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Where Cardiac Surgery and Interventional Cardiology Merge: The Future of Catheter-based Interventions for Cardiovascular Disease

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INTRODUCTION

Although angioplasty and coronary stenting are now used for more than 800,000 patients in the United States each year, a wide array of patients with coronary disease still require surgical revascularization. Surgery remains the only option for many patients with heart failure and valvular disease. New technology, with an emphasis on bioengineering, may expand catheter-based interventions for hundreds of thousands of patients. Cardiologists and cardiac surgeons have an unusual opportunity to join forces and develop a new generation of endovascular cardiovascular specialists.

In the first 25 years of catheter-based cardiac interventions, endovascular technology has swiftly evolved from the original, fixed wire, wide-profile, non-steerable Gruentzig DG catheter to an expansive selection of intracoronary devices that include:

- Flexible, low-profile, compliant and non-compliant coronary dilatation catheters
- Intra-coronary steerable guide wires
- Balloon expandable and self-expanding stents
- Cut and retrieval catheters (Directional Coronary Atherectomy—DCA™)
- High speed rotational atherectomy devices (Rotablator™)
- Thrombus extraction devices (POSSIS AngioJet™)
- Excimer and Ho:YAG laser catheters
- Cutting balloons
- Gamma- and beta-emitting brachytherapy catheters
- Percutaneous transmyocardial laser revascularization devices (PMR)
- Distal protection/emboli containment devices

This expanding collection of intra-coronary devices has propelled the growth of catheter-based revascularization procedures from less than 1,000 cases in 1980 to the present level of more than 850,000 in the U.S. and nearly two million worldwide.

BACKGROUND

The success of catheter-based interventions for cardiovascular disease has been demonstrated for

- Discrete stenoses in native coronary artery vessels of greater than 2.5 mm size
- Discrete stenoses in vein grafts, particularly at anastomotic sites
- Angioplasty for acute MI

Although restenosis has hampered the durability of angioplasty, the routine use of intracoronary stents has substantially reduced the need for repeat procedures. The advent of brachytherapy and drug eluting stents in 2001 leaves most cardiologists with a conviction that restenosis can be either successfully treated or primarily prevented.

Randomized trials of coronary surgery versus angioplasty where diabetics are excluded have not demonstrated superiority for either therapy when mortality and myocardial infarction are used as outcomes, but patients having aorto-coronary bypass experience fewer symptoms in follow-up [King 1994, Pocock 2001, Serruys 2001]. The introduction of stent coatings [Sousa 2001] may favorably slant outcomes towards angioplasty in the coming years. The ability to manipulate vascular biology has made great advances in recent years, and bioengineering is likely to be a common component of endovascular device development in the next decade.

Over the last 15 years, catheter-based technology has been applied in a myriad of diverse diagnostic and therapeutic applications with substantial success, replacing surgical approaches for many patients. These percutaneous successes include:

- Mitral valvuloplasty or balloon valvotomy for mitral stenosis
- Atrial septal defect and patent foramen ovale closures
- Pericardial windows for effusions
- Alcohol ablation for obstructive cardiomyopathies due to asymmetric septal hypertrophy
- Aortic aneurysm repair
- Aortic dissection repair
- Carotid angioplasty and stenting
- Renal angioplasty and stenting
- Patent ductus arteriosus closure

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- Percutaneous vessel closure
- Endomyocardial biopsy
- Brachytherapy for restenosis

Failures of Percutaneous Catheter-based Therapies in 2001

Interventional cardiologists and radiologists have experienced many recent advances, but our present failures, shortcomings, and lack of imagination are also evident. A simple list of unmet needs provides a challenging view of the applications likely to be part of the catheterization laboratory of 2010:

- Heart failure
- Degenerative vein graft disease
- Diffuse small vessel coronary disease
- Chronic total coronary occlusions
- Primary prevention of myocardial infarction
- Aortic valve stenosis
- Aortic valve insufficiency
- Mitral valve insufficiency
- Atrial fibrillation
- Ventricular tachycardia

Each of these clinical challenges is potentially treatable with catheter-based technologies. Most already have solutions in prototype or more advanced phases of development. It is also likely that the lessons of genomic research will teach us how to recognize gene defects and conceivably correct them in utero, further obviating the need for corrective surgery for many patients. Ten years of further research and development could bring catheter-based technology to a point where endovascular specialists will be treating not 800,000 patients but potentially more than two million patients each year in U.S. catheterization laboratories.

