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Current Methods In Preclinical Aneurysm Models

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Citation

Grüter, B.E. Current Methods In Preclinical Aneurysm Models. *J. Vis. Exp.* (199), e64935, doi:10.3791/64935 (2023).

Date Published

September 8, 2023

DOI

10.3791/64935

URL

jove.com/video/64935

Editorial

Growing knowledge on the pathophysiology of human intracranial aneurysms (IAs) has led to a deeper understanding of the processes of IA growth and rupture. In past decades, research and therapeutic strategies focused predominantly on lumen-oriented mechanical concepts to prevent or occlude blood flow into the aneurysm. However, further insights in recent years have revealed the fundamental role of biological characteristics related to the diseased vessel wall, such as aneurysm wall degeneration, thrombus remodeling, the capacity for growth, and potential IA rupture[1,2].

Preclinical animal experiments have contributed much toward the understanding of the pathophysiology of IAs. Therefore, the development and use of an appropriate animal model is of utmost importance in order to study this clinical condition in preclinical settings[3]. In preclinical models, the slight modification of experimental parameters or outcome measurement techniques may greatly affect the outcomes[4]. As a result of the increased awareness of the widespread methodological bias and obvious translational roadblocks, the establishment of standardized protocols for all steps of animal experiments, including the planning, design, execution, and reporting, is crucial to achieve reproducibility of the findings and to ultimately ensure clinical translation[5].

This collection aims to present the currently used preclinical methodologies and outcome measurement techniques to study the pathophysiology of human IAs in preclinical models.

Among the abundant preclinical aneurysm models, the endovascular perforation model for subarachnoid hemorrhage (SAH) in mice is one of the most popular. However, many studies using this model do not report on the experimental parameters, and there is huge variability in the selection of parameters (such as the filament size or anesthetics used). Consequently, the literature using this model is characterized by significant heterogeneity in the reported animal mortality and measured outcomes. Liu et al. present technical details and suggest a selection of parameters to set a standard for the endovascular perforation model[6]. Furthermore, they refine the model by performing standard magnetic resonance imaging (MRI) within 24 h of SAH induction for verification of the bleeding and the exclusion of other intracranial pathologies.

The work of Wanderer et al. describes a new aneurysm model in the rabbit[7]. Human histopathological studies have shown that IAs prone to growth and rupture are characterized by

a loss of cellularity in the aneurysm walls. Taking this fact into account, the modification of the experimental aneurysm wall—specifically to decellularize the aneurysm wall—was first described in the Helsinki rat sidewall aneurysm model[8]. Moving up the translational ladder, the presented rabbit model also takes the hemodynamic situation into account by creating autologous arterial pouch aneurysms in a true bifurcation constellation to mimic different wall conditions. The decellularized aneurysms in this model show persisting long-term patency and patterns of growth over time.

Taking the abovementioned rabbit bifurcation model as a starting point and strictly applying the 3R principles (reduce, replace, refine), Boillat et al. present a refinement of the rabbit aneurysm model[9]. Their slight modification of the surgical steps enables the creation of a stump and a true bifurcation aneurysm in one surgery. This allows for the testing of novel endovascular devices in aneurysms with different angioarchitecture and hemodynamic conditions within a single animal, as well as allowing for different wall conditions.

The article of Popadic et al. is dedicated to the creation of giant aneurysms in rabbits[10]. An autologous venous sac derived from the external jugular vein is sutured in the artificially created bifurcation between the common carotid arteries. The postoperative administration of acetylsalicylic acid and the prolonged administration of low molecular heparin are crucial points in this protocol. If the experimental steps are carefully executed, this model has extremely low morbidity and a high aneurysm patency rate and is, thus, ideal for testing novel endovascular devices.

