

Structural Heart Disease

Introduction:

The focus of this discussion is on device-based therapies to treat symptoms of heart failure, on myogenesis (combined skeletal myoblasts and mononuclear bone marrow stem cells) for myocardial repair post infarct, on the percutaneous treatment of valvular heart disease and on patent foramen ovale (PFO) devices for the treatment of recurrent thromboembolic events. The information presented below was derived from the references listed at the end of this monograph.

Scope of the Problem/Background

Congestive Heart Failure. CHF is a disease affecting 25 million people worldwide. In CHF patients, the heart enlarges (cardiomyopathy) to compensate and consequently causes the annulus to dilate. The progressive pump enlargement and dysfunction is collectively referred to as ventricular remodeling. Scientists now recognize that progression of heart failure is due to neurohormonal activation and abnormal mechanical stresses on the myocardium (increased preload and afterload). The goal of many heart failure treatments is to prevent, slow, or reverse this process. Randomized studies have shown that a pharmacologic blockade of neurohormonal activation and abnormal mechanical stresses on the myocardium may not be effective and, therefore, extensive efforts have been made toward the development of device-based therapies for patients with both acute and congestive heart failure.

Valvular Dysfunction. Aortic and mitral valve repair and replacement are common surgical procedures and are typically effective in eliminating or significantly reducing regurgitation; however, these procedures remain controversial as sole treatments for patients with a low ejection fraction. The treatment for mitral regurgitation due to dysfunction involves the achievement of properly aligned valvular leaflets, an optimally sized annulus, and a geometrically coordinated subvalvular apparatus (chordae tendinae and papillary muscles).² The challenge in treating patients with CHF due to mitral regurgitation is deciding the mode of repair to address these multiple factors. Aortic regurgitation is typically remedied surgically through heart valve replacement. 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. With minimally invasive, catheter-based treatments, more patients can be treated for this disease.

Patent Foramen Ovale (PFO). PFO is a congenital, flap-like opening between the atrial septa primum and secundum that persists after age 1 year. In utero, the foramen ovale serves as a physiologic conduit for right-to-left shunting (blood flow directly from the right atrium to the left atrium). Once the pulmonary circulation is established after birth, left atrial pressure increases allowing functional closure of the foramen ovale and anatomical closure of the septum primum and septum secundum.³ PFO is usually permanently shut by the first birthday, however, one person in five still has an open PFO into adulthood. When the PFO is not completely closed, individuals are predisposed to hemostasis and clot formation if any conditions occur that increase right atrial pressure more than left atrial pressure. The end result is paradoxical embolism (venous embolus that crosses the PFO and embolizes to the cerebral circulation). Studies of cryptogenic stroke in young patients have shown that the incidence of PFO is higher than in patients with established causes of stroke.⁴ Although the optimal management of patients with a symptomatic PFO remains controversial, therapeutic options for secondary stroke prevention include long-term drugs or oral anticoagulation and more invasive strategies such as surgical or percutaneous PFO closure.

Structural Heart Disease - Current Therapies

Congestive Heart Failure. Surgical approaches to CHF treatment have involved surgical reshaping of the dilated heart and heart valves and have been performed for several years with mixed results. Therapies such as ventricular reduction surgery (VRS) and aneurysmectomy (removal of scar tissue on the myocardium caused by infarctions) as well as ventricular restraint devices used for cardiomyoplasty (latissimus dorsi muscle wrapped around the heart stimulated to contract in synchrony with the native heart), have been limited in showing clinical benefit.

Other devices, such as ventricular assist devices, provide a bridge to transplant. These devices are capable of completely supporting the circulation and are assuming an increasingly important role in heart failure therapy. Very sick patients already in cardiogenic shock (inadequate blood pressure and cardiac output to meet the body's metabolic needs) can benefit from acute hemodynamic support through devices such as the TandemHeart, a percutaneous, catheter-based pump approved for short term hemodynamic support.