What will be left for the cardiovascular surgeons in 2010? If the paths of endovascular specialists and surgeons do not merge, surgeons may be left to treat constrictive pericardial disease, cardiac tumors, papillary muscle disruption, and the rare but challenging array of complex congenital defects that include single ventricle physiology, truncus arteriosus, endocardial cushion defects, and tetralogy of Fallot.

Is this revolutionary change likely to happen? Let us briefly look at potential catheter solutions to many of the remaining challenges for treatment of cardiovascular diseases.

DISCUSSION

Congestive Heart Failure

Congestive heart failure (CHF) is among the most frequent diagnoses for patients admitted to acute care hospitals. CHF is associated with the longest lengths of hospital stay for any of the cardiac diagnostic-related groups (DRGs). The acute and chronic care of patients with heart failure consumes billions of health-care dollars each year. Beyond diuretics and other pharmaceutical preparations that "unload" failing hearts, there are few effective treatments for advanced heart failure.

Orthotopic cardiac transplantation has become more widely practiced over the last three decades, but its application remains limited [Anguita 1993]. The supply of whole organ donors is small and grossly inadequate to meet the staggering demand. Although the introduction of Cyclosporin A has mitigated the severe immunological rejection commonly associated with allogenic transplantation, recipients continue to suffer from induced immune deficiency. The acute and chronic costs associated with orthotopic heart transplantation present formidable barriers to broad usage, even if donor organs were to become more plentiful.

Years of work on mechanical or "artificial" hearts have yielded only a few devices of questionable suitability for long-term implantation. Several left ventricular assist devices are approved, but these devices serve primarily as "bridges" to orthotopic heart transplantation. Investigators have explored novel surgical approaches for profound heart failure, including cardiomyoplasty [Salmons 1990] and partial left ventricular reduction (regional myomectomy) [Batista 1999]. These palliative operations are associated with significant morbidity and are of questionable benefit.

To date, catheter-based treatments for severe heart failure are essentially non-existent, with the possible exception of biventricular pacing for a small and very select group of patients [Cazeau 2001]. Recent investigation has raised the possibility of "rejuvenating" failing myocardial tissue by replacement with healthy contractile cells. Many investigators are pursuing percutaneous strategies with this goal in sight.

Replacement biology is an evolving discipline that includes related processes of *tissuegenesis* and *organogenesis*. The possibility of using somatic cell transfer for functional restoration has been demonstrated in several organ systems, including skeletal muscle [Kinoshita 1994], brain [Iacono 1992], liver [Ribeiro 1990], and pancreas [Socci 1991]. It is widely believed that cardiomyocyte cell transfer could be an alternative to whole organ transplantation for severe congestive heart failure [Soonpaa 1995].

At Indiana University, in 1994, Soonpaa et al. established the feasibility of transplanting fetal cardiomyocytes in mice [Soonpaa 1994]. Embryonic cardiomyocytes from transgenic mice were injected directly into the myocardium of normal syngeneic hosts. This cell transfer resulted in stable grafts that were identified by β-galactosidase activity. A chronic immune reaction was not induced in the host mice. These investigators provided electron microscopic evidence that engrafted fetal cardiomyocytes and host cells formed nascent intercalated disks, which suggests that the grafted cells could potentially contribute to myocardial function.

Leor et al. asked, and answered, a more relevant question: Can transplanted myocardial tissue survive in infarcted myocardium? They subjected rats, after myocardial infarction, to injection of fragments of either cultured human fetal ventricles or fetal rat ventricles. Their data confirmed successful engraftment and survival of tissue transplants for up to 65days [Leor 1994].

