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Invited review

Animal models of cerebral arterial gas embolism

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ABSTRACT

Cerebral arterial gas embolism is a dreaded complication of diving and invasive medical procedures. Many different animal models have been used in research on cerebral arterial gas embolism. This review provides an overview of the most important characteristics of these animal models. The properties discussed are species, cerebrovascular anatomy, method of air embolization, amount of air, bubble size, outcome parameters, anesthesia, blood glucose, body temperature and blood pressure.

Contents

1. Introduction

Cerebral arterial gas embolism (CAGE) is defined as the presence of gas in the cerebral vessels. It can either occur after pulmonary barotrauma, which is the most common etiology in divers, or iatrogenically for instance during cardiopulmonary bypass and interventional radiology (Muth and Shank, 2000; van Hulst et al., 2003a). CAGE can be regarded as multifocal cerebral ischemia with specific characteristics, for instance a transient nature and the immediate occurrence of blood–brain barrier damage (van Hulst et al., 2003a).

In the past, reviews have addressed the different ways of induction of focal cerebral ischemia in animals (Hossmann, 1998; Howells et al., 2010). However, these reviews did not or only briefly discuss CAGE. The clinical picture of CAGE is heterogeneous and patients can present with signs ranging from slight transient neurological dysfunction to coma with brain herniation (Bessereau et al., 2010). Many different animal models have been used in CAGE research, which is in line with the large clinical variance of the disease. In this review we discuss the existing animal models of CAGE, by analyzing the most important parameters to take into account in the development and evaluation of these models.

2. Methods

We searched MEDLINE and Embase for relevant articles (Fig. 1). The MEDLINE search strategy was ("embolism,

Abbreviations: CAGE, cerebral arterial gas embolism; CPB, cardiopulmonary bypass; HBOT, hyperbaric oxygen therapy.

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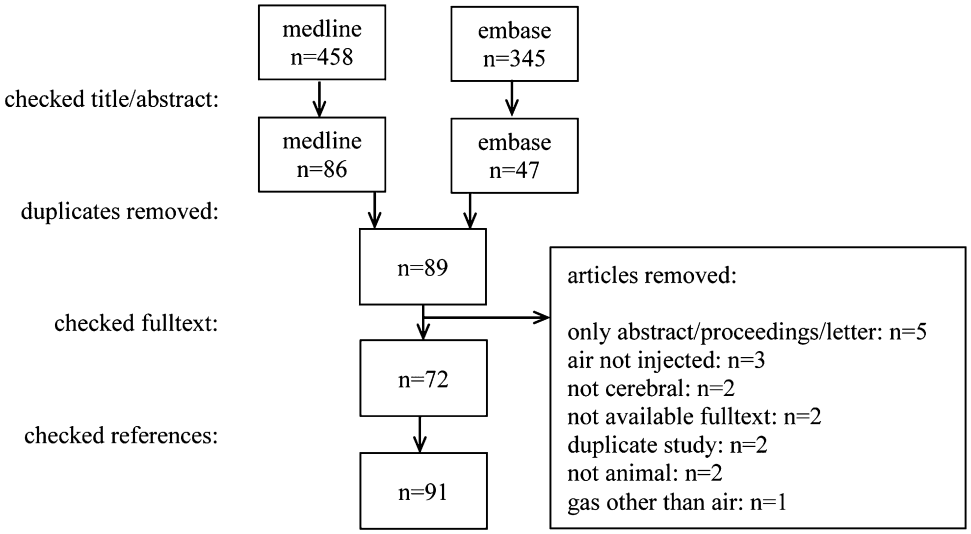

Fig. 1. Search strategy.

air"[mesh] OR "air embolism"[tiab] OR "gas embolism"[tiab] OR (("embolism"[mesh] OR "embolism"[tiab]) AND ("air"[mesh] OR "air"[tiab] OR "gas"[tiab]))) AND ("brain"[mesh] OR "brain"[tiab] OR "cerebrum"[tiab] OR "cerebral"[tiab] OR "arteries"[mesh] OR "arterial"[tiab]) and a similar strategy was used for Embase. The search was last performed august 2011. Search results were limited to studies on animals, written in English. No constraints on publication date were imposed. Articles were initially selected based on title and abstract, after which the fulltext article was read to confirm article relevance. Relevant studies were defined as experiments in which air was actively administered to the circulation with the intent of entrance of air into the cerebral arteries. We excluded studies in which gases other than air were used, as well as studies that were only available as an abstract or as proceedings. References of included papers were checked to identify additional articles. In total, this search strategy resulted in 91 animals studies of CAGE (Table 1). In this review, we provide an overview of these animal models by summarizing their most important characteristics (Table 2).

3. Species

As in all animal research, the first question to answer in the development of a CAGE model is which species to use. Naturally, no animal perfectly resembles the human situation. Generally, animals can be divided into small and large species, although this is a somewhat arbitrary division. Both groups have advantages and disadvantages (Duhaime, 2006) and it is therefore not possible to prefer one species over the others. Larger brains usually bear more anatomic similarity to the human brain than smaller brains, for instance with regard to gyration. Cardiovascular and cerebral physiology more closely resemble the human situation in larger animals as compared to smaller animals. Furthermore, the closer brain size approaches human brain size, the easier techniques used in humans, such as imaging modalities and placement of cerebral probes, are applied. Advantages of smaller animals are lower cost and greater ease of breeding and handling. In addition, small animals, especially mice and rats, are much better known from a genetic and metabolic point of view. Fig. 2 displays the various species used in CAGE research. The dog, cat and rabbit are the most widely used animals. It is interesting to note a shift in the large animals used. Almost no studies using monkeys, dogs or cats have been performed since 1995. Instead, the pig has gained much interest as a large animal model. One of the reasons for this change may be the lower emotional value of pigs as opposed to monkeys, cats and dogs.

4. Cerebrovascular anatomy and the carotid rete

An important consideration in the choice of a model for CAGE research is the cerebrovascular anatomy of the selected species. As will be shown below, the majority of animal models involve active injection of air into an artery feeding the brain. After injection of air, the specific cerebrovascular anatomy of the animal under study will determine distribution of the bubbles through the brain. In this paragraph we will mostly consider the five species that have most frequently been used in CAGE research, namely the dog, cat, rabbit, rat and pig. In all these animals the blood supply to the brain is provided through an arterial circle comparable to the circle of Willis as present in man (Daniel et al., 1953). Considerable differences exist between species in regard to which vessels supply the circle of Willis (Fig. 3). While in man the internal carotid artery is the most important artery, this vessel is only present as such in the rabbit, dog and rat. In the dog the internal carotid artery is very small and the largest contribution to cerebral perfusion is through the internal maxillary artery, a branch of the common carotid artery (Gillilan, 1976). In the cat, the internal carotid artery is only present as a thin fibrous cord and the main blood supply is again through the internal maxillary artery (Gillilan, 1976). In the pig, the majority of blood supply to the circle of Willis comes from the ascending pharyngeal artery, a branch of the common carotid artery (Daniel et al., 1953). The contribution of the vertebral

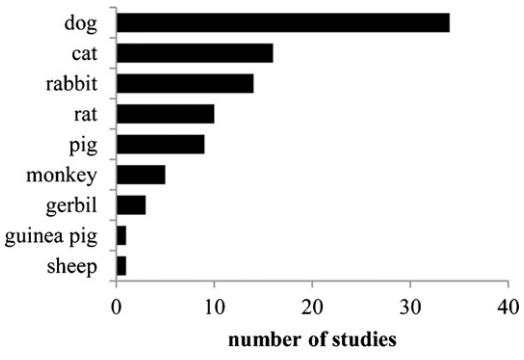

Fig. 2. Species used in animal studies of CAGE. In two studies more than one species was used.

