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EMERGING TECHNOLOGIES: AN INTRODUCTION TO THE SIS YEARBOOK 2006

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Executive Summary

The pessimistic view of 2006 includes a potential battle between endovascular specialists, a shortfall of training for cardiothoracic surgeons, and declining reimbursement rates. However, there are plenty of reasons to be optimistic. The development of new technology and the ongoing refinement of established techniques continue to evolve, and the borders between interventional cardiologists, cardiothoracic and vascular surgeons, neurologists, and interventional radiologists continue to fade. Cooperation between these specialties has been a key component of the progress that has been made. We open with an introduction to the emerging technologies in vascular therapy (coronary and peripheral), non-invasive imaging, catheter-based treatment of structural heart disease, cell based therapy and ventricular assist devices for the failing heart, and catheter-based arrhythmia treatment.

Introduction

Vascular Therapy

From coronary intervention to percutaneous graft placement, recent years have borne witness to rapidly evolving therapeutic modalities in vascular therapy. All large, and most midsized, arteries are currently amenable to some type of intravascular treatment (Figure 1).

Percutaneous Coronary Intervention

Since their introduction in 2003, drug-eluting stents (DES) have become the gold standard for percutaneous coronary intervention (PCI). DES are now used in the majority of elective cases and increasingly utilized during primary PCI for acute myocardial infarction. The first generation of DES has the disadvantage of being based on standard bare metal stents and requiring a polymeric coating that elutes only a single drug. New stent designs dedicated to drug-elution are emerging. The Conor stent (Conor Medsystems, Menlo Park, CA), for example, incorporates hundreds of small holes, each acting as a reservoir into which drug-polymer compositions can be loaded. This design has the potential to deliver multiple drugs, control the rate of drug release, and modify the direction of drug delivery. Likewise, the Janus™ stent (Sorin Biomedica, Saluggia, Italy) has reservoirs on its external surface in which drug is housed, but without the need for a polymer. This differential coating technique (abluminal vs. adluminal) allows drug to be delivered directly into the vessel wall without being lost in the blood stream.

Since drugs do not adhere to the metal surface of stents, drug-carrying polymers have been used. However, polymeric coatings may contribute to late stent thrombosis, restenosis, and delivery challenges. The polymers need to be biocompatible, such as phosphatidylcholine, which is already in use, and preferably they should be biodegradable, such as the polymer matrix poly(DL-lactide-co-glycolide (PLGA), which is currently being tested in human trials. Carrying this idea further, future stents will likely be made from bioabsorbable material. Such stents hold promise as a temporary scaffolding and drug delivery vehicle that ultimately absorbs, leaving nothing behind but the native vessel. These stents will complement evolving non-invasive imaging technologies, which are currently hampered by the presence of metal, and may reduce the need for prolonged anti-platelet therapy. Preliminary data on bioabsorbable magnesium stents has demonstrated short-term safety and efficacy.

Finally, next generation DES will use different drugs, in multiple combinations, and with varying delivery kinetics. In addition to drugs that are currently available or in advanced testing (Table 1), interesting candidates have entered animal studies. Moving away from immunosuppressants and antiproliferatives, stents that incorporate tryphostin AGL-2043, which interferes with platelet-derived growth factor (PDGF) signaling, or adenovirus vectors which express metalloproteinase inhibitors, hold promise in reducing neointima formation. Others are studying gene eluting stents which deliver naked plasmid DNA encoding human vascular endothelial growth factor 2 (VEGF-2) (1).

Peripheral Intervention

Other arterial beds, including the carotid, subclavian, renal, iliac, femoral, and popliteal arteries, are increasingly approached with catheter-based techniques. Most notably, carotid artery stenting has emerged as an alternative to surgical endarterectomy for the prevention of stroke, particularly since the advent of distal embolic protection devices. Once stroke has occurred, various thrombolytic combinations combined with novel devices for retrieving or mechanically disrupting clot are available. Multiple modalities of ultrasound delivery for clot disruption, as well as novel neuroprotective agents are currently being studied. Investigations focusing on hypothermia in the setting of focal cerebral ischemia are on the horizon.

While DES may not have the same importance in the peripheral arteries as in the coronary arteries, partially because of larger vessel size, percutaneous intervention in these other vascular beds, particularly in the lower extremities, is being improved by newer atherectomy devices as well as self-expanding nitinol stents. Bioabsorbable technology also holds promise in the infra-inguinal arterial beds where restenosis and stent fracture continue to be a significant problem.

