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Animal models of vascular stenting

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Throughout the 30-year history of vascular stents, from their initial conception to current drug-eluting and bioresorbable technologies, animal models have played an instrumental role in the development of vascular stents. From rodents to rabbits, dogs, sheep, and swine, a variety of animal models for the evaluation of vascular stents exist, each being balanced with a unique set of advantages and shortcomings. With the appropriate selection of species and anatomy, animal models can be used to provide insight into the pathophysiology of vessel healing and restenosis, to confirm the feasibility of new endovascular technologies, to assess the potential efficacy of a stent at improving specific clinical outcomes, and to establish reasonable safety of a stent for a specified clinical use. This review provides an overview of the predominant animal models used for evaluating vascular stents and the translation of these models to the clinical setting.

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Introduction

From the earliest, relatively primitive ''coil spring graft'' designs to today's more complex combination stents with bioactive components, animal models have played an integral role in the development of vascular stents over their 30-year history [1–3]. Stents are endovascular prosthetics designed to provide mechanical support to maintain patency of a vessel following the treatment of a luminal occlusion. While used to treat a variety of arteries and even veins, the most common application of vascular stents is in the treatment of coronary artery disease, the leading cause of morbidity and mortality worldwide [4]. As such, the coronary application is largely the focus of this review on animal models; however, many of the principles discussed herein are applicable across the breadth of anatomies treated with vascular stents.

Fundamentally, there are three families of vascular stents used in clinical practice today, including:

- Bare metallic stents (BMS), the first family which established the feasibility of stents in improving clinical outcomes over balloon angioplasty alone,
- Drug-eluting stents (DES), which use BMS as a platform for the localized delivery of bioactive agents to prevent restenosis and/or promote healing, and
- Bioresorbable scaffolds (BRS), which deliver bioactive agents like a DES but from a transient, fully resorbable platform.

Through the history of vascular stents, animal models have been developed, evaluated, and matured in parallel in order (a) to provide insight into the pathophysiology of vessel healing and restenosis, (b) to test the feasibility of new endovascular technologies, (c) to assess the efficacy of a stent

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at potentially improving specific clinical outcomes, and (d) to establish reasonable safety of a stent for a specified clinical use. An important point of distinction in regards to animal models for vascular stents, the subject of this review, is that these are not one and the same as animal models for atherosclerosis or cardiovascular disease (CVD) for which references are provided [5–9]. While the latter models for CVD are designed for the investigation of the pathophysiology of vascular diseases and can be applied as models for vascular stenting, animal models for vascular stents alternatively focus on the process of vascular healing and potential complications associated with an endovascular implant, one of the most critical of which being in-stent restenosis (ISR).

Animal models

A variety of species have been employed for the evaluation of vascular stents, including rodents, rabbits, swine, sheep, goats, dogs, and nonhuman primates. Each model has both advantages and shortcomings in the application of vascular stenting as detailed in the following.

Small animal models

Small animal models, inclusive of mice, rats, guinea pigs, and rabbits, have been used extensively in the evaluation of atherosclerosis, vascular responses to injury, and restenosis following device implantation. Collectively, small animals have the attributes of being low cost, readily available, and easy to house and handle and are available in a range of genotypic and phenotypic backgrounds. Further, in rodents in particular, an array of molecular markers is available for investigating biological mechanisms. Shortcomings of rodent models include the size limitations, the requisite design of custom devices for implant, the requisite use of elastic arteries (e.g. aorta) which tend to be less prone to injury relative to muscular arteries, and the tendencies for minimal thrombus formation, only modest neointimal hyperplasia, and largely smooth muscle rich neointima that bears little resemblance to that observed in humans [10]. Together these features, as well as underlying differences in metabolism, have brought into question the translational applicability of these models to the clinical setting, as a number of false positives have been obtained in rodent studies evaluating anti-restenotic therapies [11–13]. Nonetheless, the use of rodents as models for vascular stenting has and continues to provide valuable mechanistic insight into device-related vascular healing and can serve as a high throughput screening tool for novel therapeutic targets and anti-restenotic therapies, especially considering the diversity of transgenic and knockout strains available that can mimic human conditions [14–18].

In contrast to rodents, rabbits as a model for vascular stenting offer a balance of attributes of small and large animal models, being readily available, easy to house and handle, and offering modified or transgenic models while being of sufficient size to allow for the evaluation of commercial stents, clinically relevant *in vivo* imaging (e.g. angiography), and paired evaluation of two devices (one in each iliac artery) in the same animal. Thus, rabbits are a commonly employed model for vascular stents. With regards specifically to the safety evaluation of coronary stents, the rabbit iliac artery model has served as a reliable model secondary to the porcine coronary artery model [19–21]. However, the shortcomings of using the rabbit iliac model is that it utilizes a nontarget site for coronary stents, and its response is more akin to that of an elastic artery, having only modest neointimal proliferation as compared to muscular porcine coronary arteries even with high overstretch injury [10,19,22].

Large animal models

Swine

Swine are the standard model used in the evaluation of vascular stents as their heart and vasculature are of similar anatomy and size to that of humans. This anatomical similarity enables the use of procedures, products and target endpoints (e.g. stent thrombosis, myocardial infarction) of direct clinical relevance [23]. In particular, the ability to use imaging tools, such as optical coherence tomography (OCT) and intravascular ultrasound (IVUS), and to be able to directly correlate this *in vivo* imaging to histology has proven valuable for the interpretation of imaging in the clinical setting [24–26]. The general physiology and coagulation systems of swine closely parallel that of humans, and the character of the neointima induced following injury or implant likewise parallels that of humans [27–30]. The disadvantages of animal and housing costs are partially offset by the ability to implant two to three devices in the main coronary arteries, and other arteries, such as the internal thoracic, also are appropriate for implantation. A key limitation to the common use of domestic farm swine is their rapid growth rate and high body weight potential (>400 kg) that imparts logistical challenges in long term studies, including limitations on handling and equipment. This has been overcome, in part, through the use of miniature swine, such as Yucatan, Sinclair, Göttingen and Hanford strains that maintain more modest body weights into adulthood [31–35]. And while notably more limited than those available for small animal models, there has been increasing development of swine-specific products and assays to expand the tools available for more in-depth analysis of tissues, such as microarrays for gene expression following stent implantation [35,36].

Sheep

Sheep have a docile nature, a coagulation and fibrinolytic system with similarities to humans, and a coronary anatomy well-suited to the evaluation of vascular stents [10,37]. The responses to stent-induced injury in ovine coronary arteries

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