Table 1
Animal models of CAGE. When a model was used in multiple studies, this can be seen in the first column. Differences between studies within a specific animal model can be seen in the last column. When too few model properties were shared between studies, the studies were regarded as using different models, even when the studies were performed by the same research group. When 'carotid artery' is mentioned as the location of air injection, it is not known whether this was the common carotid artery or one of its branches.

References	First use	Animal	Weight	Anesthesia	Location	Air dosing	Outcome	Remark
van Allen et al. (1929)	1929	Dog	5.5–22.4 kg	Ether	Pulmonary vein	Weight	Clinical	
Fine and Fischmann (1940)	1940	Rabbit	Unknown	Ether	'Carotid artery'	Fixed	Clinical	
Fries et al. (1957)	1957	Dog	Unknown	Pentobarbital	CCA	Weight	CBF clinical	
Redo (1958)	1958	Dog	Unknown	Unknown	CCA	Titrated (death)	Craniect EEG	
Lee and Olszewski (1959)	1959	Cat, rabbit	0.9–2.8 kg	Pentobarbital	CCA	Fixed	BBB	
Meyer et al. (1962)	1962	Cat, monkey	Unknown	Ether d-tubo-cumarine pentobarbital	ICA	Fixed	BrOx CBF craniect EEG	
De la Torre et al. (1962a,b)	1962	Dog	15–20 kg	Pentobarbital	ICA	Fixed	BBB clinical hist ICP	1 2 4
Atkinson (1963)	1963	Cat	Adult	Pentobarbital	Lung overpressure	N/a	Craniect	
Danis and Willman (1963)	1963	Dog	Unknown	Pentobarbital	ICA	Weight	Hist WD	
Meijne et al. (1963)	1963	Rabbit	2.2–3.6 kg	Pentobarbital succinylcholine	'Carotid artery'	Titrated (EEG)	EEG	
Pate and Birdsong (1964)	1964	Cat	1.5–2.7 kg	Ether	'Carotid artery'	Weight	Neuro-qual	
Worman and Seidel (1966)	1966	Dog	Unknown	Pentobarbital	CCA	Weight	EEG ICP	
Broman et al. (1966)	1966	Rabbit	1–3 kg	Urethane	CCA	Fixed	BBB	5
Wyant and Dobell (1967)	1967	Dog	10–15 kg	Pentobarbital	Ascending aorta	Fixed	Neuro-qual	
Hollon and Maginn (1969)	1969	Dog	10–15 kg	Unknown	Innominate artery/CPB	Fixed	EEG	
Currie et al. (1970)	1970	Dog	Adult	Thiopental	CCA	Fixed	Neuro-qual	
Simms et al. (1971, 1972)	1971	Dog	10–21 kg	Gallamine-triethiodide pentobarbital	VA	Weight	AvOx CBF CSFOx ICP	1 3
Meldrum et al. (1971)	1971	Monkey (baboon)	3–6 kg	Pentobarbital	CCA	Fixed	CBF EEG	
Gomes et al. (1973)	1973	Dog	10–12 kg	Thiopental	Multiple	Weight	Clinical EEG neuro-qual	6
Johansson (1980, 1981), Persson et al. (1978), Rosengren et al. (1977)	1977	Rat	200–300 g	Pentobarbital	CCA	Fixed	BBB EM WD	1 2 3 5
Fritz and Hossmann (1979), Haller et al. (1986, 1987), Hossmann and Fritz (1978)	1978	Cat	1.9–5 kg	Gallamine-triethiodide pentobarbital	Innominate artery	Fixed	AvOx BBB CBF craniect EEG EM ICP qEEG	1 2 3
Herbaczynska-Cedro et al. (1978)	1978	Dog	8–14 kg	Alpha-chloralose hexobarbital urethane	ICA	Fixed	BBB	
Garcia et al. (1981), Lossinsky et al. (1979), Nishimoto et al. (1978)	1978	Gerbil	50–80 g	Pentobarbital	ICA	Fixed	BBB BrMetab CBF EM hist neuro-qual WD	2 3
Hekmatpanah (1978)	1978	Monkey	Unknown	Pentobarbital	ICA	Unknown	Craniect EEG EM	
Dutka et al. (1988, 1989), Hallenbeck et al. (1979, 1982, 1984, 1986), Kochanek et al. (1987, 1988), Obrenovitch et al. (1984)	1979	Dog	8–16 kg	Pentobarbital xylazine	ICA	Titrated (SSEP)	CBF EM hist SSEP	1 2 3
Evans et al. (1981)	1981	Cat	2.5–4.0 kg	Alpha-chloralose keta	VA	Weight	Clinical	
Furlow (1982)	1982	Rat	300–450 g	Halothane	ICA	Fixed	CBF EEG	
Huddleston et al. (1983)	1983	Dog	Unknown	Morphine nitrous-oxide succinylcholine	Descending aorta	Weight	CBF clinical neuro-quant	
Evans and Kobrine (1987), Evans et al. (1984)	1984	Cat	2.5–4.0 kg	Alpha-chloralose keta	VA	Fixed	ICP SSEP WD	1 2
Dutka et al. (1987, 1992a,b), Leitch et al. (1984a,b,c,d)	1984	Dog	8–16 kg	Pentobarbital xylazine	ICA	Fixed	CBF ICP SSEP WD	1 2
Menasche et al. (1985)	1985	Rat	300 g	Gallamine-triethiodide pentobarbital	CCA	Titrated (EEG)	BrOx CBF EEG	

Table 1 (*Continued*)

References	First use	Animal	Weight	Anesthesia	Location	Air dosing	Outcome	Remark
Gorman and Browning (1986)	1986	Rabbit	2–5 kg	Halothane	Femoral artery	Fixed	Craniect	
Spiess et al. (1986)	1986	Rabbit	2–3 kg	Acepromazine atracurium halotane keta	ICA	Titrated (EEG)	EEG neuro-qual	
Butler et al. (1988)	1988	Dog	14–31 kg	Halothane isoflurane thiopental	Left ventricle/asc. aorta	Fixed	Doppler (carotid)	
Chang et al. (1988)	1988	Monkey (macaque)	±7 kg	Keta thiopental	Radial artery	Fixed	Gammascan	
Evans et al. (1989), McDermott et al. (1990, 1992a,b)	1989	Cat	2.4–4.5 kg	Alpha-chloralose ketamine	CCA	Titrated (SSEP)	SSEP	1 3 7
Helps and Gorman (1991), Helps et al. (1990a,b)	1990	Rabbit	2.1–2.4 kg	Gallamine-triethiodide urethane	CCA	Fixed	CBF craniect SSEP	8
Hills and James (1991)	1991	Guinea pig	850 ± 50 g	Pentobarbital	ICA	Fixed	BBB	
Annane et al. (1994, 1995)	1994	Dog	10.3 ± 2.5 kg	Thiopental	ICA	Titrated (CT)	Clinical CT EEG EM hist neuro-quant	2
Bunegin et al. (1994)	1994	Monkey (macaque)	5–8 kg	Pentobarbital	CCA with ECA ligated	Fixed	TCD	
Hindman et al. (1998, 1999), Reasoner et al. (1996, 1997), Ryu et al. (1996)	1996	Rabbit	2.5–3.4 kg	Isoflurane methohexital succinylcholine	ICA	Weight	BrT hist neuro-quant SSEP	1 2
Juncker et al. (1998)	1998	Pig	25.8 ± 3.2 kg	Keta lidocaine sufent	CCA	Fixed	BAER	9
Williams et al. (2001)	2001	Sheep	±50 kg	Halothane thiopenthal	CCA	Fixed	ICP TCD	
Medby et al. (2002)	2002	Pig	24.1 ± 2.9 kg	Azaperonium diazepam keta thiopental	CCA with ECA ligated	Fixed	Brmetab (MD) CBF hist	
Yamaguchi et al. (2003)	2003	Cat	2.3–3.5 kg	Alpha-chloralose keta pancuronium	CCA	Weight	Intravital-microscopy	
Drenthen et al. (2003), van Hulst et al. (2003b, 2004, 2005)	2003	Pig	30–35 kg	Keta midazolam pancuronium	CCA	Weight	Brmetab (MD) BrOx BrT ICP qEEG	1 2
Martens et al. (2004)	2004	Pig	37.7 ± 6.1 kg	Buprenorphine keta midazolam xylazine	CCA	Weight	MRI	
Jungwirth et al. (2006, 2007), Qing et al. (2011)	2006	Rat	363 ± 17 g	Atracurium fentanyl isoflurane midazolam	ICA	Fixed	Hist neuro-quant	1 3 10
Gerriets et al. (2010)	2010	Rat	255–326 g	Isoflurane	CCA	Fixed	Hist neuro-quant	11
Weenink et al. (2011, 2012)	2011	Pig	35–40 kg	Keta midazolam pancuronium sufent	Ascending pharyngeal art.	Weight	Brmetab (MD) BrOx ICP qEEG	2 12