Endovascular Aortic Repair

Endovascular repair of abdominal aortic aneurysms has emerged as a viable alternative to open surgical repair. In elective cases suitable for endovascular aortic repair (EVAR), aneurysm related mortality is lower than with surgery, however, in high-risk patients deemed unsuitable for surgery, the results are less convincing (2). In selected patients with symptomatic aneurysm or rupture, EVAR has demonstrated lower mortality, less need for transfusion, and shorter operative and intensive care unit time compared to open surgery (3). Future developments aim to decrease complications like endoleak and graft migration. Similarly, thoracic aortic dissections are now being approached with endovascular techniques. New developments for the treatment of aortic coarctation are focused on devices such as covered stents for treating aneurysms that can occur following coarctation repair, and bioabsorbable stents in newborns who eventually outgrow conventional metal stents (4,5).

Cardiac Imaging

Non-invasive Angiography and Functional Imaging

Advances in multi-detector computed tomography (MDCT) have yielded dramatic results, with the 64-slice MDCT rapidly becoming a standard imaging tool. Correlation with quantitative coronary angiography and intravascular ultrasound (IVUS) has demonstrated an excellent negative predictive value in the diagnosis of CAD. Progress is being made in improving the correlation with stenosis grade and imaging plaque morphology. MDCT angiography may also prove to be a reliable method for evaluating the aortoiliac and lower extremity arteries.

MDCT holds promise for myocardial perfusion and imaging of valve morphology, but is inferior to cardiac magnetic resonance (MR) imaging in that respect. Indeed, cardiac MR has found a niche in imaging congenital heart disease and right ventricular function, and is gaining ground on echocardiography and nuclear stress testing. In terms of MDCT, manufacturers are working on improving two limiting factors, resolution (both spatial and temporal) and dosimetry. A "dual source" MDCT that uses two detector arrays and two x-ray sources offset at 90 degrees recently became available and promises to improve upon both. Future 256-slice MDCT will be able to image the heart in one beat and will likely be widely available in the next few years.

Plaque Imaging

Several techniques for imaging atherosclerotic plaque are under development while some are already commercially available. Carotid intimal media thickness measurements have become commonplace as a marker of atherosclerotic burden, and the use of MR imaging to further define carotid plaque is actively under investigation. Visualizing coronary plaque with this modality is more difficult, but improving. Intravascular MRI should overcome limitations of external-field MRI, but has yet to be proven clinically. Analysis of ultrasound backscatter from IVUS allows correlation not only with plaque morphology, but also with tissue differentiation (virtual histology, VH). VH and other intravascular techniques, such as thermography, palpography, and optical coherence tomography, are not only improving our understanding of the underlying vascular biology of atherosclerosis, but may eventually be used routinely to detect vulnerable plaques and help guide therapy.

Novel molecular imaging methods that focus on the underlying biology rather than just anatomy show promise in characterizing plaque vulnerability (Table 2). These techniques use contrast agents based on MR (magnetic nanoparticles, MNP), radiopharmaceuticals, ultrasound, or optical (near-infrared fluorescence, NIRF) media. These agents depend on specific cellular activity or molecular interaction (antibodies, receptors) to generate an image (6). In general, the carotid arteries have served as a prelude to what may be seen while imaging the coronary bed.

Structural Heart Disease

Percutaneous Valves

The past few years have seen an explosion in percutaneous and microsurgical methods that have moved the field of percutaneous valves forward (Figure 2). Refinements in technique, as well as improvements in the valves themselves have made for progressively better outcomes with percutaneous aortic valve replacement. Specifically, changing to a retrograde approach and decreasing the access sheath size, while still being able to place larger orifice valves that are retrievable and repositionable has decreased complications such as anterior mitral valve leaflet injury, vascular bleeding, and perivalvular regurgitation. Percutaneous valve replacement for severe pulmonic regurgitation has been successfully performed, and initial animal experiments have confirmed the feasibility of interventional tricuspid valve replacement (7,8).

There are several techniques and devices in development for mitral valve repair. In general, these have been designed to replicate the effects of surgical repair, such as joining the middle of the anterior and posterior mitral leaflets using novel clips/suture or reshaping the mitral valve annulus using a coronary sinus approach. Further research will indicate which percutaneous modalities are promising enough to be tested against surgery itself.

