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Characteristics of Methods Performed in Vascular Neurosurgery and the Application of Various Methods

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Annotation. The basic science of cerebrovascular disease is a very extensive topic and exceeds the scope of this article. Below we will focus on specific aspects of vascular neurosurgery where animal models of both the disease pathobiology as well as treatment have come to play a significant part. These include subarachnoid hemorrhage (SAH) and the associated early and delayed brain injury, as well as the biology of cerebral aneurysm formation and growth.

Keywords: neurosurgery, hemorrhage, early brain injury (EBI), intracerebral hemorrhage (ICH), cerebral ischemia

Introduction

Vascular neurosurgery is a diverse field focused on surgical and interventional treatment of cerebrovascular disease, both the manifestations as well as the underlying causes. Specifically, the common diseases that fall in the domain of vascular neurosurgery include cerebral ischemia and ischemic stroke including occlusive vascular disease, nonlesional hemorrhagic vascular disease – which includes spontaneous, hypertensive and angiopathic intracerebral hemorrhage (ICH) – and lesional hemorrhagic vascular disease – which includes cerebral aneurysms, arteriovenous malformations, and cavernomas. Given this diverse disease pool, vascular neurosurgery spans multiple fields, including neurology, cardiology, intensive care, interventional radiology, and clinical genetics, and can affect involve both adult and pediatric patients. Furthermore, both cerebral ischemia and stroke, as well as intracranial hemorrhage, can be a manifestation of systemic disease, such as atherosclerosis or hypertension and amyloid angiopathy, respectively.

Delayed cerebral ischemia is one of the most severe complications of aneurysmal SAH. It accounts for a large proportion of morbidity and mortality. DCI has been shown to occur in approximately 30% of patients, typically between days 4 and 10 after bleeding. The pathophysiology of DCI is complex and not fully understood. While traditionally cerebral vasospasm (CVS) was treated as the primary cause, a clear paradigm shift to a multifactorial etiology can be observed with EBI playing a significant role contributing to vulnerability to subsequent ischemic insults. Ecker and Riemenschneider (1951) first documented the presence of CVS in relation to a ruptured aneurysm. Subsequently, Allcock and Drake (1963) demonstrated a clear relationship between arterial narrowing a clinical symptoms. While CVS and DCI have been recognized entities for over 70 years, the precise mechanism for vessel narrowing has not been established. Numerous compounds have been proposed.

Blood degradation products, with oxyhemoglobin being the most widely recognized, have been proposed as the trigger of a molecular cascade that leads to CVS (Macdonald et al., 1991a; Toda, 1990; Toda et al., 1980).

Diminished levels of nitric oxide (NO) and nitrous oxide synthase (NOS), both potent vasodilators, have been demonstrated after SAH (Hino et al., 1996; Pluta et al., 2005).

Endothelin-1 (ET-1), a potent vasoconstrictor, has been shown to increase after SAH (Juvela, 2000;

Seifert et al., 1995), and its administration has been shown to reduce vasospasm (Macdonald et al., 2012; Vatter et al., 2005). However, in a multicenter trial ET-1 antagonists have failed to demonstrate outcome benefits (Macdonald et al., 2011).

Blood–brain barrier (BBB) breakdown and an inflammatory response has been shown to occur following SAH (Doczi et al., 1986; Fassbender et al., 2001).

Recent reports suggest that the events occurring before the onset of DCI, during the first 72 hours after the ictus, may significantly contribute to outcome following SAH. The effect of EBI may or may not be independent of DCI. It is recognized that aneurysm rupture is accompanied by a severe rise of intracranial pressure (ICP) and decreases in cerebral perfusion pressure (CPP), often to the point of cerebral circulatory arrest. These mechanisms may be responsible for cessation of bleeding; therefore, having a beneficial effect (Nornes, 1973). The ensuing global cerebral ischemia, however, causes activation of several key pathophysiological pathways that may, in consequence, lead to direct nervous tissue injury as well as increased tissue vulnerability to secondary insults. These include initiation of cell death mechanisms, BBB disruption, inflammation, development of cerebral edema, loss of autoregulation, and cortical spreading depolarization.

Subarachnoid Injection Model

The cisterna magna blood injection model, which was introduced by Solomon et al. (1985) in rats, is the most common animal model of SAH used in experimental studies (Marbacher et al., 2010). Subsequently, injection of blood was tried in the prechiasmatic cistern (Echlin, 1971), as well as directly next to an intracranial artery (Tsuji et al., 1996) The drawback of the initial technique in the rat is the unreliability of the time course of vasospasm, which does not correlate with that seen in humans after SAH (Solomon et al., 1985; Verlooy et al., 1992). This led to expansion of the model into different species, as well as development of the second injection technique, whereby a second application of blood into the same subarachnoid cistern is performed 24–48 h after the first. The second injection resulted in a more reliable vasospasm period, peaking at day 5 in the rat (Vatter et al., 2006). Similar results were observed with different animals, confirming the reliability of the model. Clinical assessment of vasospasm in the rat remains challenging. Quantitative assessment of angiography is difficult due to the caliber of vessels; therefore, often casting methods are used, requiring sacrifice of animals and precluding longer-term observation (Turowski et al., 2007). The subarachnoid injection model was applied to the rabbit and canine with good results (Edvinsson et al., 1982; Kuwayama et al., 1972; Varsos et al., 1983; Zhou et al., 2007). Interestingly, the second injection technique was proven to be beneficial in the dog (Varsos et al., 1983) but not in the rabbit (Zhang et al., 2007). Subarachnoid blood injection remains the most common method used in canines. The temporal profile of vasospasm is very well documented in this species, with onset at day 4 and resolution at day 10 (Yoshimoto et al., 1993). Furthermore, the significant similarities of SAH induced in the canine model with that of humans, including the lack of angiographic response to treatment with calcium channel blockers, makes it attractive for research (Varsos et al., 1983). Angiographic assessment of vessel diameter is easily obtained in the dog. Similarly, neurological assessment has been proven to be reliable and standardized, making the canine injection model one of the most commonly used in SAH research (White et al., 1979; Yatsushige et al., 2005).