Abbreviations: keta, ketamine; sufent, sufentanil; CCA, common carotid artery; ICA, internal carotid artery; VA, vertebral artery; ECA, external carotid artery; CBF, cerebral blood flow; craniect, raniectomy (with visualization of cerebral vessels); EEG, electroencephalography (qualitative); BBB, blood–brain barrier damage (by injection of a tracer); BrOx, brain oxygen tension; hist, histology; ICP, intracranial pressure; WD, wet/dry ratio; neuro-qual, qualitative neurological examination; AVox, arteriovenous oxygen difference across the brain; CSFox, CSF oxygen tension; EM, electron microscopy; qEEG, quantitative electroencephalography; BrMetab, brain metabolism; SSEP, somatosensory evoked potentials; neuro-quant, quantitative neurological scoring; CT, computed tomography; TCD, transcranial Doppler; BrT, brain temperature; BAER, brainstem auditory evoked responses; MD, microdialysis; MRI, magnetic resonance imaging; CPB, cardiopulmonary bypass.

Remarks: (1) weight varied slightly between studies; (2) not all outcome parameters mentioned were used in all studies; (3) anesthetic agents varied between studies; (4) De la Torre et al. (1962b) used ICA/VA with and without clipping of cerebral arteries; (5) used CCA with ECA (and in some studies other branches) ligated; (6) used CCA/innominate artery/aorta/heart/CPB system; (7) with external maxillary artery ligated; (8) tip of catheter at origo of ICA; (9) also used alcuronium, clonidine and flunitrazepam; (10) with pterygopalatine artery ligated; (11) tip of catheter at origo of ICA with other arteries cauterized; (12) Weenink et al. (2011) used also ECA.

Table 2
Factors to consider in development and analysis of CAGE animal models.

- Species
  - Cerebrovascular anatomy
- Location of air administration
- Amount of air
- Bubble size
- Outcome parameters
- Anesthesia
- Other factor that influence outcome in cerebral ischemia
  - Temperature
  - Blood glucose
  - Blood pressure

arteries to total cerebral perfusion varies between the species, but is less than that of the carotid system in all species (Daniel et al., 1953).

Some larger animals are known to possess bilateral networks of intertwined arterioles in the arterial system proximal to the circle of Willis, termed the carotid rete. Species with such a rete include the cat, pig, ox, goat, and sheep (Daniel et al., 1953). A carotid rete does not exist in rabbits or rats, and only a few vessels that may represent a remnant rete are present in the dog. Important to consider, the carotid rete precludes direct access with a catheter to the circle of Willis from the common carotid artery and thus air has to be injected into arteries proximal to the rete. Due to the small size of the arterioles of which the carotid rete is comprised (200–300 μm in cats (Daniel et al., 1953), reported as 74 μm (McGrath, 1977) and 154 μm (Lee et al., 1989) in pigs), injection of air proximal to this structure may result in retention of the air in the plexus, which prevents access of air into the cerebral arteries. Hence, this would not result in cerebral ischemia since the circle of Willis would still be supplied through the contralateral carotid system and the vertebral arteries.

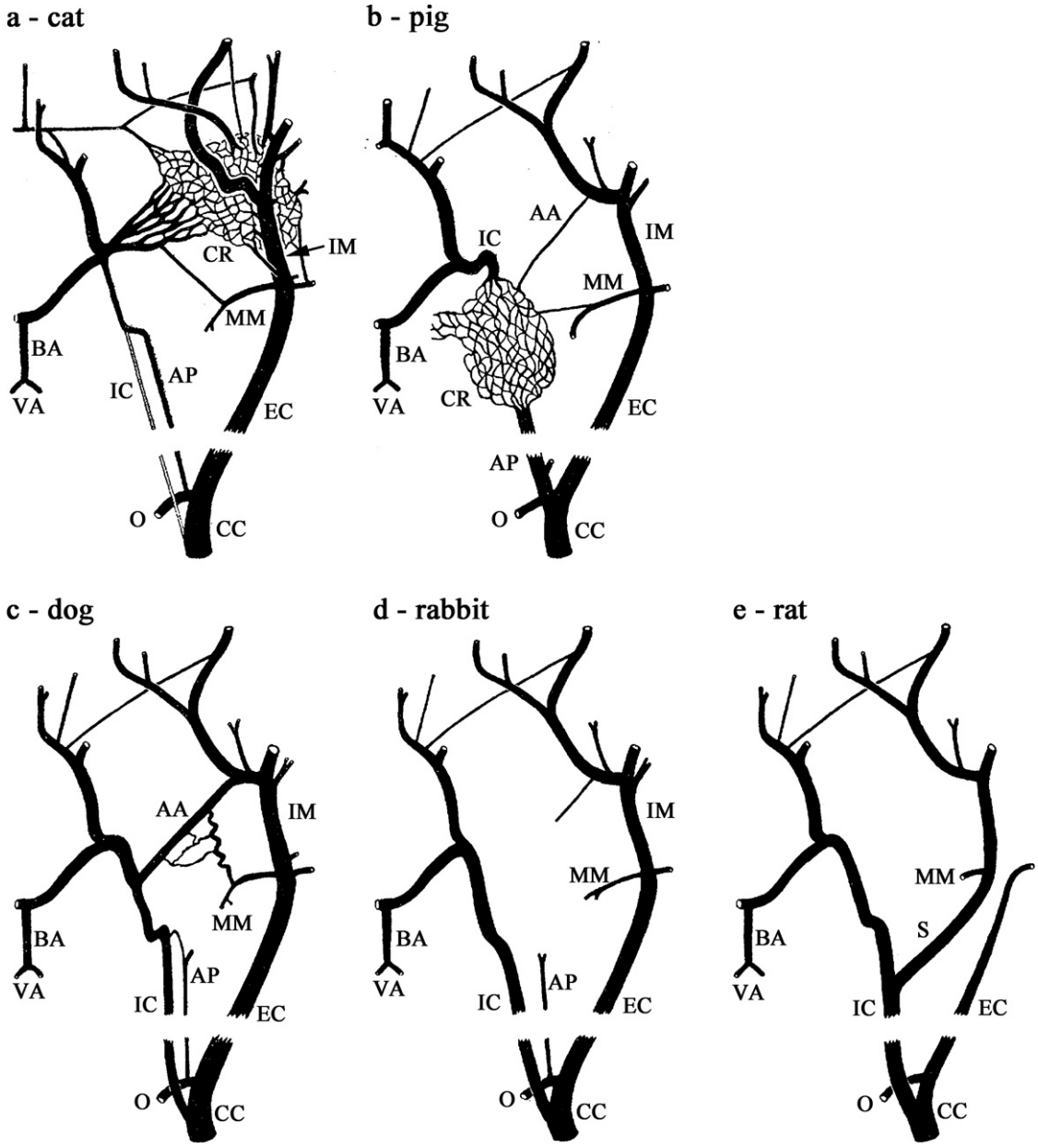

Fig. 3. Schematic comparative cerebrovascular anatomy of the five most frequently used species in CAGE animal studies. Adapted (with permission) from Daniel et al. (1953). Abbreviations: AA, anastomotic artery; AP, ascending pharyngeal artery; BA, basilar artery; CC, common carotid artery; CR, carotid rete; EC, external carotid artery; IC, internal carotid artery; IM, internal maxillary artery; MM, medial meningeal artery; O, occipital artery; S, stapedial artery; VA, vertebral artery.