Patent Foramen Ovale

Although some still consider surgical closure of interatrial shunts the gold standard, device closure has established itself as a method many patients prefer. Excellent success rates and low complications make it an attractive alternative to surgery. While the first generation of devices are in widespread use, there are several fascinating developments attempting to avoid leaving large foreign bodies permanently behind. Specifically, the first bioabsorbable device made of an acellular collagen matrix has recently undergone human testing. It was shown that the device could be successfully inserted and integrated into the septum, with closure rates at 6 months of 96%. Other innovative approaches being tested are the use of radiofrequency to fuse the patent foramen ovale (PFO) “flap” with the interatrial septum and percutaneous suture closure techniques. The potential indications for closing PFO are also undergoing modification. PFOs are currently only closed for secondary stroke prevention in patients who have failed optimal medical management, but the possibility of PFO closure to reduce the frequency and severity of migraine headaches could ultimately affect a significant subset of the population.

Myocardial Damage and Heart Failure

Cell-Based Therapy

Cell based therapies for cardiomyopathy and myocardial infarction show promise, with modest increases in ejection fraction and reductions in infarct size demonstrated in several small human trials. Strategies aim at either enhancing the body's own regenerative response to myocardial injury or transplanting cells with the (theoretical) capacity to develop a cardiomyocyte phenotype. Multiple cell types have been employed and the optimal delivery modality is being refined. New research techniques for studying cell delivery involve tagging stem cells with MR-contrast agents in order to track delivery to the sites of interest. The mechanisms by which these cell-based therapies work remains disputed, and appears to depend more on enhanced regeneration and vasculogenesis rather than transdifferentiation of cells (9,10). Further understanding of the underlying mechanisms will eventually lead to a more targeted therapeutic approach.

Ventricular Assist Devices

Despite advances in the treatment of heart failure, options for the end-stage patient are limited. In recent years, ventricular assist devices (VADs) have become an increasingly important part of the heart failure specialist's armamentarium. The first generation of devices could successfully bridge patients to transplant, but did not performed as well as a destination therapy. Mechanical failure and the risk of infection, especially drive line infections, were high. The development of rotary flow pumps over

the past decade has overcome some of the early problems. These pumps, such as the Jarvik 2000 FlowMaker® (Jarvik Heart, Inc., Manhattan, NY), the Thoratec HeartMate® II (Thoratec, Pleasanton, CA), and the CircuLite™ MicroVAD (CircuLite, Inc., Hackensack, NJ), are smaller and less prone to failure due to fewer moving parts (11). Increasingly, ventricular unloading catheters using a rotary pump can be inserted with minimally invasive surgical procedures or even percutaneously. The TandemHeart® PTVA® (percutaneous transseptal ventricular assist) (CardicAssist Inc., Pittsburgh, PA) is such a device and can be used to provide temporary cardiac augmentation at the time of a high risk coronary intervention or during recovery following an acute myocardial infarction.

Catheter-Based Arrhythmia Treatment

The ever-changing field of electrophysiology offers much excitement. The revolution in cardiac imaging has led to improvements in mapping techniques, which is paramount when accuracy is of essence. Novel catheters and alternative energy sources, such as microwave, high intensity focused ultrasound, laser, and cryotherapy are increasingly making arrhythmia ablation more accurate, thorough, and safe. In addition, the use of robotic catheter manipulation aims to improve the stability, precision, and dexterity of the operators, and has the potential for remote operation. Such futuristic techniques are actually already undergoing small-scale investigational use. Finally, a move from the standard transvenous implantable cardioverter defibrillator (ICD) to a totally subcutaneous ICD may be underway.

Conclusions

With all of the emerging technologies in cardiovascular imaging and percutaneous interventions, it's hard not to be excited. Much of this progress has been achieved through the interaction of multiple specialties with a common goal. A multi-specialty interconnected field in cardiovascular disease is emerging and the future looks bright.

