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From Bench to Bedside: Utility of the Rabbit Elastase Aneurysm Model in Pre-Clinical Studies of Intracranial Aneurysm Treatment

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Summary

Pre-clinical studies are important in helping practitioners and device developers improve techniques and tools for endovascular treatment of intracranial aneurysms. Thus, an understanding of the major animal models used in such studies is important. The New Zealand rabbit elastase induced arterial aneurysm of the common carotid artery is one of the most commonly used models in testing the safety and efficacy of new endovascular devices. In this review we discuss 1) various techniques used to create the aneurysm, 2) complications of aneurysm creation, 3) natural history of the arterial aneurysm, 4) histopathologic and hemodynamic features of the aneurysm 5) devices tested using this model and 6) weaknesses of the model. We demonstrate how pre-clinical studies using this model are applied in treatment of intracranial aneurysms in humans. The model has a similar hemodynamic, morphological and histologic characteristics to human aneurysms and demonstrates similar healing responses to coiling as human aneurysms. Despite these strengths however, the model does have many weaknesses including the fact that the model does not emulate the complex inflammatory processes affecting growing and ruptured aneurysms. Furthermore the model's extracranial location affects its ability to be used in preclinical safety assessments of new devices. We conclude that the rabbit elastase model has characteristics that make it a simple and effective model for preclinical studies on the endovascular treatment of intracranial aneurysms however further work is needed to develop aneurysm models that simulate the histopathologic and morphologic characteristics of growing and ruptured aneurysms.

Keywords

Animal Model; Endovascular Treatment; Interventional Neuroradiology; Intracranial Aneurysm

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Introduction

Intracranial aneurysms are increasingly treated with endovascular therapies. A number of devices have been developed to improve the safety and efficacy of endovascular intracranial embolization including coils, modified coils, stents, glues, intraluminal flow diverters and intrasaccular flow diverters. A number of preclinical trials based on animal studies have been performed testing the safety and efficacy of these devices prior to use in humans. Such trials have provided valuable information regarding potential pitfalls of newer devices in treatment of aneurysms as well as information regarding the mechanism of action of newer devices.

Because of the importance of pre-clinical studies in helping practitioners and device developers improve the tools used in endovascular treatment of intracranial aneurysms, an understanding of the major animal models used in such studies is important. Currently, the New Zealand rabbit elastase induced arterial aneurysm of the common carotid artery is one of the most commonly used model in testing the safety and efficacy of new endovascular devices. In this review we discuss 1) the various techniques used to create the aneurysm, 2) complications of aneurysm creation, 3) the natural history of the arterial aneurysm, 4) the histopathologic and hemodynamic features of the aneurysm and 5) devices that have been tested using this model. Our primary focus is to demonstrate how pre-clinical studies using this model have been applied in the treatment of intracranial aneurysms in human patients.

Aneurysm Creation

The New Zealand White Rabbit Elastase induced arterial aneurysm is created through a combination of open and endovascular techniques. The classic techniques used to create the arterial aneurysm have been previously described¹. Following administration of anesthesia, the right carotid sheath and the right common carotid artery (RCCA) are surgically exposed. A 1-2mm beveled arteriotomy is created in the RCCA and a 5-French vascular sheath is inserted retrograde into the mid portion of the RCCA. The origin of the RCCA is identified with a small injection of iodinated contrast. Then, using fluoroscopic guidance, a 3-French balloon catheter is advanced through the sheath to the RCCA origin and inflated with iodinated contrast material. Following confirmation of occlusion of the RCCA origin with another small injection of contrast material, 100U of Elastase is incubated within the lumen of the proximal RCCA for 20 minutes. After this, the balloon is deflated and the catheter system is removed. The vessel is then ligated in its midportion and the skin is closed. Two weeks following the treatment, the saccular aneurysm is formed. Figure 1 demonstrates the steps used in the creation of the aneurysm model.

