kinugasa K, Meguro T, Hirotsune N, Tokunaga K, Kamata I, et al. Experimental study of intracisternal administration of tissue-type plasminogen activator followed by cerebrospinal fluid drainage in the ultra-early stage of subarachnoid haemorrhage. Acta Neurochir (Wien). 1999;141(12):1331–8.

27. Bunc G, Kovacic S, Strnad S. Evaluation of functional response of cerebral arteries by a new morphometric technique. Auton Neurosci. 2001;93(1–2):41–7. doi:10.1016/S1566-0702(01)00327-7.
28. Kovacic S, Bunc G, Ravnik J. Correspondence between the time course of cerebral vasospasm and the level of cerebral dopamine-beta-hydroxylase in rabbits. Auton Neurosci. 2006;130(1–2):28–31. doi:10.1016/j.autneu.2006.05.002.
29. Mapara M, Thomas BS, Bhat KM. Rabbit as an animal model for experimental research. Dent Res J (Isfahan). 2012;9(1):111–8. doi:10.4103/1735-3327.92960.
30. Fukami M, Tani E, Takai A, Yamaura I, Minami N. Activity of smooth muscle phosphatases 1 and 2A in rabbit basilar artery in vasospasm. Stroke. 1995;26(12):2321–7.
31. Nakagomi T, Kassell NF, Sasaki T, Lehman RM, Hongo K, Ogawa H, et al. Time course of the blood-arterial wall barrier disruption following experimental subarachnoid haemorrhage. Acta Neurochir (Wien). 1989;98(3–4):176–83.
32. Chen G, Zhang S, Shi J, Ai J, Hang C. Effects of recombinant human erythropoietin (rhEPO) on JAK2/STAT3 pathway and endothelial apoptosis in the rabbit basilar artery after subarachnoid hemorrhage. Cytokine. 2009;45(3):162–8. doi:10.1016/j.cyto.2008.11.015.
33. Fang Q, Chen G, Zhu W, Dong W, Wang Z. Influence of melatonin on cerebrovascular proinflammatory mediators expression and oxidative stress following subarachnoid hemorrhage in rabbits. Mediators Inflamm. 2009;2009:426346. doi:10.1155/2009/426346.
34. Li S, Xue J, Shi J, Yin H, Zhang Z. Combinatorial administration of insulin and vitamin C alleviates the cerebral vasospasm after experimental subarachnoid hemorrhage in rabbit. BMC Neurosci. 2011;12:77. doi:10.1186/1471-2202-12-77.
35. Zhuang Z, Zhou ML, You WC, Zhu L, Ma CY, Sun XJ, et al. Hydrogen-rich saline alleviates early brain injury via reducing oxidative stress and brain edema following experimental subarachnoid hemorrhage in rabbits. BMC Neurosci. 2012;13:47. doi:10.1186/1471-2202-13-47.
36. Johshita H, Kassell NF, Sasaki T, Ogawa H. Impaired capillary perfusion and brain edema following experimental subarachnoid hemorrhage: a morphometric study. J Neurosurg. 1990;73(3):410–7. doi:10.3171/jns.1990.73.3.0410.
37. Marbacher S, Neuschmelting V, Graupner T, Jakob SM, Fandino J. Prevention of delayed cerebral vasospasm by continuous intrathecal infusion of glyceroltrinitrate and nimodipine in the rabbit model in vivo. Intensive Care Med. 2008;34(5):932–8. doi:10.1007/s00134-008-0995-x.
38. Neuschmelting V, Marbacher S, Fathi AR, Jakob SM, Fandino J. Elevated level of endothelin-1 in cerebrospinal fluid and lack of nitric oxide in basilar arterial plasma associated with cerebral vasospasm after subarachnoid haemorrhage in rabbits. Acta Neurochir (Wien). 2009;151(7):795–801. doi:10.1007/s00701-009-0350-1. discussion −2.
39. Nihei H, Kassell NF, Dougherty DA, Sasaki T. Does vasospasm occur in small pial arteries and arterioles of rabbits? Stroke. 1991;22(11):1419–25.