Only few studies on CAGE in animals with a carotid rete have directly addressed this issue. We have recently shown in the pig that air injected into the artery proximal to the carotid rete does enter the cerebral vessels and results in injury measured as increased brain lactate and intracranial pressure (ICP) (Weenink et al., 2011). Other researchers have chosen to inject air proximal to the carotid rete after ligation of branches that do not contribute to cerebral circulation, in order to force air through the plexus. In these studies, performed in cats, entrance of air into the cerebral vessels was evident by a decrease of somatosensory evoked potentials (SSEP) (Evans et al., 1989). In some models air was injected into the common carotid artery, or a more proximal artery, without measures to prevent flow of air to the external carotid territory (Hossmann and Fritz, 1978; Juncker et al., 1998; Lee and Olszewski, 1959; Martens et al., 2004; Pate and Birdsong, 1964; van Hulst et al., 2003b; Yamaguchi et al., 2003). Other than cats and pigs, species that possess a carotid rete have not been studied in CAGE, except in one study in which air was injected into the common carotid artery in sheep (Williams et al., 2001) and entrance of air into the brain vessels was demonstrated by ultrasonic Doppler. In general it can be stated that if no measures are taken to prevent flow of air into the extracerebral arteries, it cannot be ascertained that all air passes through the rete into the brain. The amount of undesired air flow will depend on various parameters such as diameter of the arterioles and local perfusion characteristics and may result in heterogeneous effects of the embolism. We have recently observed that air can be selectively directed through the carotid rete of the pig by inflating a balloon in the ascending pharyngeal artery and injecting the air between the balloon and the carotid rete. After embolization this balloon is deflated in order to restore the normal cerebral perfusion situation (unpublished results).

Another way of circumventing the problems caused by the carotid rete is by introduction of air through the vertebral artery. This is not possible in the pig, since the vertebral arteries of the pig contain a rete of their own (Reinert et al., 2005). In dogs, however, it has been shown that the middle cerebral artery can be reached with a catheter through the vertebral artery (Rink et al., 2008). Indeed, in one CAGE model air has been successfully injected into the vertebral artery in dogs (Simms et al., 1971). The vertebral artery in cats does not have a carotid rete and although the size of this artery is very small, CAGE has been generated by injection of air into the cat vertebral artery (Evans et al., 1981, 1984). The problems that may potentially arise after embolization of the vertebral artery, namely respiratory and cardiovascular compromise due to brain stem infarction, will be discussed in the next paragraph.

Avoiding injection of air proximal to the rete is also possible by directly accessing one of the cranial arteries through opening of the skull and subsequent microsurgical approach to the cranial base. Although such techniques have been described for many species and have been used in other animal models, this approach has not been used in any of the CAGE models. Reasons may be the surgical complexity of these procedures or the fact that the operation itself may have an effect on cerebral metabolism, which complicates analysis of injury due to CAGE.

In summary, while the intracranial cerebrovascular anatomy is grossly similar between most species used in CAGE research, there are important differences in the more proximal vasculature. The presence of a carotid rete in the species under study is of great significance in the development of an adequate animal model. There are several ways to inflict CAGE in animals with this structure.

5. Location of air administration

One of the most important factors of influence on the effects of CAGE on the brain and the stability and reproducibility of the animal model is the method of administration of the air. Throughout the published animal studies, the location of air administration into the circulation can be classified as (1) the arterial system proximal to the brain (2) the pulmonary venous circulation (3) an artery not responsible for brain perfusion (4) a cardiopulmonary bypass (CPB) system.

The vast majority of researchers has employed the first method. It makes sense to inject the air as close to the cerebral vasculature as possible, in order to generate the most standardized effects on the brain. In most models the tip of the catheter is therefore placed in the main artery supplying the cerebrum, usually the internal carotid artery, either with or without ligation of vessels not supplying the brain (Annane et al., 1994; Danis and Willman, 1963; De la Torre et al., 1962a; Furlow, 1982; Hallenbeck et al., 1979; Hekmatpanah, 1978; Herbaczynska-Cedro et al., 1978; Hills and James, 1991; Jungwirth et al., 2006; Leitch et al., 1984a; Meyer et al., 1962; Nishimoto et al., 1978; Ryu et al., 1996; Spiess et al., 1986; Weenink et al., 2011). In some studies the vertebral artery was chosen instead of the carotid (Evans et al., 1981, 1984; Simms et al., 1971). Others have administered air in a more proximal artery such as the common carotid artery with ligation of vessels not supplying the brain (Broman et al., 1966; Bunegin et al., 1994; Evans et al., 1989; Gerriets et al., 2010; Medby et al., 2002; Rosengren et al., 1977). One would suspect that air injection into a proximal artery without ligation of external carotid vessels is likely to result in larger variance of results because of distribution of air between external and internal carotid territories. This might be especially true in species that are known to have a smaller internal carotid artery (or equivalent main supplier of the brain) as compared to the external carotid artery, such as the pig (Reinert et al., 2005). Nevertheless, in many models adequate results have been obtained after embolization of the common carotid artery (Currie et al., 1970; Fine and Fischmann, 1940; Fries et al., 1957; Helps et al., 1990b; Juncker et al., 1998; Lee and Olszewski, 1959; Martens et al., 2004; Meijne et al., 1963; Meldrum et al., 1971; Menasche et al., 1985; Pate and Birdsong, 1964; Redo, 1958; van Hulst et al., 2003b; Williams et al., 2001; Worman and Seidel, 1966; Yamaguchi et al., 2003) or even the innominate artery (Gomes et al., 1973; Hollon and Maginn, 1969; Hossmann and Fritz, 1978), ascending aorta (Butler et al., 1988; Gomes et al., 1973; Wyant and Dobell, 1967) or heart (Butler et al., 1988; Gomes et al., 1973).

Although it makes sense to ligate certain branches not participating in cerebral perfusion when air is injected into a more proximal artery, this practice has disadvantages, as mentioned by Furlow (1982). Disturbance of normal cerebral perfusion characteristics may result in undesired flow changes. For instance, if the external carotid artery is ligated and the animal has anastomoses between external and internal carotid territories (as are present in many animals) then shunting of blood (and air) from cerebral to extracerebral tissues may occur. It is desirable to minimize alterations to cerebral perfusion characteristics in CAGE models.

With regard to the choice between carotid or vertebral artery, the study of De la Torre et al. (1962b) is of interest. Blood foam (blood thoroughly shaken with air) was injected into the internal carotid or vertebral artery of anesthetized spontaneously breathing dogs with or without clipping of both posterior communicating arteries. Without clipping, immediate effects were summarized as apnea and hypertension with bradycardia in most animals, with no obvious differences between injection sites. However, in dogs in which the posterior communicating arteries were effectively clipped, no respiratory or cardiovascular changes were seen after injection into the internal carotid artery. These animals showed severe reactions after injection into the vertebral artery. These findings, which are explained by the presence of respiratory and autonomic nuclei in the brainstem, demonstrate the different

reactions that can occur after embolization through the internal carotid versus the vertebral artery.

