The Importance of Pre-Clinical Animal Testing in Interventional Cardiology

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Summary

The treatment of cardiovascular disease has changed dramatically over the past 2 decades, allowing patients to live longer and better quality lives. The introduction of new therapies has contributed much to this success. Nowhere has this been more evident than in interventional cardiology, where percutaneous cardiovascular intervention has evolved in the past 2 decades from a quirky experimental procedure to a therapeutic cornerstone for patients with symptomatic cardiovascular disease. The development of these technologies from the earliest stages requires preclinical experiments using animal models. Once introduced into the clinical arena, an understanding of therapeutic mechanisms of these devices can be ascertained through comparisons of animal model research findings with clinical pathological specimens.

This review provides an overview of the emerging role, results of preclinical studies and development, and evaluation of animal models for percutaneous cardiovascular intervention technologies for patients with symptomatic cardiovascular disease.

Introduction

To improve human health, scientific discoveries and technologies must be translated into practical applications. Such advances typically begin at “the bench” with basic research where scientists study disease at a molecular or cellular level and then progresses to the clinical level, or the patient’s “bedside.” Translational research is an interchangeable term that underscores the pressing need to translate the practical benefits for those affected by symptomatic cardiovascular disease with the extensive investments divested by the private and public sectors in biomedical research. Translational research should be viewed as a two-way road: bench to bedside, and bedside to bench. In particular, to facilitate a more effective translation process, a new road map should be implemented to foster interaction and cooperation between basic researchers, clinicians, laboratory professionals and device manufacturers.

Experimental animal model for restenosis and coronary intervention technologies

A new era in the field of percutaneous coronary intervention has arrived: the drug-eluting stent (DES). These stents are coated with antiproliferative drugs such as sirolimus, and have been shown to limit in-stent restenosis in discrete lesions. Other drug coatings, such as paclitaxel analogs, have shown similar efficacy. The success of these antiproliferative agents is founded not only in initial human clinical data but also on preclinical studies using the porcine coronary restenosis model. 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 most animal models currently available can still provide mechanistic insight into fundamental biological processes and response. These animal models can therefore help prove critical hypotheses regarding putative mechanisms of action of an intervention yet cannot be used to predict efficacy. The following section will summarize an overview of current coronary stent technologies as well as the animal models used in their evaluation.

Brief overview of each animal model

Small animal model

The rat carotid artery model was developed in the 1960s, and from it the foundations of vascular biology were derived. Although initially used to gain insight into human atherosclerosis, this model was later adapted to better understand restenosis and to test restenosis therapies. This model has become a standard for studying smooth muscle cell proliferation after endothelial denudation. One advantage of the model is that it provides an opportunity to
study molecular biology\(^{14-16}\). Conversely, this model assumed less importance after several early studies of angiotensin-converting enzyme inhibitors\(^{17-21}\), where failure of this model to predict negative clinical trial results caused it to lose favor among investigators.

The mouse arterial injury as a restenosis model developed from the availability of the mouse genome and molecular methods to study events after arterial injury\(^{22,23}\). Since this model has very small vessels, traditional injury methods by balloon or stent are not practical. Vascular injury may instead be performed by rotating a small guide wire in the vessel or electrical injury, and placement of a non-constrictive peri-vascular cuff around the mouse femoral artery\(^{24,25}\). Through the use of these methods, variable focal neo-intimal thickening forms at injury sites proportionate to the amount of injury with little thrombus formation. A thin neointima (roughly 0.03 mm\(^2\)) forms by three weeks. The power of molecular biology and genetics in the mouse model will permit substantial advances in understanding the interactions between cell proliferation, cell migration, thrombus formation, and remodeling.

**Large animal model**

The rabbit iliac restenosis model has also been studied extensively to test restenosis therapies and to understand cellular and molecular mechanisms\(^{26-28}\). Blood cholesterol levels are typically >1,000 mg/dl and cause biochemical arterial injury which can be further supplemented by mechanical injury. These models can have initial injury induced by air desiccation to hypercholesterolemic diets and then balloon inflation to further injure the vessel. Histopathology in this model shows foam cells (macrophages that have ingested excessive lipid) and voluminous extracellular matrix. One criticism of this model is that foam cells are rare in human restenotic neointima. However, balloon angioplasty in this model does cause histopathologic injury comparable to that seen with human angioplasty, with medial desication and plaque fracture. Platelet deposition occurs rapidly at sites of a balloon-induced plaque fracture. Thus, antplatelet agents, as a potential anti-restenosis therapy, were studied early in the history of this model\(^{29,30}\) and showed efficacy in reducing neointimal thickness.