Modifications to the Model

A number of investigators have proposed modifications in creating the elastase arterial aneurysm model. The occurrence of collateral vessel branches between RCCA and arteries supplying the trachea could lead to washout of elastase to the trachea resulting in hemorrhagic necrosis. Krings et al proposed the following modifications to the abovementioned model: 1) injection of elastase by the region of the aneurysm neck rather than the mid RCCA, 2) rule out elastase leakage to arteries supplying the trachea using

angiography and 3) lowering the dose of elastase to 20U instead of 100U². Hoh et al demonstrated that by applying an aneurysm clip to the RCCA origin rather than a balloon catheter, elastase could be kept within the RCCA during incubation with consistent results³. Ding et al proposed a modified aneurysm creation technique in which the entirety of the RCCA including its origin at its junction with the subclavian and brachiocephalic arteries was completely exposed and isolated. This allowed for assessment of the presence of branch vessels which could be ligated avoid complications from flow of elastase to the trachea and allow for increased concentrations of elastase in the aneurysm sac⁴. Other modifications such as adjusting the position of the ligation, adjusting the position of the inflated balloon, injuring the aneurysm neck, and using the LCCA instead of the RCCA, have been proposed as techniques to alter the volume, neck size and configuration of the aneurysm respectively⁵⁻⁸.

Complications of Aneurysm Creation

Creation of aneurysms using the rabbit elastase model approach is not without complications. One of the most commonly reported complications is tracheal necrosis following application of elastase to the RCCA. This complication occurs due to the origin of the tracheoesophageal artery arising from the RCCA leading to elastase deposition in the trachea^{9,10}. One series of over 700 procedures in rabbits demonstrated that the aneurysm creation process is associated with an 8.4% risk of mortality related to factors such as anesthesia, failure to thrive, self mutilation (by biting at sutures) and stroke¹¹. Other complications that have been reported are creation of thoracic aortic aneurysms, laryngeal paralysis due to damage of the recurrent laryngeal nerve, tracheitis-laryngitis due to intubation, pneumonia and vessel thrombosis¹²⁻¹⁴.

Aneurysm Natural History, Morphology and Histology

Histopathologic studies of aneurysms created using the rabbit elastase model demonstrate many similarities to aneurysms in humans. In the elastase model, the elastic lamina within the aneurysm wall is markedly attenuated secondary to elastase deposition. This feature simulates the characteristics of human aneurysms where the internal elastic lamina is substantially diminished. The aneurysm wall of the rabbit elastase model has a high concentration of smooth muscle cells, similar to human aneurysms. The endothelium of the aneurysm remains intact, also simulating features found in human aneurysms^{13,15}. Other models which use a venous pouch fail to simulate the histological characteristics of human aneurysms. The use of sutures in the venous pouch model at the aneurysm neck and dome results in an extensive healing and fibrotic response about the sutures thus limiting the applicability of these types of models in assessing post-embolization healing¹⁶⁻¹⁸.

Another advantage of the rabbit elastase model is its favorable natural history. When left untreated, these aneurysms remain patent for long periods of time¹⁹⁻²¹. One study followed 20 elastase-induced saccular aneurysm models for 24 months and found no cases of spontaneous thrombosis and no changes in aneurysm geometry over this time period²². This long-term stability is important as it simulates the characteristics of most unruptured intracranial aneurysms in humans. One disadvantage of this stability is that it is difficult to

simulate the characteristics of growing and ruptured aneurysms. The long term patency of saccular RCCA aneurysms in the rabbit elastase model differs substantially from the spontaneous healing seen in the rabbit elastase abdominal aortic aneurysm model. This is thought to be due to differences in the hemodynamic stresses in the side-wall type abdominal aortic aneurysm and bifurcation type RCCA aneurysm. The side-wall abdominal aortic aneurysm model is exposed to lower shear stresses than the RCCA aneurysm, thus resulting in a higher propensity to spontaneously thrombose and heal²³²⁴. The swine model of intracranial aneurysms, another popular model, also has short-term aneurysm patency¹⁶²⁵. The spontaneous healing of these aneurysms is thought to be due to the robust neointimal proliferation response seen in pigs following endothelial injury. Such a robust reaction is not appreciated in rabbit models¹⁶²⁶.