Scorsin et al. successfully injected and engrafted neonatal cardiomyocytes into the border zone of myocardial infarcts in rats [Scorsin 1996]. The Leor and Scorsin studies both focused on morphological endpoints—neither demonstrated that their tissue grafts were functional. Scorsin subsequently did establish that allogenic fetal cardiomyocytes could be engrafted into partially infarcted myocardium and achieve an improvement in ejection fraction and cardiac output [Scorsin 1997]. These findings were compared to findings for control rats that had only culture medium injected into their infarct zones.

Li et al., at the University of Toronto, reported that transplantation of cultured fetal cardiomyocytes into myocardial scar tissue of rats could improve heart function while limiting scar expansion or aneurysm formation [Li 1996]. These investigators used a technique of cryo-injury to effect homogeneous myocardial injury in the recipient rats. Allogenic fetal cardiomyocytes were injected into scar tissue four weeks after injury, and the animals were sacrificed at eight weeks. Histological studies were performed to quantify the extent of scar formation and the presence of transplanted cells. Function in both transplant and control hearts was assessed using a Langendorff preparation.

Gojo and colleagues extended the work of Menasché and Weisel by demonstrating that fetal cardiomyocytes can be genetically marked or modified before being grafted to the heart [Gojo 1997]. They used a replication-defective recombinant adenovirus that carried the β-galactosidase reporter gene, and delivered it to cultured murine fetal cardiomyocytes. These cells were then transplanted to the myocardium of syngeneic adult recipient mice. Gene expression was manifest from 7 days to 12 weeks after cell transfer. This study also highlighted the potential for cell transfer as a vehicle for therapeutic gene delivery. Additionally, survival and proliferation of cardiomyocytes after transplantation may rely on the presence of adjunct growth factors or oncogenes that could be introduced in the cell line prior to transplantation.

Nearly all investigations of cardiomyocyte and myocardial tissue transfer have used rodents. The experiments employed an open-chest procedure because engraftment requires direct application, in most cases by injection. However, percutaneous catheter-based techniques have been developed for stimulating angiogenesis, either by gene therapy or transmyocardial laser. These minimally invasive therapies have been successfully applied in a variety of animal models and are now being investigated in human trials with variable success [Kim 1997, Henry 1998, Knopf 1998, Oesterle 2000]. It is likely that the same catheter systems used for gene transfer and percutaneous transmyocardial laser revascularization (PMR) could be modified and used as delivery systems for myocardial cell and tissue transplantation.

The development of a percutaneous catheter system for cardiomyocyte delivery would be viewed as a major advance. This less invasive approach should diminish morbidity while expanding the application of these therapies to a broad spectrum of patients. The development of appropriate devices is inextricably linked to choice of cells, biodegradable matrices, growth factors, and means of quantifying success of implementation, differentiation, and functional restoration.

Several companies are already pursuing cellular cardiomyoplasty, most notably Bio-Heart™ (Weston, FL). The first use of cell transfer for heart failure in a human was reported in late 2000 [Menasché 2001], and it is clear that more cases will soon follow. Although the surgeons in that case transferred the cells using direct injection techniques, the potential for cell transfer by catheter-based technology is vigorously being investigated at several institutions, including Massachusetts General Hospital. Extensive animal experimentation will be required before broad-based application is undertaken, but a 10-year window for this type of therapy is reasonable. Figure 1 (◎) outlines the fundamental steps that will require validation prior to human application.