The coronary arteries of domestic pigs after injury respond in similar fashion as human coronary arteries\(^{31,32}\). Furthermore, when porcine coronary arteries are injured, thick neointima will be seen within 28 days and is identical to human restenotic neointima. When a balloon-only injury is performed, a typical medial laceration occurs and is filled at 28 days by neointima. 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\(^{33,34}\).

Experience suggests that the coronary arteries in domestic swine and iliac arteries of rabbits are suitable in that their size, access, and injury response are similar to human vessels, and therefore allow assessment of devices that might be used in clinical evaluation\(^{35}\). Although armed with fewer collateral vessels, there are pertinent similarities between the pig and human cardiovascular system, including the distribution of epicardial coronary arteries.

**Technical consideration of porcine coronary model**

Porcine coronary models using vascular injury methods are now accepted standards by which potential restenosis therapies are studied\(^{36}\).

In the porcine model, the left main coronary artery (LMCA) generally bifurcates early into the left anterior descending (LAD) and circumflex (LCx) coronary arteries (Fig.1). These vessels are of similar diameter to those in the human (2.0–4.0 mm). Similarly, the LCx commonly has 1–3 marginal branches and the LAD supplies the septum (Fig.1). Furthermore, the porcine right coronary artery (RCA) is usually of similar diameter to the human RCA, although it is less often dominant than in humans, where RCA dominance occurs in 80% of cases (Fig.1).

**Cardiac catheterization techniques**

Cardiac catheterization techniques in the pig are similar in many ways to the techniques used in humans. Procedures are often performed under general anesthesia. Intubation can be achieved using human endotracheal tubes, although the pig’s longer pharynx may make this more technically challenging. Arterial access can be achieved via the carotid or femoral arteries, using a cut-down approach or by direct percutaneous puncture using a modified Seldinger technique, respectively.

Standard human diagnostic and interventional equipment may be used, with catheter choice dependent on the approach. In general, via the carotid approach, our group has usually used a Judkins left 3.5 or 4.0 guide catheter\(^{36-39}\). Via the femoral approach, the hockey stick guide catheter may be used for both left main and RCA ostia\(^8\), or Judkins right 4.0 guide catheter for the RCA (Fig.1).

Antiplatelet therapy is recommended, using aspirin (300 mg) started the day before the procedure and continuing until sacrifice\(^{6,40}\). Clopidogrel (75 mg) has also been used in addition to aspirin\(^{36,40}\). Heparin (100–300 U/kg) is often used during the procedure as an antithrombotic although stent thrombosis may still occur with this regimen, as in the human\(^{41}\).

**Stent implantation**

Only one stent should be implanted per artery except when issues of stent overlap or multiple stent dosing are considered. The stent may be placed in multiple different arteries in the same animal including bare metal stents such as copper and/or gold stents for development of restenosis model, carrier-only such as polymeric material, and carrier plus DES for evaluation of DES. Regarding DES evaluation, recommendations from a preclinical studies consensus group suggest that the stent should 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\(^8\).

Stent overlap frequently occurs during clinical implant and overlapping DES present the possibility of a combined effect from drug released from the 2 stents.

**Evaluation of stent performance**

A rigorous, (semi)quantitative and defined scale for device evaluation should be presented as well:
1) Injury and inflammation score: Inflammation by histopathologic evaluation can include an injury score at each stent strut site (Fig. 2), an inflammation description (absent, or cell types and location), and an inflammation score for the overall vessel as well as for the adventitia, media, neointima, and at stent strut sites. When possible, cell density in tissue compartments should be recorded as number of cells per area.\(^{32,42}\)

2) Stent strut position and adjacent tissue: Other observational data should include stent strut apposition to the vessel wall and stent struts covered by tissue or endothelium. A subjective description should also be rendered for adjacent tissue, including medial thinning, loss of cellularity, and hyalinization.