The second mentioned method for induction of CAGE, entrance of air through the pulmonary venous circulation, is of interest since in some instances – mostly in divers – CAGE is caused by pulmonary barotrauma. Only two studies were performed using this method, probably because it generates heterogeneous results due to dispersion of air through essentially the whole body. In their classic study van Allen et al. (1929) introduced air into the pulmonary vein of dogs and demonstrated that the air can be directed somewhat selectively to the cerebrum by positioning the subject in an upright posture. Another mode of administration of air in the pulmonary veins was used by Atkinson (1963) who induced pulmonary barotrauma by adding one vital capacity to the lungs of cats, after which air bubbles were seen in the cerebral vessels.

Some authors have demonstrated that CAGE can be induced by introducing air into an artery not responsible for brain perfusion such as the descending aorta (Huddleston et al., 1983), femoral artery (Gorman and Browning, 1986) or radial artery (Chang et al., 1988). In these studies, the purpose of generating CAGE was to demonstrate movement of air bubbles against the direction of arterial flow. The fact that these air bubbles can potentially reach the brain is either caused by their buoyancy or reflects a volume effect (i.e. the volume and speed of air injection result in a temporary reversal of arterial flow) (Lowenstein et al., 1971).

Historically, air embolism has been a risk in CPB. This risk has been largely abolished since bubble oxygenators have been replaced by membrane oxygenators, although gaseous microemboli can still be generated in these systems (Kurusz and Butler, 2004). Occasionally, cases of massive CAGE due to malfunctioning of CPB machinery or human error in handling the system continue to be reported (Guy et al., 2009). A review on animal CPB models has been published recently (Jungwirth and de Lange, 2010). We do not report on studies in which air was passively generated by the oxygenator in a CPB system, since we only included studies in which air was actively administered to the circulation. There is essentially no difference in results between injection into a proximal artery and introduction of air in the arterial part of the CPB system, with the same remark regarding dispersion of air to unwanted vessels as mentioned above (Gomes et al., 1973).

In order to simulate human CAGE as closely as possible, it would be interesting to know about patterns of cerebral infarction in clinical or diving-related CAGE. Griese et al. (2009), in a retrospective analysis of probable CAGE cases after CPB, reported a higher incidence of right hemispheric lesions, mostly located in the cortex of the border zone between middle and anterior cerebral artery territories. They hypothesized this preponderance of right sided infarction to result from the fact that the brachiocephalic artery is the first artery branching from the aortic arch, thus catching the largest amount of air. No further studies on human CAGE infarction patterns are available which makes resemblance of the human situation in animal models difficult. It may be advantageous to create unilateral injury, so that the contralateral hemisphere can be used as internal control. Some authors have demonstrated unilateral injury in their model (Gerriets et al., 2010), but in general strict unilateral distribution is difficult to obtain. The first reason for this difficulty is the fact that changes in cerebral perfusion characteristics occur due to air introduction, which may shunt part of the air to the contralateral hemisphere (Furlow, 1982). Secondly, in animals with a carotid rete there are usually many anastomoses between the left and right rete, which results in bilateral dispersion of air after unilateral injection (Weenink et al., 2012). Therefore, one cannot assume that unilaterally injected air remains in the ipsilateral hemisphere.

In conclusion, most CAGE models involve air injection through an intravascular catheter placed close to the cerebral circulation. This is obviously different from the etiology of CAGE in almost all clinical and diving-related cases, but is the best way of ensuring the most standardized effect on the cerebrum. Little is known about infarction patterns in human CAGE, which complicates accurate mimicking of the human situation in animal models.

6. Amount of air

With a given species and location of air administration, one of the important factors determining the level of injury inflicted in the animal is the amount of air injected. The main limitation in determining the optimal volume of air is that the amount of air involved in clinical cases of CAGE is usually not known. Furthermore, in many instances the duration of the air flow into the vessels is unknown. This especially holds true for cases in which air enters the circulation due to lung damage, for instance in pulmonary barotrauma in divers. The amount of air involved and the duration of the exposure in human cases of CAGE are probably quite variable, given the great scattering of symptoms and signs encountered in CAGE (Bessereau et al., 2010). The lower end of the CAGE spectrum is characterized by the subtle neuropsychological dysfunction that may be encountered after CPB. This type of CAGE has been coined cerebral air microembolization (Gerriets et al., 2010). There is no clear transition between cerebral air microembolization and 'normal' CAGE in regard to the amount of air involved. The higher end of CAGE symptomatology involves widespread cerebral infarction visible on computed tomography (CT) or magnetic resonance imaging (MRI) scans, severe cytotoxic and vasogenic edema with ensuing rise in ICP followed by brain herniation and death. Clinical and diving-related patients can present anywhere between these extremes.

Given this heterogeneous clinical presentation, it is not surprising that the amount of air introduced varies greatly between animal models of CAGE. The amount depends on the desired level of damage, which in turn depends on the research question and the outcome parameters under study. Models that rely on very sensitive measures of cerebral function, such as SSEP or electroencephalography (EEG), require less air than models that use for instance ICP to quantify brain injury. The largest amount of air used in a CAGE model was by Martens et al. (2004), being an average of 37 ml into the common carotid artery of pigs. On the opposite side of the spectrum, Gerriets et al. (2010) have recently shown that amounts as little as 0.1 μl injected into the common carotid artery of rats (with extracerebral arteries ligated) can cause quantifiable neurological deficits. In general, studies in which only effects of CAGE on the blood–brain barrier were investigated used small amounts of air while research into the effects of CAGE on cerebral metabolism (brain oxygenation, brain glucose metabolism) and cerebral hemodynamics (cerebral blood flow (CBF), ICP) required larger amounts of air. It is, however, difficult to directly compare amounts of air used between publications. The reason for this is the fact that most authors either choose a standard amount of air, or correct the volume for the animal's weight. One may question the validity of these approaches to air dosing. In most species brain weight does not increase linearly with body weight as the animal grows. Brain weight tends to reach a plateau in adolescence while body weight can increase greatly thereafter (Blinkov and Glezer, 1968). Furthermore, smaller animals tend to have proportionally larger brain mass relative to body mass than larger animals (Williams, 2002) so comparing volume based on body weight between species can be misleading. It would be more appropriate to base the amount of air on the animals brain weight or perhaps on its cerebral blood flow, but these approaches have not been undertaken in any of the CAGE animal models.

Despite the disadvantages of fixed amounts of air and relating air volume to body weight, some authors have published adequate volume-response relationship after embolization using these approaches in the rabbit (Reasoner et al., 1996; Ryu et al., 1996) and the rat (Gerriets et al., 2010; Jungwirth et al., 2007). In contrast with these positive results, it has been shown that even within a single species and a narrow weight range the cerebral effects of a standardized air bolus can be quite variable (Weenink et al., 2012). This was also demonstrated by Simms et al. (1972), who injected various amounts of air (ranging form 0.05 ml/kg to 1.00 ml/kg) into the vertebral artery in dogs weighing 13–24 kg. There was no statistically significant difference between any of the air volumes with regard to cerebral venous blood oxygen tension and cerebrospinal fluid oxygen tension.

One way to circumvent these problems is to titrate the amount of air injected to a certain parameter. Repeated air boluses are administered until the desired amount of damage has been inflicted. This results in varying amounts of injected air, but possibly more standardized effects on the brain. The parameters used to titrate the air volume should have a high temporal resolution, therefore this approach has been followed using SSEP and EEG. These methods are discussed in greater detail below.