40. Pasqualin A, Tsukahara T, Kassell NF, Torner JC. Effect of nicardipine on basilar artery vasoactive responses after subarachnoid hemorrhage. Neurosurgery. 1992;31(4):697–703. discussion −4.
41. Vollmer DG, Hongo K, Kassell NF, Ogawa H, Tsukahara T, Lehman RM. Effect of intracisternal antithrombin III on subarachnoid hemorrhage-induced arterial narrowing. J Neurosurg. 1989;70(4):599–604. doi:10.3171/jns.1989.70.4.0599.
42. Zuccarello M, Marsch JT, Schmitt G, Woodward J, Anderson DK. Effect of the 21-aminosteroid U-74006 F on cerebral vasospasm following subarachnoid hemorrhage. J Neurosurg. 1989;71(1):98–104. doi:10.3171/jns.1989.71.1.0098.
43. Erdi MF, Guney O, Kiyici A, Esen H. The effects of alpha lipoic acid on cerebral vasospasm following experimental subarachnoid hemorrhage in the rabbit. Turk Neurosurg. 2011;21(4):527–33. doi:10.5137/1019-5149.JTN. 4431-11.1.
44. Firat MM, Gelebek V, Orer HS, Belen D, Firat AK, Balkanci F. Selective intraarterial nimodipine treatment in an experimental subarachnoid hemorrhage model. AJNR Am J Neuroradiol. 2005;26(6):1357–62.
45. Guney O, Erdi F, Esen H, Kiyici A, Kocaogullar Y. N-acetylcysteine prevents vasospasm after subarachnoid hemorrhage. World Neurosurg. 2010;73(1):42–9. doi:10.1016/j.surneu.2009.06.003. discussion e3.
46. Miller CA, Lombard FW, Wu CT, Hubbard CJ, Silbajoris L, Borel CO, et al. Role of vascular mitogens in subarachnoid hemorrhage-associated cerebral vasculopathy. Neurocrit Care. 2006;5(3):215–21. doi:10.1385/NCC:5:3:215.
47. Seckin H, Simsek S, Ozturk E, Yigitkanli K, Ozen O, Besalti O, et al. Topiramate attenuates hippocampal injury after experimental subarachnoid hemorrhage in rabbits. Neurol Res. 2009;31(5):490–5. doi:10.1179/016164108X339369.
48. Alafaci C, Salpietro F, Grasso G, Sfacteria A, Passalacqua M, Morabito A, et al. Effect of recombinant human erythropoietin on cerebral ischemia following experimental subarachnoid hemorrhage. Eur J Pharmacol. 2000;406(2):219–25.
49. Aydin MV, Caner H, Sen O, Ozen O, Atalay B, Cekinmez M, et al. Effect of melatonin on cerebral vasospasm following experimental subarachnoid hemorrhage. Neurol Res. 2005;27(1):77–82. doi:10.1179/016164105X18331.
50. Barbosa MD, Arthur AS, Louis RH, MacDonald T, Polin RS, Gazak C, et al. The novel 5-lipoxygenase inhibitor ABT-761 attenuates cerebral vasospasm in a rabbit model of subarachnoid hemorrhage. Neurosurgery. 2001;49(5):1205–12. discussion 12–3.
51. Buemi M, Grasso G, Corica F, Calapai G, Salpietro FM, Casuscelli T, et al. In vivo evidence that erythropoietin has a neuroprotective effect during subarachnoid hemorrhage. Eur J Pharmacol. 2000;392(1–2):31–4.
52. Foley PL, Caner HH, Kassell NF, Lee KS. Reversal of subarachnoid hemorrhage-induced vasoconstriction with an endothelin receptor antagonist. Neurosurgery. 1994;34(1):108–12. discussion 12–3.
53. Grasso G, Passalacqua M, Sfacteria A, Conti A, Morabito A, Mazzullo G, et al. Does administration of recombinant human erythropoietin attenuate the increase of S-100 protein observed in cerebrospinal fluid after experimental subarachnoid hemorrhage? J Neurosurg. 2002;96(3):565–70. doi:10.3171/jns.2002.96.3.0565.