3) Quantitative histomorphometry: Histomorphometry of histopathologic sections is essential for stent evaluation. Measurements at all sections should include medial area, IEL area (area within the internal elastic lamina), EEL area (area within the external elastic lamina), lumen area, and stent area (area within the stent itself). Neointimal measurement is important for efficacy assessment and should include thickness at each stent strut site and total neointimal area.\(^9\)

4) 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. From numerous studies, considerable data exist on how sirolimus and paclitaxel differ in terms of their effects on the arterial wall.\(^{43,46}\)

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 (Fig. 3) and several reports have investigated the phasic, time-dependent cellular response after stenting.\(^{47-49}\)

Preclinical studies of both sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) have demonstrated the efficacy compared with BMS.\(^{6,8}\) However, enthusiasm for this technology has recently dampened by concerns of late stent thrombosis. A major criticism of earlier preclinical studies leading to the United States Food and Drug Administration (FDA) approval of both stents was their failure to detect significant differences in the healing response of the arterial wall when compared with BMS at 28 days while human angioscopic and autopsy data clearly demonstrated significant differences in healing.\(^{50,51}\) Most preclinical studies have failed to show any significant differences between DES and BMS in the extent of endothelial coverage when a 1.1:1 balloon artery ratio was chosen. It was not until the results of a study using overlapping commercially available SES and PES stents in the rabbit iliac artery model showed incomplete endothelialization...
compared with matched BMS controls that these differences were recognized. Recently, Nakazawa et al. have reviewed the comparison of preclinical data from SES, PES, and the phosphorylcholine-coated Endeavor zotarolimus-eluting stent (ZES; Medtronic Vascular, Santa Rosa, CA). In this review, incomplete endothelial coverage was seen in non-overlapping and overlapping sites of both SES and PES compared with both ZES and BMS, though the differences were more pronounced in overlapping segments (Fig.4). Accompanying these findings were more increases in fibrin and inflammatory cells in SES than in either ZES or BMS, which persisted out to 90 days after stent implantation. Two studies using human autopsy samples suggested that incomplete endothelial coverage of stent struts played one of the very important roles as the morphometric predictor of late stent thrombosis although the cause of late stent thrombosis is likely multifactorial, with delayed re-endothelialization in combination with other clinical and/or procedural risk factors.

Two time points should be used for the evaluation of stent performance, the first at 28 days to observe for neointimal hyperplasia, and at least one later time point to examine long term effects. The later time point (3 or 6 months) depends on when “healing” and drug release are both complete. Of note, the FDA has typically recommended 6 months follow up as the interval to acquire preclinical stent data.

Porcine heat-injury restenosis model

The porcine coronary stent restenosis model is a well-accepted standard. However, the fundamental drawback of this model is that there is no stenosis lesion in coronary arteries and that the stent itself is foreign material. As a result, this model may not be suitable to evaluate the performance of bifurcation or bioabsorbable stents due to lack of a true stenosis lesion. Also, results of coronary artery imaging such as computed tomography (CT), magnetic resonance imaging (MRI), intravascular ultrasound (IVUS), and optical coherence tomography (OCT) may be hampered as the stent can produce artifact.

Radiofrequency thermal balloon angioplasty was introduced as a new technique for percutaneous arterial dilatation in the 1990’s, yet due to increased restenosis rates observed in patients receiving this therapy, it was soon abandoned as a percutaneous interventional treatment option. Using this system, Staab et al. and our laboratory have investigated a porcine heat-injury restenosis model.

In our study using 22 swine with a total of 54 coronary arteries, coronary artery stenoses were consistently developed at 4 weeks after heat-injury (Fig.5). In light of these results, this porcine coronary restenosis model might be useful for the evaluation of bifurcation stents and bioabsorbable stents, coronary imaging studies such as MRI, CT, IVUS, and OCT, and for the technical training of complex percutaneous coronary interventions such as bifurcation stenting and atherectomy.

Experimental animal model for chronic total occlusion (CTO)

Recent advances of DES technology has shifted focus within interventional cardiology from restenosis prevention...
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Figure 3 - A - Photomicrographic section shows gross neointimal proliferation causing a significant stenosis (Elastic-van Gieson stain, x30). The gross proliferation and luminal compromise by neointima is obvious; B - Microscopic section in a case in which, fortuitously, not all coil wires penetrated into the vessel media. In this section, the two coils farthest left penetrated the media (arrows) and resulted in substantial proliferation; A short segment of vessel media at the lowermost portion of the figure is entirely normal, without any proliferation, although this segment was stretched by the balloon; Elastic- van Gieson stain was used (x30); L - lumen; M - media; NI - neointima; *, holes from coil wires 31.

