

Preclinical Investigations for Thrombectomy Devices—Does it Translate to Humans?

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In the United States, 4 devices have received Food and Drug Administration clearance for intra-arterial mechanical removal of the embolus in a large vessel occlusion causing acute ischemic stroke (AIS). A number of other devices with similar indication are either beginning trials in the United States or are available for clinical use in the European Union. The goal of preclinical modeling for the intra-arterial treatment of AIS is to evaluate the safety and the efficacy of these devices quantitatively to predict how they will perform in patients, identify effective techniques for their use, or to optimize the design before introducing them into clinical trials. Safety studies should ascertain the potential for vascular trauma, propensity to generate distal emboli, and effect on the blood brain barrier, particularly in the case where the device is used to deliver energy for clot disruption. Efficacy metrics include the ability to restore flow through the occluded vessel (recanalization), the amount of flow restored to the distal territory (reperfusion), and the time needed to remove the embolus.

Large animal models of stroke amenable to the study of endovascular mechanical thrombectomy are challenging because of the anatomy of the cerebrovasculature in commonly used laboratory animals.¹ To date, most preclinical modeling uses large vessel occlusion in the extracranial circulation of the pig^{2–5} or dog,^{4,6} wherein the selected vessel is embolized with an autologous clot of varying composition. Notably, these are not models of AIS and, therefore, the traditional end points of infarct volume and neurological outcome are not applicable. Therefore, the end points of these studies are typically angiographic evidence of recanalization and pursuant damage to the vessel in which the device was operated. Importantly, the architecture of the extracranial vasculature with substantial perivascular support, external elastic lamina, and robust tunica media is quite different than the cerebrovascular arteries and, therefore, extrapolation of vascular safety in these models to the human intracranial circulation may not be appropriate. Moreover, this approach does not provide a means to measure distal emboli or flow restoration.

Currently, most preclinical models to validate thrombectomy technologies have not directly translated to the clinical arena. Herein, we review our strategy that combines in vitro and in vivo modeling to assess thrombectomy device safety and efficacy quantitatively.

In Vitro Modeling

Mechanical thrombectomy in a reproducible in vitro model system of the cerebrovascular occlusion provides novel insight into therapeutic strategies for efficient removal of clot burdens. The stability of clot engagement within the device can be visualized, and potential device-related complications can be investigated. Outcome measures which are not available in clinical trials, such as real-time quantification of flow restoration and characterization of distal emboli generated during the procedure, can be obtained.⁷ The aforesaid reproducible measurements are unique and are significant because they are associated with the device efficacy and safety, and are related to the treatment outcomes. In addition to being used for pre-clinical device testing, the mock occlusion model system acts as a promising tool for physician training. A model system of cerebrovascular occlusion is a composite that contains multiple elements, including a vascular replica, flow loop, and valid clot model.

Several methods have been developed for making a patient-specific silicone replica of regional vessel segments by modeling the cerebrovasculature from casts in human cadavers or 3 dimensional (3D) reconstructions on the basis of imaging data.^{8–11} Recently, incorporation of vessel characterization in 3D^{12–14} during the replica preparation transforms the computer design into a physical population-based model¹⁵ and vascular models with a wide range of anatomic variations.^{16,17} This progress leads to a significant reduction in the use of laboratory animals and makes the results of device testing more relevant to patients.

Human cerebral hemodynamics is achieved by connecting the aforesaid vascular replica to a precisely calibrated pulsatile flow loop. Flow sensors and pressure transducers are used to record the real-time flow and pressure during the mechanical thrombectomy, respectively. In addition to the recanalization rate, which is used as an indication of device efficacy in clinical studies, the flow sensors establish a quantitative measure of reperfusion that is the ratio of the postprocedure flow to the preocclusion flow through the test site. The previously reported data demonstrated that despite angiographic evidence of recanalization, the partial remnant embolus at the middle cerebral artery bifurcation reduced the amount of flow restored.⁷ This finding shows the importance of acquiring the flow rates because they provide an objective

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measure of the ability of the device to restore flow, which is the primary goal of the procedure.

The experimental setup allows for determination of the trajectory of the microemboli into the circle of Willis.¹⁸ By collecting and analyzing the effluent, the size and number of the disrupted microemboli generated during the thrombectomy procedure can be studied. It should be noted that these microemboli are invisible on follow-up imaging; however, their existence could predispose patients to poor clinical outcomes.