To summarize this paragraph, the amount of air used in CAGE models varies greatly and depends primarily on the desired amount of cerebral injury and the parameters used to monitor the brain. Fixed or weight-related amounts of air have been used with success, but have in some models resulted in large variances between animals. Titration of air volume to obtain a certain amount of cerebral injury may increase reproducibility of results.

7. Bubble size

Not only the amount of air injected, but also the size of the bubbles may have influence on the effects on the brain. Furlow (1982) has described the properties that have to be controlled in order to generate uniform bubble size, namely the size of the orifice from which the bubble emerges, the pressure of injection, the blood flow velocity behind the orifice and the surface tension of the blood. Although most authors inject a known volume of air without paying attention to the size of the bubbles generated, some researchers have used uniform bubble sizes in their animal model (Gerriets et al., 2010). However, the size and homogeneity of the size of bubbles generated in clinical cases of CAGE is unknown. It is therefore debatable whether or not generating bubbles with a known and uniform size is useful in experimental research.

In this regard, several aspects of intravascular bubble behavior are of importance (Mitchell and Gorman, 2002). Intravascular bubbles that are larger than the diameter of the vessel they occupy are present not as spheres but as cylinders of air with rounded caps. Bubbles may not stay intact when they encounter a branch in the vessel, but can split up with both parts following their own way. Consequential air bubbles in the same vessel will either merge or line up one after the other, forming a 'string of pearls' (named for its appearance as viewed through a craniectomy). The position where the embolus ultimately lodges is determined by the tradeoff between the surface tension at the leading edge of the bubble (promoting trapping) and the sum of the surface tension and the arterial pressure at the trailing edge (both promoting propagation). Small air bubbles (diameter < 15 μm) may not lodge at all and pass to the venous circulation immediately (Feinstein et al., 1984). However, this does not imply that these small bubbles do not cause cerebral injury, because even bubbles as small as 10–20 μm have been shown to cause blood–brain barrier disruption (Hills and James, 1991).

Air bubbles are often reported to lodge in arterioles of 30–60 μm diameter, although the articles referred to in support of this statement do not actually provide proof of this allegation. Gorman and Browning have shown that bubbles smaller than 200 μm diameter generally lodge in arterioles of 50–200 μm diameter (Gorman and Browning, 1986). It has been demonstrated that bubbles preferentially lodge in areas with low cerebral perfusion pressure, namely the watershed areas between arterial territories and the grey-white matter junction (Dutka et al., 1988). Although it is reasonable to assume that bubbles of different size will lodge in vessels of different size, this hypothesis has not been tested. Given the abovementioned characteristics of intravascular air behavior a clear size-response relationship seems unlikely. Until studies investigating the effect of bubble size on cerebral damage have been performed, it may be more practical to titrate air introduction to a certain level of injury, as mentioned in an earlier paragraph.

8. Outcome parameters

Many different outcome parameters have been studied in CAGE animal studies. For general monitoring of the anesthetized animal, most researchers report on the use of one or more parameters, generally heart rate, blood pressure, body temperature and/or electrocardiogram. In this paragraph, we will focus on the methods that have been used for assessment of cerebral condition. Fig. 4 displays the most commonly used parameters, which will be discussed here. Rogatsky et al. (1999) have reviewed the methods used for physiologic and biochemical monitoring during hyperbaric oxygen therapy (HBOT) in human studies, including some methods for assessing cerebral functioning. This study is of interest, since HBOT is the generally accepted treatment for CAGE and is therefore applied in many of the animal studies under review here.

Together with SSEP, the most commonly studied parameter in CAGE models is CBF. Several different techniques have been used, of which [^{14}C]-iodoantipyrine is the most common (Sakurada et al., 1978). This technique relies on the diffusion of a chemically inert tracer into the brain tissue. The amount of tracer can be visualized by an autoradiographic procedure and CBF can be quantified from the optical density. This method requires removal and sectioning of the brain and can thus only be performed postmortem. Methods used in CAGE research that provide continuous or repetitive CBF values include xenon (Meldrum et al., 1971) or hydrogen (Furlow, 1982) clearance, and thermocouple (Hossmann and Fritz, 1978) methods. Modern techniques for measuring CBF such as xenon CT, perfusion CT and functional MRI have not yet been employed in CAGE animal studies.

Another frequently used method for assessing neuronal function in CAGE models is SSEP. The most important advantage of this method is that it provides information on the functional status of the brain, albeit in a specific neuronal pathway. The most frequently used model measures SSEP after median nerve stimulation in the dog (Hallenbeck et al., 1979; Leitch et al., 1984a). Other researchers stimulated the sciatic nerve in the cat (Evans et al., 1984, 1989) or the median nerve in the rabbit (Helps et al., 1990b; Ryu et al., 1996). The high temporal resolution of SSEP measurements enables the use of this technique to determine appropriate air volume, i.e. titrating the amount of air to obtain a certain degree of response depression. The most commonly used protocol involves injection of 50 μl of air into the internal carotid artery of the dog, followed by 20–50 μl boluses in order to suppress the amplitude between the first positive peak and the first negative peak to 10–20% of baseline value. This suppression by means of repeated air boluses is maintained during one hour (Hallenbeck et al., 1979; Leitch et al., 1984a). In the cat model the amplitude between the second positive peak and the first negative peak is suppressed to less than 10% of baseline

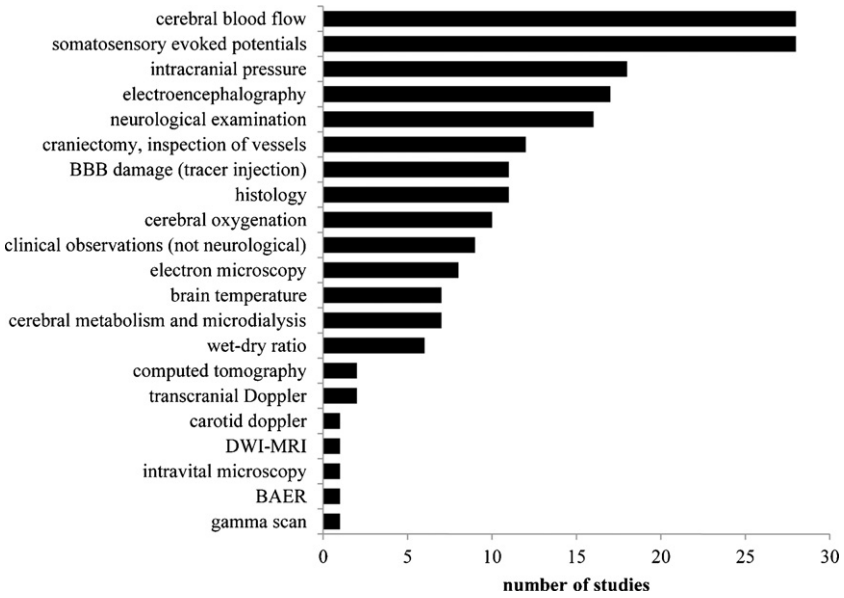

Fig. 4. Methods used for monitoring of cerebral function in CAGE animal studies. In most studies more than one method was used. Methods that were only used in one study were omitted from this figure for the sake of conciseness. Abbreviations: BBB, blood–brain barrier; DWI, diffusion-weighted imaging; BAER, brainstem auditory evoked response.

value during 15 min by repeated infusion of 80 μl air boluses into the common carotid artery with ligation of the external maxillary artery (Evans et al., 1984, 1989). In the rabbit model SSEP was not used for titration of air volume, instead fixed amounts of air were injected (Helps et al., 1990b; Ryu et al., 1996). After completion of the embolization period, recovery of the SSEP amplitude can be followed and used as a measure of cerebral function. One has to bear in mind that latency and amplitude of SSEP waves can be altered by certain anesthetics, which will be discussed later.