54. Kikkawa Y, Kameda K, Hirano M, Sasaki T, Hirano K. Impaired feedback regulation of the receptor activity and the myofilament Ca^{2+} sensitivity contributes to increased vascular reactiveness after subarachnoid hemorrhage. J Cereb Blood Flow Metab. 2010;30(9):1637–50. doi:10.1038/jcbfm.2010.35.
55. Sen O, Caner H, Aydin MV, Ozen O, Atalay B, Altinors N, et al. The effect of mexiletine on the level of lipid peroxidation and apoptosis of endothelium following experimental subarachnoid hemorrhage. Neurol Res. 2006;28(8):859–63. doi:10.1179/016164106X115099.
56. Takahashi S, Kassell NF, Toshima M, Dougherty DA, Foley PL, Lee KS. Effect of U88999E on experimental cerebral vasospasm in rabbits. Neurosurgery. 1993;32(2):281–8. discussion 8.
57. Wanebo JE, Arthur AS, Louis HG, West K, Kassell NF, Lee KS, et al. Systemic administration of the endothelin-A receptor antagonist TBC 11251 attenuates cerebral vasospasm after experimental subarachnoid hemorrhage: dose study and review of endothelin-based therapies in the literature on cerebral vasospasm. Neurosurgery. 1998;43(6):1409–17. discussion 17–8.
58. Bavbek M, Polin R, Kwan AL, Arthur AS, Kassell NF, Lee KS. Monoclonal antibodies against ICAM-1 and CD18 attenuate

cerebral vasospasm after experimental subarachnoid hemorrhage in rabbits. Stroke. 1998;29(9):1930–5. discussion 5–6.
59. Bilginer B, Onal MB, Narin F, Soylemezoglu F, Ziyal IM, Ozgen T. The effects of intravenous cilostazol and nimodipine on cerebral vasospasm after subarachnoid hemorrhage in an experimental rabbit model. Turk Neurosurg. 2009;19(4):374–9.
60. Cengiz SL, Erdi MF, Tosun M, Atalik E, Avunduk MC, Sonmez FC, et al. Beneficial effects of levosimendan on cerebral vasospasm induced by subarachnoid haemorrhage: an experimental study. Brain Inj. 2010;24(6):877–85. doi:10.3109/02699051003789260.
61. Cheng G, Chunlei W, Pei W, Zhen L, Xiangzhen L. Simvastatin activates Akt/glycogen synthase kinase-3beta signal and inhibits caspase-3 activation after experimental subarachnoid hemorrhage. Vascul Pharmacol. 2010;52(1–2):77–83. doi:10.1016/j.vph.2009.12.001.
62. Foley PL, Kassell NF, Hudson SB, Lee KS. Hemoglobin penetration in the wall of the rabbit basilar artery after subarachnoid hemorrhage and intracisternal hemoglobin injection. Acta Neurochir (Wien). 1993;123(1–2):82–6.
63. Grieb P, Ryba MS, Sawicki J, Chrapusta SJ. Oral coenzyme Q10 administration prevents the development of ischemic brain lesions in a rabbit model of symptomatic vasospasm. Acta Neuropathol. 1997;94(4):363–8.
64. Hirashima Y, Endo S, Otsuji T, Karasawa K, Nojima S, Takaku A. Platelet-activating factor and cerebral vasospasm following subarachnoid hemorrhage. J Neurosurg. 1993;78(4):592–7. doi:10.3171/jns.1993.78.4.0592.
65. Iseda K, Ono S, Onoda K, Satoh M, Manabe H, Nishiguchi M, et al. Antivasospastic and antiinflammatory effects of caspase inhibitor in experimental subarachnoid hemorrhage. J Neurosurg. 2007;107(1):128–35. doi:10.3171/JNS-07/07/0128.
66. Kaneko A, Moritake K, Kimura Y. Inhibitory effect of deuterium oxide on cerebral vasospasm after experimental subarachnoid hemorrhage in a rabbit model. Neurol Res. 2005;27(4):446–51. doi:10.1179/016164105X49201.