Figure 4 - A - Photomicrographs showing the amount of neointimal thickness, extent of inflammation, and fibrin score at 28 days after the placement of Endeavor zotarolimus-eluting stents (ZES), Cypher sirolimus-eluting stents (SES), Taxus paclitaxel-eluting stents (PES), and Driver bare metal stents (BMS) in rabbit iliac arteries; The extent of neointimal thickness, the grade of inflammation, and the fibrin score were highest with PES. With SES, there were focally uncovered stent struts, which were associated with inflammation consisting of heterophils or eosinophils and giant cells; B - X-rays of longitudinally cut rabbit iliac arteries at 21 days after the placement of overlapping ZES, SES, and PES. The extent of stent coverage by endothelial cells was greatest with ZES, with almost complete coverage in the proximal and distal segments and significantly greater coverage in the overlapped segment compared with SES and PES. Adapted from the reference 53.
to the treatment of CTO. It is often stated that successful chronic total occlusion (CTO) recanalization represents the “last frontier” of percutaneous coronary intervention. This interest has stimulated the development of specialized devices such as the Frontrunner (Lumend Inc., Redwood City, CA) that performs blunt micro-dissection\textsuperscript{59}, and the Safecross (Intraluminal Therapeutics Inc., Carlsbad, CA) that utilizes optical coherence reflectometry for traversing the CTO\textsuperscript{60}.

Despite its common occurrence, there is surprisingly little information about the pathophysiology of CTO, and why some CTO can be crossed while in others, crossing is unsuccessful. For the past several years, researchers have developed CTO models to guide therapeutic investigations, including image-guidance intervention and device development.

**Overview of animal model for CTO**

Spontaneous atherosclerotic plaque rupture and subsequent arterial occlusion do not occur naturally in any animal model, even among those models that have been genetically engineered to have increased atheroma formation. For the past several years, researchers have tried to develop several kinds of animal CTO models. The initial method of producing a total occlusion utilized external ligature or ameroid constriction\textsuperscript{61,62}. However, a fundamental drawback of this method is the inability to facilitate the development of devices to recanalize CTO. Subsequent techniques for endoluminal formation of CTO in coronary and peripheral arteries have differed in their fundamental approach. Murphy et al.\textsuperscript{63} evaluated 4 methods in a rabbit iliac model for developing peripheral arterial thrombosis obliterans. Of these, gas-drying with thrombin and a high-cholesterol diet was deemed the most efficacious. Strauss et al. subsequently modified the thrombin injection model by infusing collagenase before wire passage\textsuperscript{64}. Several characteristics of human CTO were evident in this model, including mature fibrous tissue, multiple small intraluminal vascular channels, occasional extracellular lipid deposits, and disruption of the internal elastic lamina (Fig.6). Their reports suggested that the microchannels may be a critical determinant of successful CTO guide wire crossing\textsuperscript{65}. Other CTO models have included stents with occluded outflow and even direct alcohol injection to promote thrombosis\textsuperscript{66}. Developing an accurate and reproducible human-like coronary CTO model has been a complex undertaking because 1) coronary vessels are less amenable to a direct surgical approach; 2) simulating luminal and medial pathology, including microcalcification, has been difficult; and 3) an inflammatory component must be present to mimic human CTO lesions\textsuperscript{67,68}. Balloon angioplasty and stent implantation in animal coronary arteries, both standard
methods of denuding the vessel and engendering neointimal proliferation, rarely result in CTO development. More aggressive measures tried have involved the use of thermal injury and copper stent implantation as described above. Polymers have also been used to invoke chronic coronary occlusions. Early polymeric implants were abandoned as stent platforms because they induced severe inflammatory responses and vessel occlusion. Prosser et al. reported placement of a microporous poly L-lactic acid polymer into pig and dog coronary arteries. The polymer is absorbed by 28 days, resulting in a micro-channeled occlusion histologically similar to a human CTO. These animal models may contribute to a deeper understanding of the biology of human CTO and enable new device and pharmacological investigation to improve recanalization success in these challenging lesions.