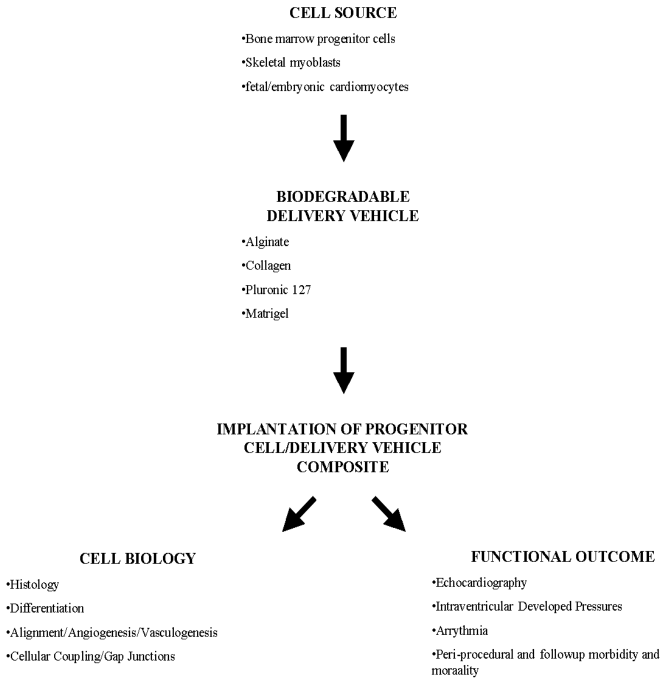

Figure 1.

Degenerative Vein Graft Disease

Although distal emboli containment devices have reduced the complications of vein graft intervention [Oesterle 1999, Webb 1999], it is widely acknowledged that angioplasty and stenting of badly degenerated vein grafts suffer from high complication rates [Mathew 2000]. Furthermore, degenerative vein graft disease is rarely discrete but tends to be diffusely spread throughout the vein graft. Spot-stenting of short segments usually offers only short-term benefit; hence, degenerative vein graft disease is a frequent reason for surgical referral. Redo surgeries also have a higher incidence of complications and are frequently compromised by inadequate availability of conduits. Several catheter-based approaches are currently being tested, including long stent grafts using ePTFE that could reline the vein graft while entrapping debris. Concern over long-term biocompatibility of the synthetic covering has led to several tissue engineering projects focused on the development of small vessel conduits that are tissue-engineered using the patient's own cells and then deployed as replacement conduits [L'Heureux 1998, Niklason 1999]. Delivery of these tissue-engineered small vessel stent grafts seems to be feasible.

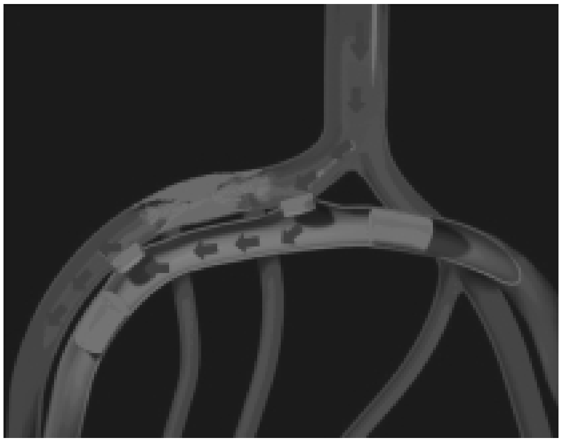

Figure 2. PICAB

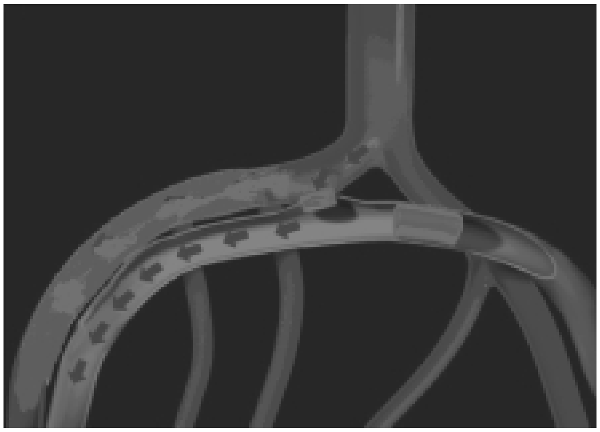

Figure 3. PICVA

Alternatively, the possibility of using the parallel coronary vein for percutaneous in situ coronary artery bypass (PICAB) has been explored in animal feasibility studies [Fitzgerald 1999]. Figure 2 (◎) presents a schematic representation of this concept. It is envisioned that PICAB could be used as an alternative to redo CABG in many patients with suitable proximal anatomy.

