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STATE-OF-THE-ART PAPER

The Pre-Clinical Animal Model in the Translational Research of Interventional Cardiology

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Scientific discoveries for improvement of human health must be translated into practical applications. Such discoveries typically begin at "the bench" with basic research, then progress to the clinical level. In particular, in the field of interventional cardiology, percutaneous cardiovascular intervention has rapidly evolved from an experimental procedure to a therapeutic clinical setting. Pre-clinical studies using animal models play a very important role in the evaluation of efficacy and safety of new medical devices before their use in human clinical studies. This review provides an overview of the emerging role, results of pre-clinical studies and development, and evaluation of animal models for percutaneous cardiovascular intervention technologies for patients with symptomatic cardiovascular disease. (J Am Coll Cardiol Intv 2009;2:373–83) © 2009 by the American College of Cardiology Foundation

The invasive/noninvasive therapies of cardiovascular disease have advanced dramatically over the last 2 decades. Such advances typically begin with basic research, then progress to the clinical level. Scientists are increasingly aware that this bench-to-bedside approach to translational research is really a 2-way street. Basic scientists provide clinicians with new tools for use in patients and for assessment of their impact, and clinical researchers make novel observations about the nature and progression of disease that often stimulate basic investigations. In particular, in the field of interventional cardiology, percutaneous cardiovascular intervention has evolved from a quirky experimental procedure to a therapeutic cornerstone for patients with symptomatic cardiovascular disease. In the development of these technologies, the role of pre-clinical testing using animal models, especially large animal models such as porcine, rabbit, and ovine, is a very important part of the regulatory process that is used to determine the safety of devices before human clinical trials. Once these technologies enter the clinical arena (bench to bedside), a further understanding of their therapeutic mechanisms can be realized through comparative analysis of animal model research findings with those of clinical pathological specimens (bedside to bench).

This review will provide an overview of the clinical application status and limitations of current percutaneous cardiovascular intervention technologies, and results of pre-clinical studies including animal models.

Experimental Animal Model for Coronary Intervention

Drug-eluting stents (DES) have driven a new era in the field of percutaneous coronary intervention (1,2). The first-generation DES coated with antiproliferative drugs have been shown to limit instent restenosis in discrete lesions (3,4). The success of these DES technologies is founded not only in initial human clinical data but also on preclinical studies using the porcine coronary restenosis model (5–8). Presently, it is unclear whether any single animal species is more predictive of the human response to such coated stents. As such, we maintain that animal models can still provide mechanistic insight into fundamental biological processes and response. Therefore, these animal models can help prove critical hypotheses regard-

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ing putative mechanisms of action of an intervention, yet they cannot be used to predict efficacy (9).

The rabbit iliac restenosis model has been studied extensively to test restenosis therapies and to understand cellular and molecular mechanisms (10–12). Although balloon angioplasty in this model does cause histopathologic injury comparable to that seen with human angioplasty, a criticism of this model is that foam cells are rare in human restenotic neointima.

The coronary arteries of domestic pigs after injury respond in a similar fashion as human coronary arteries, and thick neointima will be seen within 28 days and is identical to human restenotic neointima (Fig. 1) (13,14). In addition, the amount of neointimal thickening is directly proportional to injury, thereby permitting the creation of an injury-response regression relationship that can further quantify the response to potential treatment therapies (15,16).

Abbreviations and Acronyms

AS = aortic stenosis
CTO = chronic total occlusion
DES = drug-eluting stent(s)
LAA = left arterial appendage
MI = myocardial infarction
MR = mitral regurgitation
PES = paclitaxel-eluting stent(s)
PFO = patent foramen ovale
SES = sirolimus-eluting stent(s)
VHD = valvular heart disease

Experience suggests that the coronary arteries in domestic swine and iliac arteries of rabbits are suitable for assessment of devices that might be used in clinical evaluation (17).