A common drawback for all traditional subarachnoid injection models is its inability to reproduce the acute injury accompanying SAH, i.e., early brain injury consisting of mechanical trauma, transient, global reduction of blood flow, and the subsequent pathological events. Sehba et al. (2013) have described a method to overcome this shortfall. They propose a controlled injection of blood in the cisterna magna with concomitant monitoring of ICP to allow targeting of a specific CPP reduction, resulting in transient global ischemia, thus mimicking human SAH (Nornes, 1973; Trojanowksi, 1984b). While few studies have used this method, it provides an attempt at standardizing the end point of the induced SAH. Currently, there is no consensus as to the desired duration of infusion and volume of blood to be deposited in the subarachnoid

space, leading to difficulty in comparing results.

Subarachnoid hemorrhage does not start in the cisterna magna in humans and, therefore, uncertainty exists whether some observed physiologic changes in the injection models described may be a result of direct irritation to the brain stem, e.g., blood pressure elevation (Schwartz et al., 2000). Secondly, measurement of ICP from the cisterna magna during infusion of blood may not give reliable information. Finally, the degree of ICP elevation is slower and artificially controlled with the rate of blood infusion, and does not mimic the acute nature of SAH.

Direct and Endovascular Arterial Puncture

The main limitation of the subarachnoid injection method related to the lack of a distinct ictal event and associated physiologic alterations has been addressed with the development of the direct arterial puncture method. First described by Barry et al. (1979) using an open transclival approach to access the basilar artery, more recently, endovascular techniques using a microfilament have been use to puncture either the basilar artery, the internal carotid artery, or the middle cerebral artery (Bederson et al., 1995; Parra et al., 2002; Schwartz et al., 2000; Veelken et al., 1995). The direct puncture model, whether using an open approach or endovascular techniques, results in significant rates of vasospasm (Parra et al., 2002; Saito et al., 2001). The degree of vessel constriction has been demonstrated to be between 20% and 62% (Kamii et al., 1999; McGirt et al., 2002). The time course of vessel constriction after SAH using the endovascular puncture method in mice demonstrated an initial phase on day 1 and a second phase on day 3 after puncture (Kamii et al., 1999; Lin et al., 2003). The endovascular puncture has also been performed using rat (Bederson et al., 1995; Veelken et al., 1995), rabbit (Logothetis et al., 1983), and primate (Landau and Ransohoff, 1968; Simeone et al., 1972) models with similar high rates and predictable time course of vasospasm.

Mouse models, due to size constraints, do not allow assessment of vasculature by means of angiography. The corrosion casting method, in which a polymer is used to replace blood in the cerebral vasculature, has been introduced to study the degree of vasospasm in mice. The corrosion casting method requires sacrificing the animals, precluding longitudinal follow-up and exact, real-time assessment of the degree of spasm, clinical symptoms, and response to proposed treatment (Hossler and Douglas, 2001). In the arterial puncture technique, the severity of the hemorrhage cannot be reliably controlled. Whether performed endovascularly or through a surgical exposure the model results in 26–50% mortality (Barry et al., 1979; Bederson et al., 1995; Logothetis et al., 1983; Parra et al., 2002). Furthermore, due to the varied severity of hemorrhage, results are often difficult to interpret. Schwartz et al. (2000) aimed to address this by introducing a “modified filament model,” where the severity of hemorrhage could be controlled by altering the diameter of the filament used to make the arterial puncture. They report being able to obtain two distinct severities of hemorrhage. Furthermore, the group where a smaller puncture was used on post-mortem examination had smaller SAH volumes than the cisterna magna injection group. However, there are no data on mortality of either group. Finally, the arterial puncture method suffers from the intrinsic limitation of not being compatible with a sham control.

On the other hand, there is now a standardized postmortem SAH grading scale to determine the degree of hemorrhage caused during an arterial puncture (Parra et al., 2002). Furthermore, reliable neurobehavioral assessment batteries have been used and show a good correlation with the degree if spasm in the mouse, allowing for study of therapeutic interventions (Parra et al., 2002). Finally, the benefits of using mice models, where the arterial puncture technique predominates, are related to the very well characterized murine genome. Readily available tools allow accurately mapping of the molecular alterations following SAH, as well as introduction of “knockout” or “transgenic” mice to determine the functions of specific genes and proteins.

All in all, despite the accumulation of vast amounts of knowledge about the pathophysiology of aneurysmal SAH and the development of cerebral aneurysms, there has been very little translation into routine clinical practice. Similar to other diseases where emphasis needs to be placed on prevention of

secondary injury, such as traumatic brain injury and stroke, neuroprotection in SAH has not, thus far, proven successful. The only medical treatment available for SAH remains nimodipine, with multiple failed clinical trials demonstrating a poor success rate in translation from animal models to humans.

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