Diffuse Small Vessel Disease

Diffuse small vessel disease is frequently encountered during diagnostic coronary angiography. Patients with such advanced disease have not been successfully treated with either angioplasty or stents. Surgical revascularization opportunities are similarly limited, and most of these "no-option" patients are left to suffer with severe and oftentimes intractable angina. Mukherjee and colleagues at the Cleveland Clinic have estimated that more than 100,000 patients in the United States each year fall within such a no-option rubric [Mukherjee 1999]. Many of these patients have been subjects in trials of novel revascularization strategies, including transmyocardial laser revascularization (TMR, PMR), and gene therapy. These angiogenesis trials are flawed by the failure to account for adequate inflow to regions where new blood vessels may be developed. Borrowing from surgical experiences [Beck 1948, Hochberg 1977, Park 1975, Hochberg 1979], cardiologists have embarked on a human trial of retrograde myocardial perfusion using catheter-based therapy—percutaneous in-situ coronary venous arterialization (PICVA). See Figure 3 (◎). This catheter-based approach is a variant of PICAB and has the potential to substantially relieve angina in patients with otherwise untreatable coronary disease. A feasibility trial was begun in Germany in 1999, and the first human patient remains free of angina 18 months after the procedure [Oesterle 2001].

Chronic Total Occlusions

The inability to cross coronary chronic total occlusions (CTOs) with a guidewire is directly related to the duration and length of the occlusion. Beyond 6-12 months, the majority of total occlusions extending more than 15-20 mm cannot be negotiated with a guidewire and are thus unapproachable by angioplasty, atherectomy, or stenting. Although several devices have been developed to enhance wire crossing, none have been approved for human use. The Spectranetics™ laser wire has demonstrated promise in the hands of some investigators, but nearly half of CTOs are refractory to crossing even with this powerful tool [Oesterle 1998]. Patients with chronic total occlusions of major epicardial arteries are frequent candidates for bypass surgery, as standard angioplasty techniques cannot be applied. Such patients may have particularly ideal anatomy for PICAB and are the targets of planned clinical trials.

Primary Prevention of Myocardial Infarction

Although both coronary bypass surgery and angioplasty are effective therapies for relief of coronary insufficiency, neither has been shown to prevent subsequent myocardial infarction in treated patients. More than 1.5 million Americans suffer from acute myocardial infarction each year, with more than 500,000 deaths.

It is generally accepted that most infarcts result from "vulnerable" non-occlusive plaques that are susceptible to rupture [Fuster 1994]. Sudden plaque disruption initiates a thrombotic cascade, which quickly results in acute vessel occlusion. Because both angioplasty and aorto-coronary bypass are generally directed at stenoses of functional significance, vulnerable plaques are rarely recognized or treated. Likewise, angiography is of no predictive value because it cannot characterize plaque. Intravascular ultrasound (IVUS) is incapable of resolution below 100 microns and offers limited tissue characterization; hence, IVUS is not well-suited for identifying the hallmarks of plaque vulnerability: thin, fibrous caps covering lipid-laden pools. Several catheter-based imaging techniques are being developed to recognize vulnerable plaques. These new imaging techniques include optical coherence tomography (OCT), mid-infrared and Ramman spectroscopy, thermography, and MRI. Each has shown promise but is not yet of proven value.

It is probable that a catheter-based imaging technique capable of distinguishing vulnerable plaque from non-threatening plaque will emerge in the near future. Meanwhile, interventionists will be working in parallel on a variety of

Figure 4. Infiltrator Catheter

strategies for passivating plaque, rendering it less vulnerable to rupture.