Another important factor in designing intracranial aneurysm models is ensuring that the pre-clinical model has similar morphological characteristics to human aneurysms. The average diameter and height of the rabbit elastase aneurysm model is 4.5mm and 7.5mm respectively¹. The distribution of sizes seen in creation of this model are similar to the distribution of sizes seen in human aneurysms²⁷. In addition, the diameter of the parent artery is similar to that of intracranial arteries (approximately 4mm)²⁷. Modifications can be made to increase the size of the aneurysm as well. Ding et al demonstrated that by creating a RCCA right-jugular arteriovenous fistula, larger aneurysms, measuring approximately 15mm in maximum dimension, can be formed²⁸. As mentioned above, changing the position of the ligation can be used to change aneurysm size; and neck size can be adjusted by changing the position of the balloon at the RCCA origin⁶⁷. In general, the morphology and size of the aneurysm can be designed to model the type of aneurysm that is desired with consistent and predictable results⁴⁵²⁹³⁰.

Because hemodynamic factors play a large role in aneurysm formation, growth and recanalization following endovascular treatment, it is important for a pre-clinical model to simulate the hemodynamic characteristics of human models. In a study of 51 elastase-induced RCCA aneurysms, Zeng et al found that the range in values of pressure, wall shear stress, and oscillatory shear index were all within the ranges seen in human aneurysms. The number of recirculation regions seen within the aneurysms was also similar to that seen in human aneurysms³¹³². The hemodynamic similarities between the rabbit model and humans is due to similarities in size and vessel curvature of the rabbit aneurysms. Other animal models such as the venous pouch sidewall model found in canines fail to simulate the flow seen in human aneurysms as human aneurysms are rarely present along the side-walls of long, straight vessels. Because of the curvature of the parent vessel of the RCCA aneurysm in rabbits, there is substantial inertia-driven flow in the aneurysm. This contrasts to the shear-driven flow seen in sidewall aneurysms³³. Because most human aneurysms are located at bifurcation points or vessel curvatures, these are subject to high rates of inertia driven flow, contributing to aneurysm growth and recanalization.

Device Testing

A number of pre-clinical studies have been performed using the rabbit elastase model. Such studies have been performed to assess the safety and efficacy of aneurysm treatment as well

as the healing response following aneurysm embolization. In general, studies examining the efficacy of these devices include a combination of imaging and histopathologic studies to determine aneurysm occlusion rates and mechanism of healing. A variety of imaging modalities have been tested to evaluate the angiographic occlusion rates including conventional angiography, intravenous digital subtraction angiography, CT angiography, phase contrast MRA, time of flight MRA and contrast enhanced MRA³⁴⁻³⁹. All of these techniques have been shown to be effective, however, conventional angiography remains the gold standard for evaluation of aneurysm patency following coil embolization, stenting and flow diverter treatment^{35,40}. For histologic characterization, an ordinal histologic scale that combines data on recanalization/coil compaction, neck healing, and dome healing using both gross and microscopic images⁴¹.

Bare platinum coils have been the most extensively tested devices in the rabbit elastase model. Histopathologic and angiographic studies have demonstrated that bare platinum coils are highly effective in obliterating the aneurysm in both humans and rabbits⁴². Interestingly, the healing response of the rabbit model closely resembles that found in humans. Rabbit studies of bare platinum coil embolization demonstrate early thrombus formation within the aneurysm sac within days of embolization. This is followed by infiltration of the aneurysm dome by fibroblasts and inflammatory cells up to four weeks following embolization. Fibroblasts deposit a loosely packed extracellular matrix of fibrin and collagen in the aneurysm dome⁴². The tissue response in the aneurysm dome stops at approximately 4 weeks post-embolization due to apoptosis of the fibroblasts and inflammatory cells. After 4 weeks, the aneurysm dome is filled with acellular loose connective tissue, similar to what is seen in humans⁴³. Long-term studies of the aneurysm neck of the rabbit aneurysm demonstrate a thin hypocellular layer of tissue with a sparse number of endothelial cells⁴³. This is similar to the response seen in humans as well and contrasts to the responses seen in pigs where a thick layer of neointima forms²⁵.