Blockage of flow resulting from a selective cerebral occlusion is achieved by introduction of a clot model into the vascular replica. The sources of thromboemboli that may cause AIS are varied, and the mechanical properties of the thromboemboli are different. Parameters, such as stiffness and elasticity, have been used to describe the mechanical features of the clinical specimens and used as references for comparison with various clot analogs.¹⁹ An understanding of bulk mechanical properties of these materials is essential for the testing of a mechanical thrombectomy system. We found that thrombin-induced human clots and thrombin-induced radiopaque bovine clots made in the laboratory better mimic fresh and aged thromboemboli, respectively, extracted from patients with stroke. The former is soft and elastic, whereas the latter is hard and prone to fragmentation. The variations of mechanical behavior between clot models and the mechanism of thrombectomy contribute to the risk of distal embolic shower. For example, in our experiments thromboaspiration combined with a clot debulking separator produced more large distal emboli (>200 μ m) as compared with embolectomy with the Merci retriever.⁷

In vitro simulation of mechanical thrombectomy lays the experimental foundation for understanding device performance and prediction of clinical outcomes. However, a comprehensive preclinical device evaluation requires in vivo animal studies to elucidate the vascular response to thrombectomy devices.

In Vivo Vascular Safety

Although thrombectomy devices have become integral tools in the armamentarium of neuro-interventionalists to treat AIS,

device-induced cerebrovascular injury has not previously been studied in a preclinical model. Based solely on intuition, we hypothesized that dragging an expanded stent through the vessel lumen would produce severe vessel damage. Therefore, we assessed the operation of stent-retrievers in the canine basilar artery (BA), with a goal to evaluate their vascular safety on angiography and histopathology. This model is challenging for these devices because of the 1.5-mm caliber of the target vessel. However, this diameter is representative of the M2 segment in humans where often these devices are deployed.

Six mongrel canines (females: mean weight, 13 kg; n=2 each arm) were randomly assigned to receive 4 passes of the Solitaire FR Revascularization device (eV3, Plymouth, MN), the Enterprise VRD (Codman Neurovascular, Raynham, MA), or the Merci V 2.0 firm retriever (Stryker Neurovascular, Fremont, CA). The canine BA was accessed through the anterior spinal artery, as previously reported.²⁰

The devices were deployed in the BA and withdrawn in the expanded state to the vertebrobasilar junction. The anterior spinal artery, in which only the microcatheter was deployed, served as the control vessel. Angiographic scoring of the vasospasm and histopathologic assessment using a quantitative grading of the scanning electron microscopy and cross-sectional hematoxylin and eosin histology were used to assess vascular integrity.

The Enterprise VRD and the Solitaire performed equally with grade 3 vasospasm on the first pass (50%–75% narrowing), which quickly resolved with intra-arterial nicardipine administration and minimal vasospasm on the subsequent 3 passes (Figure 1). The Merci device produced acute perforation of the BA and resultant subarachnoid hemorrhage after a single pass. On the basis of qualitative histopathologic and scanning electron microscopy assessment, the Solitaire and the Enterprise VRD device performed comparably when tracked through the canine BA; the luminal surface assessment on scanning electron microscopy revealed damage limited to the internal elastic lamina and occasional exposure of the smooth muscle cells. The Merci device demonstrated breach of the vessel integrity on histology and acute platelet activation on

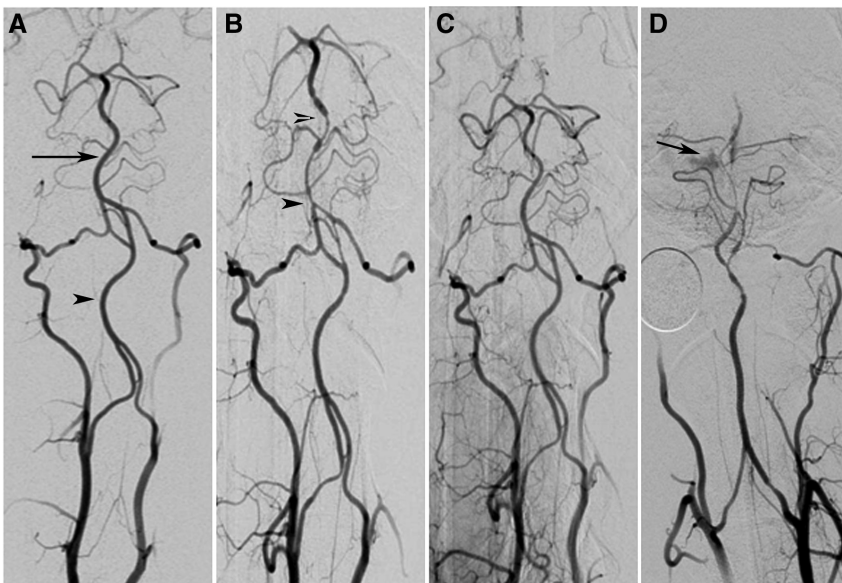


Figure 1. A, Digital subtraction angiography (right vertebral artery injection, frontal projection) showing the native anatomy of the posterior circulation in the dog before device deployment (basilar artery, arrow; anterior spinal artery, arrowhead). B, After the first pass of the Solitaire stent-triever, severe vasospasm of the basilar artery is noted (between arrowheads) that resolves with intra-arterial nicardipine (not shown). C, After 4 device deployments and passes, no further vasospasm is observed. D, A single pass of the Merci retriever produced vessel perforation with contrast extravasation (arrow) and subarachnoid hemorrhage (computed tomography not shown).