It is probable that the primary preventive benefits of the statin class of lipid-lowering drugs are related to plaque passivation. In contrast to this systemic approach, the most promising catheter strategies include modulation of local vascular biology by arterial wall gene transfer. The Massachusetts General Hospital and its partner Harvard hospitals have recently initiated a trial of local gene delivery using an infiltrating catheter (Infiltrator™, see Figure 4, ◎) to distribute a gene encoded for inducible nitric oxide synthetase (iNOS) to the vessel wall. Nitric oxide (NO) is secreted by healthy endothelium and is recognized to be a potent endogenous inhibitor of vascular lesion formation, inhibiting platelet adhesion, leukocyte activation, and vascular smooth muscle proliferation and migration. The Harvard-initiated REGENT trial is focused on developing NO donors NO to inhibit restenosis. It is envisioned that a similar transfection strategy could be used to treat longer segments of arterial wall with diffuse atherosclerosis, rendering the vessel less susceptible to acute thrombotic occlusion.

Investigators at Stanford University have begun a multicenter trial of photo-activated local drug therapy for preventing restenosis [Rockson 2000]. Pharmacylics, Inc. has developed a porphyrin derivative, Antrin, which is selectively absorbed by plaque. After systemic administration of the drug, a fiber optic device is transported by a catheter to the areas of treatment in the coronary artery and red light is locally delivered, activating the drug and initiating a local release of oxygen radicals that are believed to inhibit proliferation. A variant of this strategy may have the potential to passivate diffuse areas of atherosclerosis.

Aortic Valve Stenosis/Aortic Valve Insufficiency

Although many patients with mitral stenosis have been successfully treated with catheter-based balloon valvotomy [Palacios 1998], valvuloplasty for aortic stenosis has been less effective and largely abandoned except as a bridge to valve replacement. The primary cause of failure for aortic valvuloplasty has been recoil of the diseased valve. The possibility of mechanically holding the valve open with a catheter-deployed stent graft has been envisioned and explored in prototypes. The "aortic valve stent" would incorporate a pliable tissue or synthetic valve that would be supported by the stent structure. Clearly, this is an approach that may only apply to a select group of patients, but it is not unreasonable to anticipate such catheter-based treatment for aortic valve stenosis by the year 2010.

A similar concept may have a more obvious application to patients with aortic valve insufficiency. A catheter-deployed stent graft with composite valve could be placed across the leaking valve to restore diastolic competence. The practicality of this application will require extensive pre-clinical investigation.

Mitral Insufficiency

Although mitral stenosis has been extensively treated using catheter-based strategies, the challenges of correcting mitral insufficiency with percutaneous techniques are formidable. A composite valve stent graft is conceivable; but secure placement in the endocardial cushion would not be easy. Redundant leaflets potentially could be plicated with catheter technology but it is unlikely that chordae and papillary muscle ruptures will disappear from the surgeon's domain in the near future.

Atrial Fibrillation

Atrial fibrillation (AF) will ultimately afflict up to one-third of the adult population. However, its treatment has been limited to pharmacological therapy of dubious benefit. Moreover, the surgical Maze procedure that has been popularized by Cox et al. [Cox 1995] requires a lengthy operation time while on cardiopulmonary bypass. Attempts to duplicate the surgical Maze procedure by creating linear lines of ablation with radio frequency (RF) catheters has met with limited success. Recently, cardiologists in France have demonstrated that isolation of the triggers of AF in and around the pulmonary veins may prove to be highly effective in aborting paroxysmal AF [Jais 1997, Haissaguerre 1998, Kuck 1998]. Several companies are now pursuing RF and cryoablation strategies. The use of MR guidance offers the hope that these procedures can be completed expeditiously and effectively.

CONCLUSION

It is clear that many of these novel strategies for catheter-based intervention are still years in the making. Cardiac surgeons will have plenty of work for the foreseeable future. This is not instigation for competition or confrontation but, rather, an unusual opportunity for collaboration. Cardiologists and cardiovascular surgeons alike have a common objective in the treatment of cardiovascular disease. The parallel pursuits of percutaneous therapies and minimally invasive surgery merge with the common goal of better care for patients. The next generation of cardiologists and heart surgeons will likely share many similar training experiences and increasingly sophisticated technology: a new endovascular-cardiovascular specialist will likely emerge in the process.

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