EEG, or sometimes electrocorticography, is another frequently employed method to study cerebral function in CAGE models. It has the advantage of rendering a more general image of neuronal function than SSEP. Furthermore, EEG can be measured non-invasively and therefore is one of the few techniques that can be readily applied in the clinical situation. EEG has a very high temporal resolution. Traditionally, however, EEG has only been analyzed in a qualitative fashion and therefore results have been difficult to compare between studies (Annane et al., 1994; Furlow, 1982; Gomes et al., 1973; Hekmatpanah, 1978; Meijne et al., 1963; Meldrum et al., 1971; Menasche et al., 1985; Meyer et al., 1962; Redo, 1958; Spiess et al., 1986; Worman and Seidel, 1966). Development and application of quantitative methods for EEG analysis (qEEG) may expand the use of this technique in CAGE models. Little information on qEEG in CAGE is available, since quantitative analysis was only conducted in 4 of 17 studies in which EEG was performed (Drenthen et al., 2003; Fritz and Hossmann, 1979; Hossmann and Fritz, 1978; Weenink et al., 2012). We have recently demonstrated the use of the temporal brain symmetry index in monitoring the acute effects of CAGE on the pig brain (Weenink et al., 2012). Like SSEP, EEG signals are altered by the use of anesthetic agents. Recent research has evolved in the application of bispectral index for monitoring depth of anesthesia. However, this method is not developed for monitoring cerebral function in disease states and should in its present form not be used for this purpose (Souter and Lam, 2009).

Histological procedures performed in CAGE models can be divided into two groups. In the first group histology is used for infarct delineation. This is done either with heamatoxylin and eosin staining or with triphenyl tetrazolium chloride staining. Tripenyl tetrazolium chloride is a white redox indicator that is reduced to a red substance in living cells. Infarcted areas remain pale and can be quantified after manual or automated delineation (Hindman et al., 1999). The second goal of histology in CAGE research is determination of blood–brain barrier damage. Methods used include injection of Evans blue-labeled albumin (Rosengren et al., 1977), Trypan blue (De la Torre et al., 1962a) or horseradish peroxidase (Persson et al., 1978) and autoradiography of labeled albumin (Johansson, 1980). Others have performed electron microscopy to investigate blood–brain barrier damage at the microscopic level (Hekmatpanah, 1978). The obvious disadvantage of histological methods is that they can only be performed postmortem.

Some methods used in CAGE research require placement of a probe in the cerebrum. These methods all provide the advantage of rendering (near) real time results. Of these, ICP is the most frequently obtained measurement (De la Torre et al., 1962a; Evans et al., 1984; Hossmann and Fritz, 1978; Leitch et al., 1984a; Simms et al., 1971; van Hulst et al., 2003b; Weenink et al., 2011; Williams et al., 2001; Worman and Seidel, 1966). ICP is a commonly used parameter in traumatic brain injury with a well defined upper limit of normal and a high clinical relevance. Although ICP is generally evenly distributed in the normal situation, pressure gradients between brain regions may exist in certain pathological states such as unilateral space-occupying lesions (Smith, 2008). This should be kept in mind when performing unilateral ICP measurements in CAGE experiments. Intraventricular probe placement (as opposed to intraparenchymal measurement) renders the most reliable results (Smith, 2008). A drawback is the fact that ICP increase is a late event in the cascade of neuronal injury. Other techniques such as SSEP, EEG, microdialysis and cerebral oxymetry provide earlier insight into neuronal function.

Determination of cerebral oxygenation by means of cerebral oxygen tension monitoring is increasingly used clinically for oxygenation targeted therapy in traumatic brain injury (Narotam et al., 2009). Since in most CAGE models the location where the bubbles lodge and the resulting ischemic area cannot be entirely controlled, it is theoretically possible that the probe is placed in unaffected tissue. Nevertheless, this technique has been successfully used in several CAGE animal models (van Hulst et al., 2003b; Weenink et al., 2011). Other researchers measured oxygen tension of cerebrospinal fluid (Simms et al., 1972) or assessed total cerebral oxygen consumption by calculation of the arteriovenous oxygen difference

across the brain (Hossmann and Fritz, 1978; Simms et al., 1972). More modern techniques for assessing cerebral oxygenation such as near-infrared spectroscopy have not yet been used in CAGE studies.

Microdialysis is a technique first described by Ungerstedt (1986) requiring placement of a double lumen probe with a semi-permeable outer membrane in the cerebral tissue. This probe is continuously flushed with a liquid resembling cerebrospinal fluid. Substances in the extracellular tissue diffuse passively over the membrane into the perfusate and can be measured after collection, bedside if necessary. Most frequently this technique is used to monitor glucose metabolism by measuring glucose, lactate and sometimes pyruvate in the dialysate (Medby et al., 2002; van Hulst et al., 2003b; Weenink et al., 2011). Some researchers have additionally measured glycerol, a marker for cell wall damage (Medby et al., 2002; van Hulst et al., 2005). The amount of a substance retrieved from the extracellular matrix into the perfusate is termed the recovery rate and depends on several factors, of which probe length and perfusion speed are the most important. Values as determined in the microdialysate must be corrected with this recovery rate, which has to be determined in vitro or in vivo (Peerdeman et al., 2000). A disadvantage of the technique is the fact that the probe itself injures cerebral tissue, although it has been demonstrated that this damage persists only for little more than an hour after implantation (Ungerstedt and Rostami, 2004) and blood–brain barrier disruption can be largely prevented by slow placement of the probe (Allen et al., 1992). When used as a global parameter of cerebral functioning it has the same disadvantage as cerebral oxygen tension monitoring, namely that the probe may be placed in unaffected tissue and that measurements may thus not be representative of the entire brain. However, we have recently shown in a swine model of CAGE that microdialysis values correlate well with other measures of cerebral function (Weenink et al., 2011).

Standardized neurological examination can be regarded as the gold standard for the assessment of cerebral functioning after neuronal injury. Qualitative neurological examination has often been part of outcome assessment in CAGE models (Currie et al., 1970; Garcia et al., 1981; Gomes et al., 1973; Pate and Birdsong, 1964; Spiess et al., 1986; Wyant and Dobell, 1967), and some researchers have performed neurological assessment using quantitative scoring systems (Annane et al., 1995; Gerriets et al., 2010; Huddleston et al., 1983; Jungwirth et al., 2006; Ryu et al., 1996). Studies investigating correlation of measured parameters with neurological outcome are few, which can pose difficulties in determining the clinical relevance of results obtained. An exception is SSEP, which in New Zeeland White rabbits has been shown to correlate well with neurological outcome after administration of 50, 100 or 150 μl/kg air (Reasoner et al., 1996). Annane et al. (1995) aimed to correlate CT findings after CAGE with clinical symptoms. CT results did not correspond well with clinical symptoms. CT scanning of the brain can therefore be regarded as an inferior method of quantification of injury due to CAGE.

In conclusion, the choice of which methods to use for assessment of the effects of CAGE on the animal brain has a close relationship to the desired amount of injury. Researchers interested in the upper limit of CAGE symptomatology could for instance obtain CBF and ICP measurements and perform histological procedures to assess macroscopic infarction. More subtle changes in cerebral function could be quantified using SSEP and qEEG, while even smaller amounts of injury might need for instance electron microscopy to investigate blood–brain barrier damage. Overall, frequently used methods are CBF measurement, electrophysiological recordings and histological procedures. The fact that many parameters have not been correlated to clinical outcome in the setting of CAGE implicates that all extrapolations to the human situation must be made with caution.