67. Kiris T, Karasu A, Yavuz C, Erdem T, Unal F, Hepgul K, et al. Reversal of cerebral vasospasm by the nitric oxide donor SNAP in an experimental model of subarachnoid haemorrhage. Acta Neurochir (Wien). 1999;141(12):1323–8. discussion 8–9.
68. Satoh M, Date I, Nakajima M, Takahashi K, Iseda K, Tamiya T, et al. Inhibition of poly(ADP-ribose) polymerase attenuates cerebral vasospasm after subarachnoid hemorrhage in rabbits. Stroke. 2001;32(1):225–31.
69. Tanaka Y, Machi T, Nihei H, Kassell NF. Effect of subarachnoid hemorrhage on serotonin uptake and release in the rabbit basilar artery. Neurosurgery. 1991;28(3):387–92. discussion 92–3.
70. Tang WH, Chen Z, Liu Z, Zhang JH, Xi G, Feng H. The effect of ecdysterone on cerebral vasospasm following experimental subarachnoid hemorrhage in vitro and in vivo. Neurol Res. 2008;30(6):571–80. doi:10.1179/174313208X297986.
71. Vorkapic P, Bevan JA, Bevan RD. Longitudinal in vivo and in vitro time-course study of chronic cerebrovasospasm in the rabbit basilar artery. Neurosurg Rev. 1991;14(3):215–9.
72. Kwan AL, Lin CL, Yanamoto H, Howng SL, Kassell NF, Lee KS. Systemic administration of the potassium channel activator cromakalim attenuates cerebral vasospasm after experimental subarachnoid hemorrhage. Neurosurgery. 1998;42(2):347–50. discussion 50–1.
73. Lin CL, Lo YC, Chang CZ, Kwan AL, Chen IJ, Howng SL. Prevention of cerebral vasospasm by a capsaicin derivative, glyceryl nonivamide, in an experimental model of subarachnoid hemorrhage. Surg Neurol. 2001;55(5):297–301.
74. Kertmen H, Gurer B, Yilmaz ER, Arikok AT, Demirci A, Gokyaprak SM, et al. The effect of thiocolchicoside on cerebral vasospasm following experimental subarachnoid hemorrhage in the rabbit. Acta Neurochir (Wien). 2012;154(8):1431–6. doi:10.1007/s00701-012-1420-3.
75. Laslo AM, Eastwood JD, Pakkiri P, Chen F, Lee TY. CT perfusion-derived mean transit time predicts early mortality and delayed vasospasm after experimental subarachnoid hemorrhage. AJNR Am J Neuroradiol. 2008;29(1):79–85. doi:10.3174/ajnr.A0747.
76. Murphy AM, Xenocostas A, Pakkiri P, Lee TY. Hemodynamic effects of recombinant human erythropoietin on the central nervous system after subarachnoid hemorrhage: reduction of microcirculatory impairment and functional deficits in a rabbit model. J Neurosurg. 2008;109(6):1155–64. doi:10.3171/JNS.2008.109.12.1155.
77. Gabikian P, Clatterbuck RE, Eberhart CG, Tyler BM, Tierney TS, Tamargo RJ. Prevention of experimental cerebral vasospasm by intracranial delivery of a nitric oxide donor from a controlled-release polymer: toxicity and efficacy studies in rabbits and rats. Stroke. 2002;33(11):2681–6.
78. Pan YX, Chen KF, Lin YX, Wu W, Zhou XM, Zhang XS, et al. Intracisternal administration of SB203580, a p38 mitogen-activated protein kinase inhibitor, attenuates cerebral vasospasm via inhibition of tumor-necrosis factor-alpha. J Clin Neurosci. 2013;20(5):726–30. doi:10.1016/j.jocn.2012.09.012.
79. Ahmad I, Imaizumi S, Shimizu H, Kaminuma T, Ochiai N, Tajima M, et al. Development of calcitonin gene-related peptide slow-release tablet implanted in CSF space for prevention of cerebral vasospasm after experimental subarachnoid haemorrhage. Acta Neurochir (Wien). 1996;138(10):1230–40.