Figure 1. Percutaneous Vascular Therapy

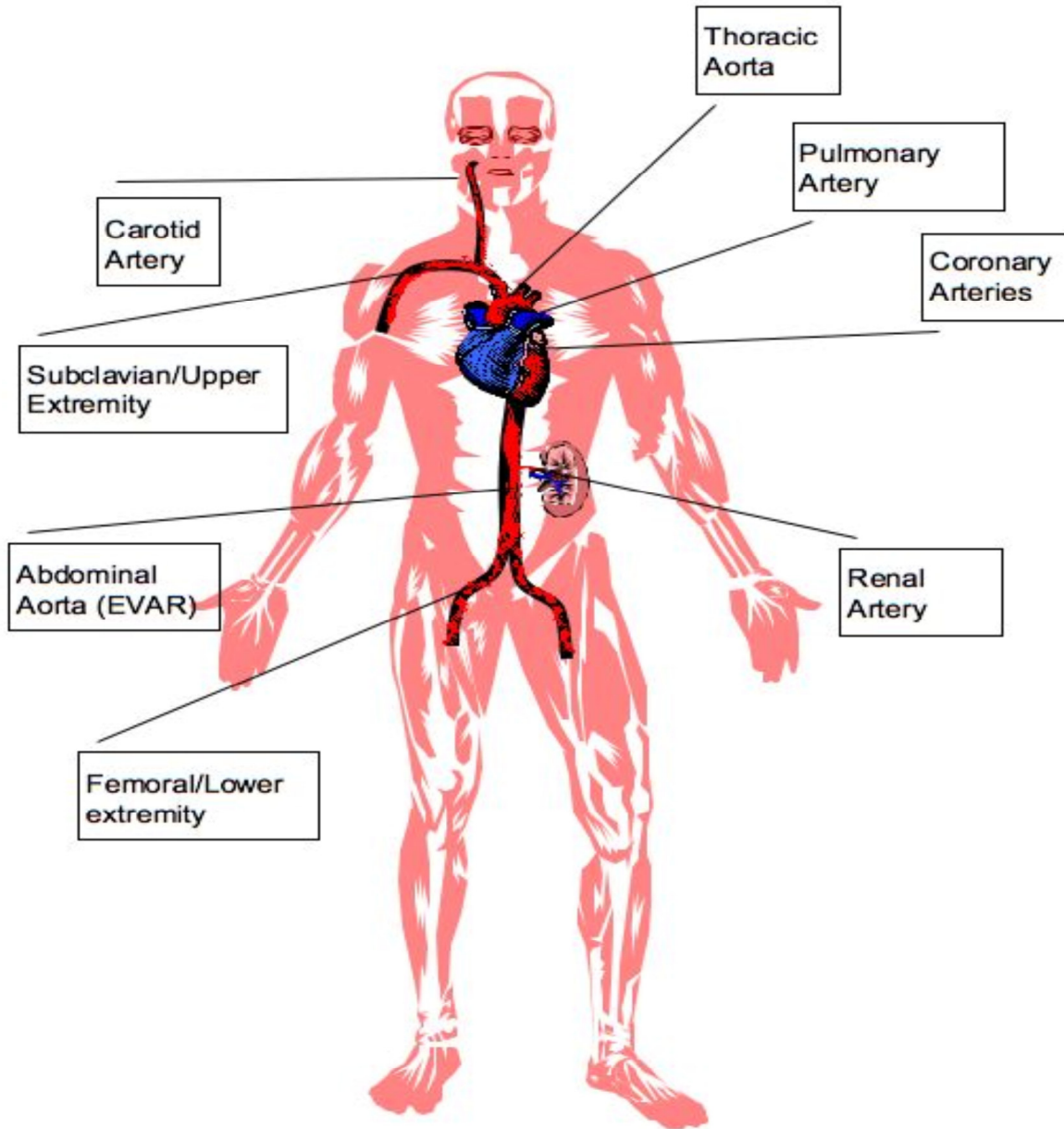


Figure 2. Approaches to Percutaneous Valve Interventions

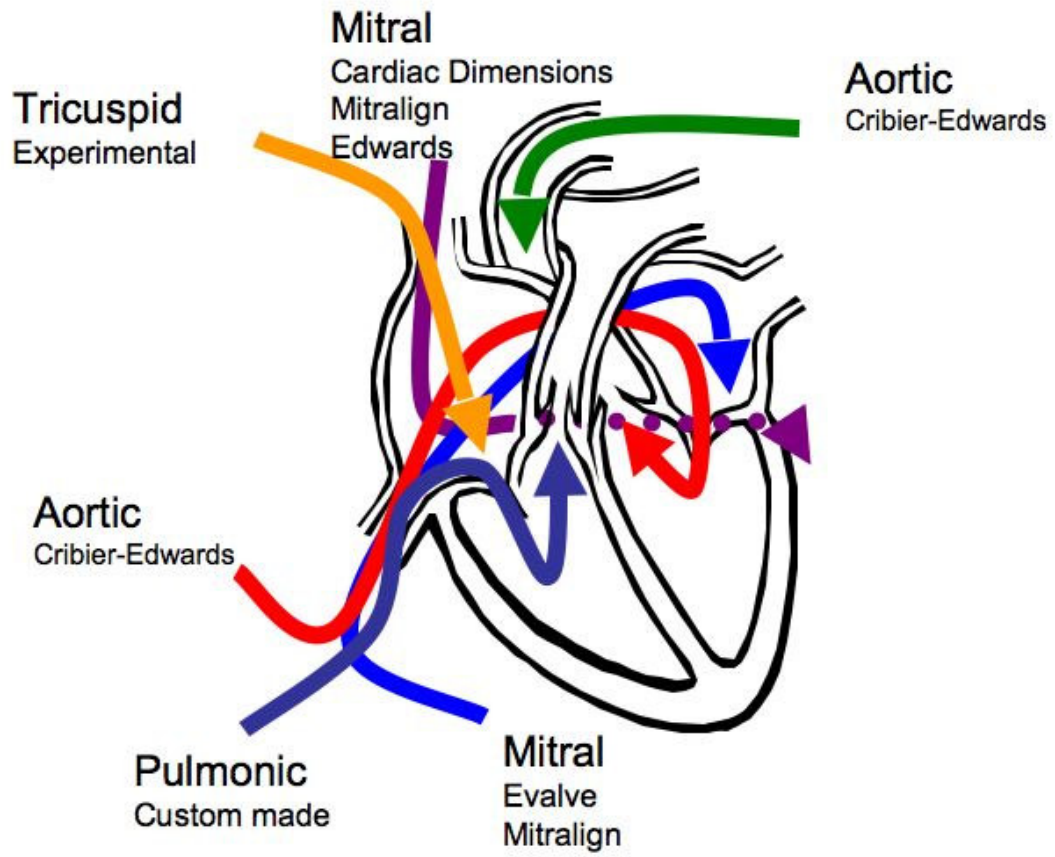


Table 1. DES and Bioabsorbable Stents Currently Approved or in Trials

Stent	Target	Drug	Material/ Polymer	Approval	Company
ABSORB	Coronary	Evorolimus	Bioabsorbable	Phase III	Guidant
Avantex	Coronary	Pimecrolimus	Duraflex	NA	Avantec
Axxess Plus	Coronary	Biolimus A9	Nitinol	NA	Devax
Axxion	Coronary	Paclitaxel	Steel/None	CE Mark	Biosensors
Biomatrix	Coronary	Biolimus A9	Steel/Bioabsorbable	NA	Biosensors
CoStar	Coronary	Paclitaxel	Cobalt Chromium/Bioabsorbable	Phase III	Conor
Cypher	Coronary	Sirolimus	Steel/None	Approved	Johnson&Johnson
Cypher Neo	Coronary	Sirolimus	Cobalt Chromium/Durable	NA	Johnson&Johnson
Cypher Select	Coronary	Sirolimus	Steel/Durable	CE Mark	Johnson&Johnson
Dexamet	Coronary	Dexamethasone	Steel	Approved	Abbott
Endeavour	Coronary	Zoralolimus	Cobalt Chromium/Durable	CE Mark	Medtronic
Infinium	Coronary	Paclitaxel	Steel/Bioabsorbable	CE Mark	SMT
Janus	Coronary	Tacrolimus	Steel+Carbofilm	CE Mark	Sorin
Nobori	Coronary	Biolimus A9	Steel/Bioabsorbable	NA	Terumo
Taxus	Coronary	Paclitaxel	Steel/Durable	Approved	Boston Scientific