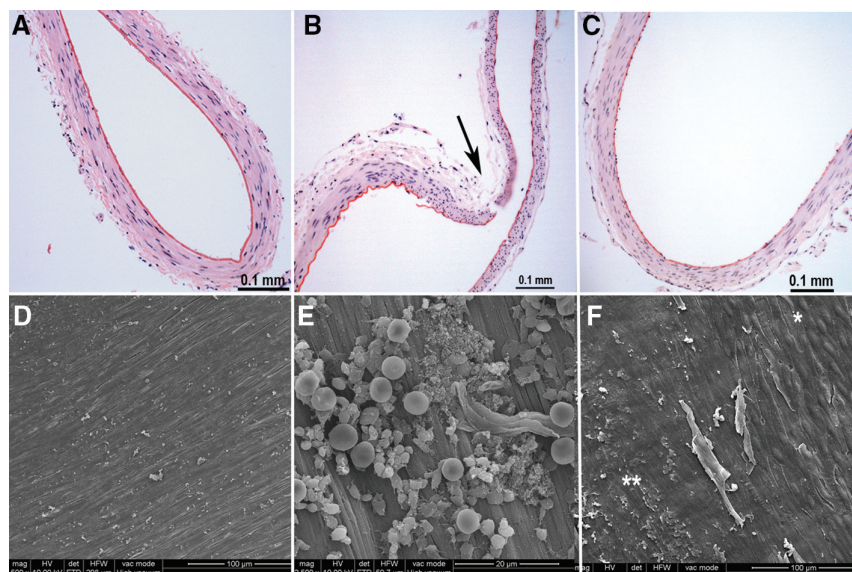


Figure 2. Cross-sectional histology (hematoxylin and eosin stain, **top**) and scanning electron microscopy (**bottom**) of the basilar artery after operation with the Solitaire stent-trieter (**A, D**) and the Merci device (**B, E**). The internal elastic lamina is intact (**A**), despite denudation of the endothelium (**D**) after operation of the stent-trieter. However, the Merci retriever induced tears to the internal elastic lamina and perforation through the media (**B**, arrow) with significant platelet aggregation (**E**). Navigation of the microcatheter through the anterior spinal artery shows an intact artery (**C**) with regions of endothelial denudation (**F**, **) along the path where the catheter is advanced. Outside the catheter track, the vessel intima is intact (**F**, *).

scanning electron microscopy (Figure 2). Microcatheter navigation in the control vessels induced focal endothelial injury along the path in which the catheter was tracked.

In summary, deployment of stent-trievers induces intimal injury that does not impact vessel integrity and is comparable to that of microcatheterization alone, albeit over a larger luminal area. In contradistinction, the Merci device in this model led to vessel perforation, contrast extravasation, and subarachnoid hemorrhage. Our hypothesis that stent-trievers produce severe vascular trauma was rejected.

Conclusions

In the future, we hope to address the limitations of the preclinical modeling approach presented herein. In particular, the interaction between the vessel wall and the embolus requires careful study to understand how the device can disrupt this bond with minimal vascular trauma and platelet activation. In addition, the fate of perforating arteries and optimization of the device to spare these small vessels must be incorporated into the modeling. Perhaps device miniaturization will soon be possible and allow for studying this technology in more relevant stroke models²¹ that account for the complexity of brain reperfusion and permit assessment of functional outcome.

Comprehensive quantitative preclinical modeling of thrombectomy that focuses on successful recanalization and reperfusion, as well as safety metrics, such as cerebrovascular safety and propensity to generate distal embolization, is needed as more devices become available. Ultimately, these models can provide a performance envelope for thrombectomy technologies that provide evidence to direct device development and best techniques to use them. In light of recent negative clinical trials^{22–24}, the need for robust preclinical optimization of intra-arterial therapies for acute ischemic stroke has never been greater.

Disclosures

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KEY WORDS: acute ischemic stroke ■ clot ■ embolic shower ■ preclinical modeling ■ recanalization ■ thrombectomy

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