80. Kubota Y, Isotani E, Mizuno Y, Ohno K, Azuma H. Alterations of intracellular calcium concentration and nitric oxide generation in pulmonary artery endothelium after subarachnoid hemorrhage of the rabbit. Vascul Pharmacol. 2007;47(2–3):90–8. doi:10.1016/j.vph.2007.04.004.
81. Mizuno Y, Isotani E, Ohno K, Nagai A, Imamura M, Azuma H. Involvement of accumulated NOS inhibitors and endothelin-1, enhanced arginase, and impaired DDAH activities in pulmonary dysfunction following subarachnoid hemorrhage in the rabbit. Vascul Pharmacol. 2008;48(1):21–31. doi:10.1016/j.vph.2007.11.002.
82. Hong T, Wang Y, Wang HT, Wang H. Inhibitory effect of gap junction blockers on cerebral vasospasm. J Neurosurg. 2008;108(3):551–7. doi:10.3171/JNS/2008/108/3/0551.
83. Tsurutani H, Ohkuma H, Suzuki S. Effects of thrombin inhibitor on thrombin-related signal transduction and cerebral vasospasm in the rabbit subarachnoid hemorrhage model. Stroke. 2003;34(6):1497–500. doi:10.1161/01.STR.0000070424.38138.30.
84. Yanamoto H, Kikuchi H, Okamoto S, Nozaki K. Preventive effect of synthetic serine protease inhibitor, FUT-175, on cerebral vasospasm in rabbits. Neurosurgery. 1992;30(3):351–6. discussion 6–7.
85. Black PM, Tzouras A, Foley L. Cerebrospinal fluid dynamics and hydrocephalus after experimental subarachnoid hemorrhage. Neurosurgery. 1985;17(1):57–62.
86. Tuncer R. Experimental basilar artery spasm caused by autologous blood application: effects of clot removal and topical nicardipine. Acta Neurochir (Wien). 1993;121(1–2):72–5.
87. Yurt A, Ozer F, Selcuki M, Erturk AR, Gorgulu O. Effect of systemic parameters following experimental subarachnoid hemorrhage and cerebral vasospasm in rabbits by injection of blood into the subarachnoidal space. Neurosciences (Riyadh). 2010;15(1):15–20.
88. Ishiguro M, Puryear CB, Bisson E, Saundry CM, Nathan DJ, Russell SR, et al. Enhanced myogenic tone in cerebral arteries from a rabbit model of subarachnoid hemorrhage. Am J Physiol Heart Circ Physiol. 2002;283(6):H2217–25. doi:10.1152/ajpheart.00629.2002.
89. Koide M, Nystoriak MA, Krishnamoorthy G, O'Connor KP, Bonev AD, Nelson MT, et al. Reduced Ca^{2+} spark activity after subarachnoid hemorrhage disables BK channel control of cerebral artery

tone. J Cereb Blood Flow Metab. 2011;31(1):3–16. doi:10.1038/jcbfm.2010.143.
90. Laslo AM, Eastwood JD, Chen FX, Lee TY. Dynamic CT perfusion imaging in subarachnoid hemorrhage-related vasospasm. AJNR Am J Neuroradiol. 2006;27(3):624–31.
91. Nelson RJ, Perry S, Burns AC, Roberts J, Pickard JD. The effects of hyponatraemia and subarachnoid haemorrhage on the cerebral vasomotor responses of the rabbit. J Cereb Blood Flow Metab. 1991;11(4):661–6. doi:10.1038/jcbfm.1991.118.
92. Otsuji T, Endo S, Hirashima Y, Nishijima M, Takaku A. An experimental model of symptomatic vasospasm induced by oxyhemoglobin in rabbits. Stroke. 1994;25(3):657–62.