Modified coils such as the Matrix and HydroCoil have been tested in the rabbit elastase model as well and have demonstrated similar angiographic results to humans⁴⁴. One series embolized 33 rabbit aneurysms with either Matrix coils, HydroCoils or bare platinum coils. This study found that HydroCoils were associated with lower rates of coil compaction, higher rates of angiographic occlusion and improved long-term occlusion rates when compared to Matrix and bare platinum coils⁴⁵. In addition, Matrix coils were not associated with improved aneurysm occlusion and recanalization rates when compared to bare platinum. These results are similar to those seen in the HELPS trial which demonstrated higher rates of aneurysm recanalization in bare platinum compared to HydroCoils⁴⁶ and the MAPS trial which demonstrated similar aneurysm occlusion and recanalization rates between Matrix and bare platinum trials⁴⁷. Cruise et al tested HydroCoils in rabbit elastase aneurysms and found high rates of long-term occlusion and a two-fold increase in volumetric filling of the aneurysm sac, similar to findings in human studies⁴⁸. These findings have been corroborated by other pre-clinical and clinical studies^{44,49}.

This model has also been used in preclinical studies of aneurysm stenting and stent-assisted coiling. In a study of 10 rabbits, Hans et al applied porous stents with and without detachable coils and found high rates of aneurysm occlusion using both techniques⁵⁰. Krings

et al tested stent assisted coiling and found that porous stents resulted in higher rates of aneurysm recanalization than covered stents⁵¹. In addition, Kring's et al demonstrated comparable rates of in-stent stenosis to those seen in human aneurysms treated with stent-assisted coiling⁵². As mentioned above, the curvature of the parent vessel of the rabbit elastase aneurysm allows for accurate characterization of intra-aneurysm flow dynamics both pre- and post-treatment. The hemodynamics of the stent-coiled and stented rabbit aneurysm closely resemble those seen in models of human aneurysms³³. This is likely the reason behind the similar rates of aneurysm occlusion seen in humans and rabbit aneurysms treated with stenting and stent-coiling.

Many animal models such as the canine sidewall aneurysm model and rabbit model were instrumental in the development and testing of flow diverters⁵³⁻⁵⁵. The rabbit model was extensively used in the development and testing of flow diverter devices created with modern braiding technology. Because flow diverters reconstruct the parent vessel, they can be used in a wide variety of aneurysm sizes and morphologies. Initial testing of flow diverter devices were focused on determining the optimum porosities and pore densities of flow diverters. Sadasivan et al found that a medium porosity performed better than high and low porosity devices in limiting intraaneurysmal flow⁴⁰. In a later study, Sadasivan and found that increasing pore density was the most critical factor in modulating efficacy of flow diverters⁵⁶. Such work paved the way for the Pipeline Embolization Device, a braided bimetallic endoluminal implant. Initial studies in the rabbit model found complete and near complete occlusion rates of 53% and 35% respectively, similar to rates seen in human studies⁵⁷. One of the concerns regarding this device was the patency of branch vessels covered by the struts. Studies in the rabbit model have demonstrated high rates (up to 100%) of branch artery patency, similar to findings in clinical studies⁵⁸. In addition, rates of parent artery compromise from neointimal hyperplasia are low^{57,59}. Mechanisms of healing following flow diverter treatment have been studied using rabbits as well. Initial studies suggest that endothelial progenitor cell migration to the flow diverters is essential to neointima formation and reendothelialization of the aneurysm neck following treatment⁶⁰.