Taxus Liberté	Coronary	Paclitaxel	Steel/Durable	CE Mark	Boston Scientific
XIENCE V	Coronary	Evorolimus	Cobalt Chromium/ Durable	CE Mark	Guidant
YUKON	Coronary	Sirolimus		Phase IV	Translumina
Zilver PTX	Peripheral	Paclitaxel	Nitinol	Phase I	Cook
ZoMAXX	Coronary	Zoralolimus	Steel	Phase II	Abbott

Grey shading=first generation

Table 2. In Vivo Molecular Imaging of the Vulnerable Plaque

Target	Location	Imaging technique	Agent	Organism
Angiogenesis	Aorta Femoral/Carotid	MRI/NIRF IVUS	Ligand Immunol	Mouse Swine
Apoptosis	Aorta Carotid	Nuclear Nuclear	Ligand Ligand	Rabbits Human
Cathepsin B Activity	Aorta	NIRF	Enzym	Mouse
Integrin $\alpha_v\beta_3$	Aorta	MRI	Ligand	Rabbit
LDL	Aorta	Nuclear	Immunol	Mice/Rabbit
Macrophage Activity	Carotid	MRI	MNP	Human
Matrix Metalloproteinases	Carotid Aorta	Nuclear NIRF	Ligand Enzym	Mouse Mouse
Myeloperoxidase	NA	MRI Nuclear	Enzym Enzym	NA
Plaque Inflammation	Carotid	Nuclear	¹⁸ F DG	Human

MRI=magnetic resonance imaging, NIRF=near-infrared fluorescence, Enzym=enzymatic activity, LDL=low density lipoprotein, NA=not available, MNP=magnetic nanoparticles, immunol=immunological, FDG=fluorodeoxyglucose

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