93. Taplu A, Gokmen N, Erbayraktar S, Sade B, Erkan N, Karadibak K, et al. Effects of pressure- and volume-controlled inverse ratio ventilation on haemodynamic variables, intracranial pressure and cerebral perfusion pressure in rabbits: a model of subarachnoid haemorrhage under isoflurane anaesthesia. Eur J Anaesthesiol. 2003;20(9):690–6.
94. Marbacher S, Andereggen L, Neuschmelting V, Widmer HR, von Gunten M, Takala J, et al. A new rabbit model for the study of early brain injury after subarachnoid hemorrhage. J Neurosci Methods. 2012;208(2):138–45. doi:10.1016/j.jneumeth.2012.05.010.
95. Liu P, Liao X, Xiang J, Pan L, Ma L. Continuous intravertebral injection of fasudil hydrochloride in the treatment of cerebral vasospasm. Neurol India. 2011;59(2):161–7. doi:10.4103/0028-3886.79127.
96. Kwan AL, Lin CL, Chang CZ, Wu HJ, Hwong SL, Jeng AY, et al. Continuous intravenous infusion of CGS 26303, an endothelin-converting enzyme inhibitor, prevents and reverses cerebral vasospasm after experimental subarachnoid hemorrhage. Neurosurgery. 2001;49(2):422–7. discussion 7–9.
97. Strong MJ, Wolff AV, Wakayama I, Garruto RM. Aluminum-induced chronic myelopathy in rabbits. Neurotoxicology. 1991;12(1):9–21.
98. Kusaka G, Kimura H, Kusaka I, Perkins E, Nanda A, Zhang JH. Contribution of Src tyrosine kinase to cerebral vasospasm after subarachnoid hemorrhage. J Neurosurg. 2003;99(2):383–90. doi:10.3171/jns.2003.99.2.0383.
99. Zhou C, Yamaguchi M, Kusaka G, Schonholz C, Nanda A, Zhang JH. Caspase inhibitors prevent endothelial apoptosis and cerebral vasospasm in dog model of experimental subarachnoid hemorrhage. J Cereb Blood Flow Metab. 2004;24(4):419–31. doi:10.1097/00004647-200404000-00007.
100. Kim CY, Paek SH, Seo BG, Kim JH, Han DH. Changes in vascular responses of the basilar artery to acetylcholine and endothelin-1 in an experimental rabbit vasospasm model. Acta Neurochir (Wien). 2003;145(7):571–7. doi:10.1007/s00701-003-0024-3.
101. Aydin MD, Kanat A, Yilmaz A, Cakir M, Emet M, Cakir Z, et al. The role of ischemic neurodegeneration of the nodose ganglia on cardiac arrest after subarachnoid hemorrhage: an experimental study. Exp Neurol. 2011;230(1):90–5. doi:10.1016/j.expneurol.2010.09.018.
102. Gurelik M, Kayabas M, Karadag O, Goksel HM, Akyuz A, Topaktas S. Cervical spinal cord stimulation improves neurological dysfunction induced by cerebral vasospasm. Neuroscience. 2005;134(3):827–32. doi:10.1016/j.neuroscience.2005.04.062.
103. Kawanabe Y, Masaki T, Hashimoto N. Involvement of phospholipase C in endothelin 1-induced stimulation of Ca^{2+} channels and basilar artery contraction in rabbits. J Neurosurg. 2006;105(2):288–93. doi:10.3171/jns.2006.105.2.288.
104. Zhang Z, Nagata I, Kikuchi H, Xue JH, Sakai N, Sakai H, et al. Broad-spectrum and selective serine protease inhibitors prevent expression of platelet-derived growth factor-BB and cerebral vasospasm after subarachnoid hemorrhage: vasospasm caused by cisternal injection of recombinant platelet-derived growth factor-BB. Stroke. 2001;32(7):1665–72.
105. Echigo R, Shimohata N, Karatsu K, Yano F, Kayasuga-Kariya Y, Fujisawa A, et al. Trehalose treatment suppresses inflammation, oxidative stress, and vasospasm induced by experimental subarachnoid hemorrhage. J Transl Med. 2012;10:80. doi:10.1186/1479-5876-10-80.