Intra-aneurysmal flow diverters are the newest devices to make the jump from bench to bedside using the rabbit elastase model. In a study using 24 elastase induced aneurysms in rabbits, Ding et al studied the efficacy of the Woven EndoBridge occlusion device. These authors found high rates of complete and near-complete occlusion. Aneurysms progressively occluded with increasing follow-up. Similar to coil embolization, histopathologic studies demonstrated loose connective tissue and organized thrombus in the aneurysm dome⁶¹. These results have been corroborated in other animal studies as well as in human studies³⁹. Current small case series have demonstrated that the Woven EndoBridge device has a lot of promise for the treatment of wide neck bifurcation aneurysms⁶².

A number of pre-clinical devices have been tested in the rabbit model that have yet to be tested in humans. Due to the poor healing and fibrotic response seen in both rabbit and human saccular aneurysms following coil embolization, Kallmes et al tested a collagen-based coil in the rabbit model and found that collagen based coils had a marked cellular response and dense matrix deposition with high rates of progressive occlusion. This contrasts to the low rates of progressive thrombosis and loose matrix deposition seen with

bare platinum coils. Other coil modifications that have been tested include polyvinyl alcohol coils covered in basic fibroblast growth factor. These coils have been found to stimulate aneurysm healing in the aneurysm dome and neck when compared to bare platinum coils⁶³. The Luna aneurysm embolization system is another intra-saccular flow diverter similar to the Woven EndoBridge system that has been tested in rabbit models and shown to be effective⁶⁴. But to date, there are no reports of the use of this device in humans. Polyurethane covered stent grafts have been tested in the rabbit elastase model as well with high rates of aneurysm occlusion and low rates of in-stent stenosis however these have not been used in humans. Other devices that have been shown to be effective in rabbits, but not yet tested in humans include asymmetric vascular stents, nanofiber covered stents, variable porosity flow diverters, biodegradable flow diverters, magnetic microparticles,⁶⁵⁶⁶⁶⁷⁻⁷¹.

Other Advantages

The rabbit elastase model has a number of other advantages. For instance, the saccular aneurysm model can be used as a training tool for neurointerventionalists. Because of the ability to “design” both easily treatable and difficult to treat aneurysms, this model can be used to train practitioners in treatment of a wide variety of aneurysm morphologies⁷². Studies using the rabbit elastase model have demonstrated that using the rabbit model helps in the development of proficiency with endovascular techniques and device deployment among neurointerventional trainees⁷³. It is important to note however that access systems are typically limited to 7 Fr systems and therefore commonly used setups with long sheaths are not possible. In addition, training multiple physicians on a single model is complicated by the limited amount of contrast and fluids that can be delivered to the animal, high rates of anesthesia related mortality and the fact that each femoral artery can only be accessed once due to the fact that the femoral artery is generally ligated after each intervention.

Pitfalls

Histologic Pitfalls

As with any disease model, the rabbit elastase model is not the perfect representative of the intracranial aneurysm disease process. As mentioned above, the rabbit elastase model serves as a model only for non-growing, stable, unruptured aneurysms. Thus, histologic and molecular studies of this model cannot be applied to growing or ruptured aneurysms as these aneurysms are more biologically complex with high concentrations of inflammatory cells, something that is not seen in the wall of the untreated rabbit elastase model⁷⁴⁷⁵. For example, in a study of 24 unruptured and 42 ruptured aneurysms, Frosen et al found that ruptured aneurysms were more likely to have macrophage and T-cell infiltration, smooth muscle cell proliferation, apoptosis, luminal thrombosis and de-endothelialization⁷⁵. The structure of the aneurysm wall in the rabbit elastase model is generally homogeneous and does not include regions of atherosclerotic thickening or regions of extremely thin walls such as those seen in both ruptured and unruptured human aneurysms⁷⁵. Prior studies in humans have demonstrated that the aneurysm wall of human aneurysms is in no way homogeneous in nature as aneurysms are known to develop atherosclerosis and have areas of mural tearing⁷⁵⁷⁶. Because these aneurysms are essentially a stump of the internal carotid artery, all created with generally similar techniques, there is very little variation in the

structure and biology of aneurysms between individual rabbits. However in humans we see a wide variability in the size, structure, vulnerability and geometry of unruptured aneurysms⁷⁵⁷⁷.