Percutaneous interventions for the treatment of valvular heart disease

Valve repair and replacement are common surgical procedures and are typically effective in eliminating or significantly reducing valve dysfunction. However, these procedures remain controversial as sole treatments for patients with a low ejection fraction. The challenge in treating patients with congestive heart failure due to valvular disease is deciding the mode of repair to address multiple factors such as alignment of the leaflets, the size of annulus, and geometries of subvalvular apparatus. Coupled with the risk of morbidity and mortality due to open heart surgery, these reconstructive procedures have proven to be a challenge to the surgeon and a risk to the patient, thereby motivating scientists to design devices that can treat valvular dysfunction in a minimally invasive manner. Based on the experience gained from the development of surgical valve prostheses, the FDA has established detailed guidelines for the assessment of fatigue, flow dynamics, and hydrodynamics of valve implants as well as processes for in vitro and in vivo preclinical testing of heart valve prostheses. In these preclinical studies, not only device development and durability testing but also optimal imaging and deployment protocols should be established and comprehensive user training should be initiated in the latter stages of the preclinical evaluation.

This section will focus on the percutaneous treatment of valvular heart disease.

**Figure 6** - Chronic Total Occlusion (CTO) in the rabbit iliac model. Lumen (L) is occluded by fibrotic intimal lesion; Small vascular channels are evident (B, arrow in C); M indicates media; A - adventitia; A and B, Movat, x10; C, Movat, x20; D, H&E, x20. Adapted from the reference 64.
Aortic valve replacement

Age-related aortic valve disease contributes to continuously increasing morbidity and mortality worldwide and is associated with an increase in aortic valve replacement procedures over the past decade. Degenerative aortic stenosis, a common adult valvular abnormality\(^7\), has been the focus of percutaneous treatments since the mid 1980s. To date, 2 percutaneous aortic valve procedures have been introduced in clinical setting\(^3,\,7\) (Fig.7).

The ovine model is preferred for in vivo assessment of percutaneous aortic valve devices. Currently there is no chronic animal model representative of aortic stenosis. While the healthy ovine model has provided validation of catheter function, prosthesis anchoring, device function post-implantation, and unimpaired coronary blood flow, this model has several limitations:

1) the size of femoral arteries (typically ≤5mm);
2) the angulation of the aortic arch (the cause of kinking of the delivery system);
3) the length of the aortic arch (shorter than that of human); and
4) the location of coronary ostia (closer to the aortic valve than in the human)\(^7\). Newer valve technologies may provide solutions to access issues and other limitations of first generation devices.

Mitral Valve Repair

The mitral valve is a complex anatomic and physiologic structure. Its proper function depends on coordinated interaction of the mitral annulus, leaflets, chordae, papillary muscles, and the left ventricle. Improved understanding of the mechanisms of mitral valve dysfunction coupled with advances in catheter-based technology has resulted in several potential percutaneous approaches to mitral valve repair\(^7\). Innovations attempt to duplicate techniques of surgical mitral repair. Similar to aortic valve devices, the ovine model is preferred for in vivo assessment of percutaneous mitral valve devices. To date, 2 types of diseased animal models were used in published data\(^7,\,8\). One type is the rapid-pacing heart failure model and the other type is the ischemic mitral regurgitation (MR) model. By using progressive rapid ventricular pacing for 5 to 8 weeks (180-240 beats/minute), the increase in left ventricular dimension results in congestive heart failure and MR. In some publications, left ventricular ejection fraction (LVEF) reduced up to 24-28% and moderate to severe MR was developed after rapid pacing\(^7,\,7,\,8\). One drawback of this model is that after recovery from rapid pacing, LV function return to levels seen in the healthy animals\(^8\). In light of this observation, researchers should pay attention to this fact with regard to evaluation of device efficacy. Ischemic MR is induced by coronary arterial occlusion, however, variable anatomy of the coronary artery tree poses a challenge. Gorman et al.\(^8\) has investigated the relationship between the coronary arterial

![Figure 7 - PHV delivery within the native valve](image-url)
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Figure 8 - A - The MitraClip device (Evalve) with the arms of the clip in the open position; B - The left atrium is accessed with the device via transseptal catheterization and the clip engages the mitral leaflets from the left ventricular surface; C - A suction port (arrow) is used to draw the leaflets into proximity of the catheter (Edwards Lifesciences) in order to suture (arrow, d) the central portion together; D - A double orifice (arrowheads) mitral valve is the result. Adapted from the reference 87.