The constant measurement of intracranial pressure (ICP) is a fundamental action taken in the clinical management of SAH. The group of Peterson et al. presents a technique to safely place a fiberoptic pressure sensor in the brain parenchyma of rats[11]. This allows the precise monitoring of the ICP with the simultaneous measurement of the mean arterial pressure (MAP) to calculate the cerebral perfusion pressure. Although specifically described for intracranial hemorrhage in rats, the same technique can be used for different pathologies characterized by an altered intracranial pressure, as well as in other rodents.

The article on cell tracing by Wanderer et al. covers more basic research-related issues[12]. In the work, the authors investigate the origin of cells that mediate aneurysm healing after endovascular treatments. In a laborious setting of surgically created sidewall aneurysms in genetically modified rats, they locally inject a lipophilic cell-tracer (CM-DiI dye) to track endothelial cells and their derivatives originating in the parent artery below the aneurysm.

In summary, the presented studies all aim toward the greater standardization of preclinical aneurysm models. The selection of the most adequate model is highly dependent on the intentions of the study. For instance, the above presented three different rabbit models all have a different focus (i.e., the aneurysm wall condition, hemodynamics, or the aneurysm size). Establishing more consistency in experimental parameters and being aware of the limitations of a selected animal model will not only increase the reproducibility of the experiments but may finally unblock the translational road from bench to bedside.

Disclosures

The author has nothing to disclose.

Acknowledgments

The author has no acknowledgments.

References

1. Gruter, B. E., von Faber-Castell, F., Marbacher, S. Lumen-oriented versus wall-oriented treatment strategies for intracranial aneurysms - A systematic review of suggested therapeutic concepts. *Journal of Cerebral Blood Flow and Metabolism.* **42** (9), 1568-1578 (2022).
2. Marbacher, S., Niemelä, M., Hernesniemi, J., Frösén, J. Recurrence of endovascularly and microsurgically treated intracranial aneurysms-Review of the putative role of aneurysm wall biology. *Neurosurgical Review.* **42** (1), 49-58 (2019).
3. Marbacher, S. et al. Systematic review of in vivo animal models of subarachnoid hemorrhage: Species, standard parameters, and outcomes. *Translational Stroke Research.* **10**, 250-258 (2018).
4. Dirnagl, U. Bench to bedside: The quest for quality in experimental stroke research. *Journal of Cerebral Blood Flow and Metabolism.* **26** (12), 1465-1478 (2006).
5. Gruter, B. E. et al. Systematic review and meta-analysis of methodological quality in in vivo animal studies of subarachnoid hemorrhage. *Translational Stroke Research.* **11** (6), 1175-1184 (2020).
6. Liu, S. et al. Endovascular perforation model for subarachnoid hemorrhage combined with magnetic resonance imaging (MRI). *Journal of Visualized Experiments.* (178), e63150 (2021).
7. Wanderer, S. et al. Arterial pouch microsurgical bifurcation aneurysm model in the rabbit. *Journal of Visualized Experiments.* (159), e61157 (2020).
8. Marbacher, S. et al. Loss of mural cells leads to wall degeneration, aneurysm growth, and eventual rupture in a rat aneurysm model. *Stroke.* **45** (1), 248-254 (2014).
9. Boillat, G. et al. Creation of two saccular elastase-digested aneurysms with different hemodynamics in one rabbit. *Journal of Visualized Experiments.* (170), e62518 (2021).
10. Popadic, B., Scheichel, F., Plasenzotti, R., Sherif, C. Microsurgical creation of giant bifurcation aneurysms in rabbits for the evaluation of endovascular devices. *Journal of Visualized Experiments.* Accepted (forthcoming).
11. Peterson, C., Hawk, C., Puglisi, C. H., Waldau, B. Intracranial pressure monitoring in nontraumatic intraventricular hemorrhage rodent model. *Journal of Visualized Experiments.* (180), e63309 (2022).
12. Wanderer, S. et al. Using a cell-tracer injection to investigate the origin of neointima-forming cells in a rat saccular side wall model. *Journal of Visualized Experiments.* (181), e63580 (2022).