9. Anesthesia

In all non-awake animal experiments, the choice of an appropriate anesthetic regimen is of crucial importance. This is even more so in experiments in which the brain is the subject of study, since anesthetics influence cerebral function by definition. The researcher should recognize the possible influences of the anesthetics on the measurements obtained. It is beyond the scope of this review to discuss in detail the effects of each anesthetic agent in the several species used in CAGE studies. In general, anesthetic agents lower cerebral metabolic rate and thus lower CBF, due to coupling of metabolism and blood flow in the brain. Notable exceptions are ketamine and nitrous oxide, which are known to increase cerebral metabolism and CBF in parts of the brain. Effects are usually concentration-dependent and some volatile anesthetics are known to increase CBF in low concentrations while decreasing CBF at higher concentrations (Patel and Drummond, 2009). Nitrous oxide is an exceptionally bad choice in CAGE, not only because it raises ICP but also because this gas diffuses rapidly into air bubbles resulting in increased size of the bubbles (Muth et al., 2001). Muscle relaxants have little effect on cerebral metabolic rate.

The effects of anesthetics on cerebral metabolic rate are most directly notable in electrophysiological recordings (Sloan, 1998). Most anesthetics cause concentration-dependent changes in the EEG, starting with an excitatory phase and followed by decrease in frequency and amplitude. Effects of anesthetics, for instance volatile agents, on SSEP are summarized as decreased amplitude and increased latency. Again, ketamine is an exception, producing high amplitude theta and beta activity in the EEG and increased amplitude of SSEP waves. Opioid analgesics have only little effect on EEG, although they can produce a decrease in frequency. Barbiturates are known for their ability to produce an isoelectric EEG, while SSEP responses can still be evoked when the EEG is already isoelectric. The main effect of muscle relaxants on EEG and SSEP is decrease of artifacts due to muscle activity.

Another matter that requires attention in this regard is the neuroprotective effect of anesthetic agents. All anesthetics provide at least some degree of neuroprotection which is inherent to their property of lowering cerebral metabolism (Patel and Drummond, 2009). In a recent review Schifilliti et al. (2010) conclude that many anesthetic drugs, such as barbiturates, propofol, xenon and most volatile inhalational agents have neuroprotective effects, although there is little evidence at this moment to choose any substance over the others in cases where neuroprotection is desirable. Of interest, some substances, of which isoflurane and ketamine are the most notable, have shown neurodegenerative effects next to their neuroprotective properties in animal studies (Hudetz and Pagel, 2010; Schifilliti et al., 2010).

Since HBOT is the generally accepted treatment modality for CAGE, many studies have involved subjecting animals to HBOT after induction of air embolism. The use of hyperbaric oxygenation in an anesthetized and ventilated animal presents the researcher with interesting challenges. Many of these concerns are practical or technical by nature and have been summarized by several authors (Camporesi, 2004; Muth et al., 2001; Severinghaus, 1965; Weaver, 2011). One of the important anesthesiological issues is that volatile anesthetics are generally not allowed inside hyperbaric chambers because of the closed environment and the consequential risk of exposure of personnel to the anesthetic, as well as the increased risk of fire due to high oxygen tensions. Total intravenous anesthesia is recommended in HBOT, use of intramuscular medication is discouraged because availability of the substance is uncertain due to vasoconstriction caused by hyperbaric oxygenation (Camporesi, 2004). There is no clinically relevant effect on the efficacy of anesthetic and analgesic agents in the pressure range used for treatment of CAGE (up to 2.8 atmospheres absolute (152 kPa)) (Moon and

Camporesi, 2009). Apart from the incompatibility of nitrous oxide with CAGE as mentioned above, administration of this gaseous anesthetic induces a great risk of decompression sickness due to its high solubility under pressure. Nitrous oxide can therefore not be used in HBOT (Severinghaus, 1965).

To summarize this paragraph, the choice for an anesthesiological regimen in an animal model of CAGE should take into account the effects of the drugs on cerebral metabolism and the parameters monitored. Some extra considerations apply when HBOT is part of the experimental protocol. By definition, no anesthetic protocol is without effects on the brain.

10. Other factors that influence outcome in cerebral ischemia

In the previous paragraphs we discussed considerations that are of specific interest in CAGE research, except of species and anesthesia, which are factors that need to be taken into account in all animal models. There are a few more variables that are known to influence outcome in cerebral ischemia. Of these factors the most extensively studied are blood glucose and body temperature, although it must be noted that neither of these parameters have been studied in the context of CAGE. Hyperglycemia (Quinn and Lees, 2009) and hyperthermia (Reith et al., 1996) are independent predictors of worse outcome in ischemic stroke in humans while hypothermia protects against neuronal injury in cerebral ischemia (Reith et al., 1996). Since CAGE is a type of multifocal cerebral ischemia, it may well be that these factors influence outcome in CAGE and it is important for the researcher to realize this. A special remark must be made on the effect of blood pressure on outcome in CAGE. Hypotension as well as hypertension can result in detrimental effects on the brain. In the case of severe hypotension cerebral perfusion will diminish which may lead to aggravation of ischemia. In a recent animal study addressing the effect of different levels of mean arterial pressure (MAP) on neurological outcome after CAGE during CPB in rats, hypotension (MAP = 50 mm Hg) was associated with worse neurological scores than normal (MAP = 60–70 mm Hg) or increased (MAP = 80 mm Hg) blood pressure (Qing et al., 2011). On the other hand hypertension, although promoting bubble redistribution to the venous circulation (Moon, 2005), increases damage to the already injured blood–brain barrier which results in increased cerebral edema (Dutka et al., 1987). Hypertension commonly occurs after air injection, as discussed above. The researcher should recognize the possible influence of both low and high blood pressure on experimental results.

11. Conclusions

In this review article, we have summarized the most important characteristics of animal models that have been used in CAGE research. It is interesting to notice the large variation in the published animal models with respect to species, method of air introduction, amount of air, measurement of outcome and anesthesiological protocol. This variation exists despite the relatively small amount of literature available on this subject, as compared to studies on other causes of cerebral ischemia. The main reason for the large differences between animal models is the fact that CAGE is a heterogeneous clinical entity. From this observation it can be inferred that there is not one ideal animal model for CAGE. The research question under study determines the desired amount of injury which in turn influences the choice of parameters to monitor. Creating the correct amount of damage can be done by injection of fixed or weight-related air volumes, but titrating the amount of air to achieve a certain amount of SSEP or EEG depression has resulted in the most standardized amounts of cerebral injury. The relevance of controlling air bubble size remains to be elucidated. Measures must be taken to deliver the air as selectively to the brain as possible, taking into account the cerebrovascular characteristics of the species under study. The carotid rete can prove troublesome in this regard, but when appropriate precautions are taken CAGE can be effectively induced in species that possess this anatomical structure. Anesthesia can produce unwanted effects on cerebral metabolism and the anesthetic regimen must therefore be chosen carefully.

We do not pretend to have produced an exhaustive review on all methodological subjects of interest in CAGE research. We have merely extracted important factors from existing animal studies on CAGE, while many interesting topics may be derived from research on human CAGE or in the field of decompression sickness and other causes of ischemic stroke. Reviewers should therefore keep informed on these subjects as well.

Adequate animal models will always be of crucial importance in CAGE research, mostly because the relatively low incidence of the disease hampers collection of large patient series (Moon, 2005). Moreover, in obvious cases of CAGE the patient is generally expeditiously treated with HBOT despite the lack of level I evidence for its efficacy. Withholding HBOT from patients would be unethical, which further limits the conduction of randomized clinical trials (Moon, 2005). It is not possible to rate one animal model as superior to the others, based on the data in this review. We have merely aimed to provide the researcher with an overview upon which to make his own decisions regarding species, method of embolization, parameters to monitor and other important factors. We hope that the continuing development and improvement of animal models will result in a better understanding of pathophysiologic processes in CAGE and lead to advances in diagnostic and therapeutic possibilities for this disease.

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