Porcine coronary restenosis model for evaluation of DES technologies. Pre-clinical evaluation of novel DES technologies has great importance for understanding safety and possibly efficacy of these technologies, and the porcine coronary restenosis model is widely used for those studies. In general, cardiac catheterization techniques in the pig are similar to the techniques used in humans (18–21) (Fig. 1). A pre-clinical studies consensus group (9,22) recommends that the stent be appropriately sized by visual or quantitative coronary artery measurement using a stent/artery ratio ≤1:1, as using a higher stent/artery ratio could induce severe arterial injury and considerable coronary artery stenosis. There is no doubt that the arteries in animals cannot be fully representative of human disease, thus the pre-clinical studies can prove only safety and not true efficacy. However, pre-clinical animal studies still have predictive value because biological processes associated with arterial repair are similar. For standardization purposes, all laboratories should use similar criteria for evaluation of histopathologic change after stent implantation as follows.

INJURY AND INFLAMMATION SCORE. Inflammation by histopathologic evaluation can include an injury score at each stent strut site. Inflammation descriptions have been published previously (14,23).

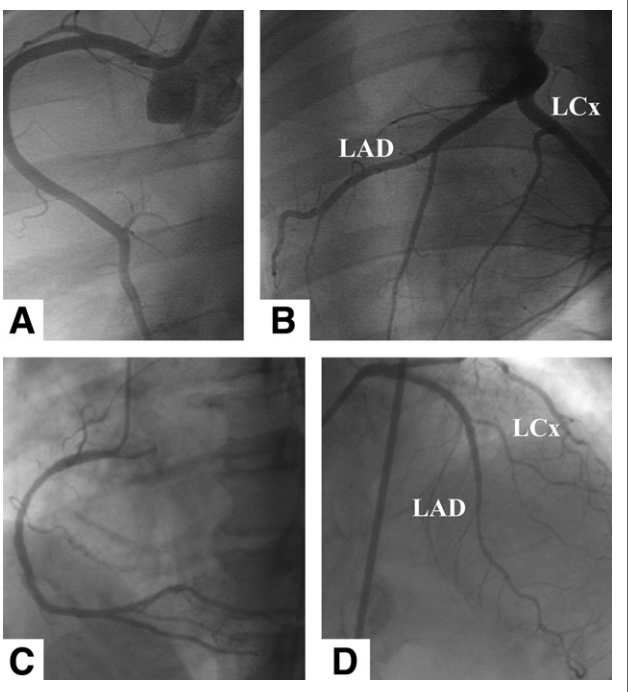

Figure 1. Porcine and Human Epicardial Coronary Anatomy

Porcine: **(A)** right coronary artery and **(B)** left coronary system. Human: **(C)** right coronary artery and **(D)** left coronary system. Similar anatomy and coronary distribution is shown of the left anterior descending (LAD), left circumflex (LCx), and right coronary arteries.

STENT STRUT POSITION AND ADJACENT TISSUE. Other observational data should include stent strut apposition to the vessel wall, stent struts covered by tissue or endothelium, adjacent tissue, including medial thinning, loss of cellularity, and hyalinization.

STENT DESIGNS. Taylor et al. (24) have studied 4 different stent designs to compare their effects on arterial injury, cellular proliferation, neointima formation, and arterial dimensions. In that study, all 4 stent designs had similar injury scores, cellular proliferation indices, and adventitial areas. Nitinol stents resulted in a 2-fold increase in neointimal area and thickness despite the lumen area being similar for all stent designs because of an offsetting expansion in vessel area in nitinol stents (20% greater than balloon-expandable stents) occurring between 7 and 14 days after stent deployment.

VASCULAR RESPONSE AND HEALING. Drug choice and release kinetics are the most important components of DES technology because they determine the type of vascular response and time course of healing (25–28). Endothelialization after stent implantation should be recorded as absent, partial, or complete in all sections and the time of re-endothelialization should be estimated. In the porcine coronary stent model, a thick neointima was reliably induced by 28 days, and several reports have investigated