Table 1 – Transcatheter Mitral valve treatment

<table>
<thead>
<tr>
<th>Repair category/Name</th>
<th>Description</th>
<th>status</th>
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<td>MitraClip (Evalve)</td>
<td>Clip for edge-to-edge repair</td>
<td>Phase II clinical trial</td>
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<td>MOBIUS (Edwards)</td>
<td>Suture-based edge-to-edge repair</td>
<td>Phase I clinical trial</td>
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<td>Preclinical</td>
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<tr>
<td>Annuloplasty</td>
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<td>Coronary-sinus based with anchors and tensioning element</td>
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<td>Carillon (Cardiac Dimensions)</td>
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<td>PTMA (Viacor)</td>
<td>Coronary-sinus based with reversible and adjustable treatment effect</td>
<td>Phase I clinical trial</td>
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<td>Coronary-sinus based with anchors and tensioning element</td>
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<td>Transventricular suture-based system using coronary sinus as anatomic guide</td>
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<td>Transventricular annular cinching</td>
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<td>PS3 (Ample)</td>
<td>Transventricular and transseptal approach to shorten septal-lateral mitral dimension</td>
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<td>Other</td>
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<tr>
<td>i-Coapsys (Myocor)</td>
<td>Transventricular epicardial remodeling with pericardial access</td>
<td>Preclinical</td>
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anatomy and development of ischemic MR and concluded that only posterior infarction by occlusion of the left circumflex could induce acute or chronic ischemic MR. The primary concern of this model is the mortality and consistence of MR development. Mortality related to myocardial infarction is about 30-40% and consistence of MR development is about 20-30%. A “diseased” model might not be necessary for device development or for durability testing of optimal deployment protocols. Two percutaneous approaches – edge to edge repair and annuloplasty – have been subjected to extensive preclinical testing and to preliminary clinical investigation as shown in the table: 1) Edge-to-Edge repair; The first phase I feasibility trial on a percutaneous mitral device has been completed. A transcatheter mitral clip (MitraClip™, EvAlve, Menlo Park, CA) placed on the free edges of the mitral leaflets through a transseptal puncture, mimics the Alfieri surgical procedure (Fig. 8).

Another edge-to-edge repair technology, the MIOBIUS leaflet repair system (Edwards Lifesciences, Irvine, CA) uses a suture-based technology to complete an Alfieri-type repair. The preclinical results have confirmed the feasibility of this approach for creation of an edge-to-edge repair. 2) Annuloplasty: A variety of percutaneous technologies have been developed to alter mitral annular geometry such as coronary sinus-based annuloplasty, direct intracavitary annuloplasty, and other novel cinching devices. Shortening or reshaping the annulus by insertion of a device into the coronary sinus has the potential to mimic surgical annuloplasty. Proof of concept has been demonstrated experimentally with recent publication of an initial human feasibility study using the MONARCH™ (Edwards Lifesciences, Irvine, CA) which consists of a self-expanding nitinol implant with distal and proximal stent-like anchors.

A variety of other percutaneous valve devices are under development. Over the next decade, clinical trials will clarify the roles of these new approaches in relation to each other and to current surgical and medical therapies. These percutaneous technologies will be carefully studied and subjected to a level of scrutiny far beyond those applied to new surgical therapies.

Conclusion
The field of percutaneous cardiovascular intervention technology is developing quickly and reflects the time sensitivity of the information contained within this chapter. The basic concepts, however, will be important to understand as all further advances will be generated by the early beginnings including preclinical studies. The success of this interventional subspecialty will be driven by the results of a collaborative relationship between the cardiologist, cardiac surgeon, and the medical device industry. A new era is coming yet again for the discipline of cardiovascular diseases, with new implications not only involving patient care but also in the area of multidisciplinary cooperation.

Acknowledgment
In the preparation of this review, we thank Heidi Bonneau, RN, MS, CCA for her editorial review.

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