Device Safety and Efficacy

While the rabbit model has been extensively used in the development and testing of various endovascular devices, it is by no means a perfect model for assessment of device efficacy and safety. As described above, the rabbit elastase model does not emulate the biologic conditions of unstable growing or ruptured aneurysms. As such, it is possible that devices or treatments that may help in improving outcomes of ruptured or growing aneurysms may not prove of benefit in the thick-walled, stable, unruptured aneurysms of the rabbit elastase model. Conversely, it is also possible that devices that are deemed effective in treating the unruptured aneurysms of the rabbit model may not be effective in treating ruptured or unstable growing aneurysms. In addition, in some cases, device efficacy studies can yield different results in the rabbit model when compared to human studies. For example, in a study of large neck bifurcation aneurysms treated with the WEB device, Cognard et al found that over 70% of aneurysms had worsening of aneurysm filling on follow-up angiography compared to a rate of just 13% in pre-clinical rabbit studies⁶¹⁷⁸. Lastly, the extracranial location of these aneurysms adjacent to the thoracic cavity exposes devices to stresses due to the respiratory and cardiac cycles that they would not be exposed to in the brain which could impact the translatability of efficacy results from preclinical to clinical studies.

Aside from concerns regarding device efficacy, device safety is difficult to assess due to the extracranial location of the aneurysms and the thick aneurysm wall. Because the aneurysm wall is thicker than that seen in most human histologic studies, certain complications such as intraoperative aneurysm wall perforation are exceedingly rare in the treatment of rabbit aneurysms. Furthermore, due to the extracranial location, it is impossible to assess the potential intracranial complications that could potentially result from placement of different coils or flow diverters. For example, there have been several reports of hydrocephalus possibly due to a chemical meningitis among patients treated with HydroCoils⁷⁹. However, there was no way that preclinical studies on treatment of extracranially located aneurysms in the rabbit model could explain or predict this complication. Likewise, with the PED, post treatment intraparenchymal and subarachnoid hemorrhages occurred in 2.4% and 0.6% of patients respectively in the IntrePED registry. The exact cause of these complications is unknown, but again, preclinical studies in the rabbit model could not have predicted this complication given the extracranial location⁸⁰. Likewise, in PED patients there have been higher rates of perforator infarcts and thromboembolic complications than would be expected from preclinical rabbit studies⁸⁰⁸¹.

Conclusions

In conclusion, the rabbit elastase model has characteristics that make it a simple and effective model for preclinical studies on the endovascular treatment of intracranial aneurysms. The model has a similar histologic appearance to human aneurysms and demonstrates a similar healing response to endovascular coiling as human aneurysms. The

morphology and hemodynamic characteristics of these aneurysms is similar to human intracranial aneurysms. In addition, many preclinical studies of new devices such as flow diverters and modified coils in rabbit aneurysms have yielded similar results in the treatment of human aneurysms. Despite these strengths however, the model does have many weaknesses including the fact that the model does not emulate the complex inflammatory processes affecting growing and ruptured aneurysms. Furthermore the model's extracranial location affects its ability to be used in preclinical safety assessments of new devices. Further work is needed to develop aneurysm models that simulate the histopathologic and morphologic characteristics of growing and ruptured aneurysms.

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Figure 1.
Creation of Rabbit Elastase Aneurysm Model

This cartoon illustrates the operative process used to create the rabbit elastase aneurysm model. Following exposure of the right carotid sheath and creation of a small arteriotomy, a sheath is introduced into the right common carotid artery. A balloon is introduced through the sheath and placed at the origin of the right common carotid artery and inflated. The right common carotid artery is ligated. Following this, elastase is introduced into the artery and allowed to incubate for 20 minutes. The sheath and balloon are then withdrawn and the

superior aspect of the aneurysm is cinched off. The aneurysm continues to grow and then generally stabilizes at one month due to a combination of elastin digestion and hemodynamic forces.

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