Valvular Dysfunction. Valvular annuloplasty and valve replacement have been common therapies for congestive heart failure caused by regurgitation and have been effective in eliminating or reducing regurgitation. However, mechanical heart valves are contraindicated for patients intolerant of long-term anticoagulation therapy and xenografts have limited durability. Total artificial

hearts, such as the Cardiwest Total Artificial Heart, are biventricular, pneumatic, pulsatile pumps implanted in the orthotopic position and replace the native ventricles and all four cardiac valves as a bridge to heart transplant. Despite the effectiveness of surgical therapies, they are limited to patients that can tolerate cardiac surgery.

Patent Foramen Ovale (PFO). Treatment of symptomatic PFO includes long term medical treatment (platelet anti-aggregating drugs or oral anticoagulation) and more invasive strategies such as surgical repair. More recent treatments involve percutaneous PFO closure devices including the Amplatzer device (AGA Medical), the PFO Star device, the CardioSeal, the Helix device, and the Proximare PFO Occluder (Proximare, Inc.)⁵. Clinicians have indicated that these devices, for the most part, are easy to use and, therefore, should be implanted in patients with known PFO.

Structural Heart Disease - New Therapies

Congestive Heart Failure.

Stem Cell Therapy. Additional methods of treatment for myocardial repair involve the transplantation of both skeletal myoblasts and stem cells into the region of infarcted myocardium resulting in improved myocardial function. Myogenesis has been demonstrated in a number of myocardial injury models and proved the potential to regenerate viable tissue after being transplanted in the infarcted heart. In these tests, skeletal myoblasts (SMs) improved myocardial performance *in vitro* and *in vivo* when delivered to the injured myocardium by intramural implantation or arterial injection. Human clinical studies have shown corresponding data to these pre-clinical data. Bone marrow stem cells have one major advantage over SMs in that they have the ability to acquire the phenotypic characteristics of their host tissue and to differentiate into cardiomyocytes and endothelial cells following engraftment into myocardium. Results from the first clinical trials suggest that injected bone marrow-derived mononuclear cells cause an improvement of myocardial blood flow and associated improvement in regional and global left ventricular function in patients.^{6,7}

Device-based Therapies. Device-based approaches are playing an increasing role particularly in patients with cardiovascular abnormalities that are largely hemodynamic and mechanical in nature. Devices such as the A-Med System and the Impella CardioSystem, now under investigation, have helical propellers which draw blood from the left ventricle through the distal end of a catheter and discharge it into the aorta. These catheters can be inserted percutaneously via the femoral artery or surgically into the proximal aorta. IMPULSE Dynamics is currently conducting a clinical trial to evaluate the safety and efficacy of cardiac contractility modulation (CCM) signals delivered by the implantable OPTIMIZER™ System in patients with NYHA class III/IV heart failure.⁸

Valvular Dysfunction. Numerous catheter-based devices are being developed to be able to perform valve repair and replacement percutaneously to reduce risk and allow it to be performed as a sole therapy to treat symptoms of heart failure. These percutaneous, catheter-based devices will enable an expanded group of patients, who are not yet surgical candidates, an option to remedy this destructive risk factor. One such device under investigation is the Mitralign System by Mitralign, Inc. (Salem, NH). The Mitralign system uses magnetic guidance to position a catheter in the left ventricle under the mitral valve. Once in place, the catheter is used to deliver a series of suture elements around the valve. These sutures are then tensioned and locked in place, reducing the circumference of the dilated valve and eliminating mitral regurgitation.⁹ Another percutaneous device intended for mitral valve repair is the Carillon Mitral Contour system which is implanted in the great cardiac vein / coronary sinus via a catheter-based delivery system. The implant is designed to reshape the mitral annulus and reduce mitral regurgitation, in effect, by mild tension or cinching of the device.¹⁰ The concept of “restrictive annuloplasty” (stringent undersizing of the mitral annulus without inducing mitral stenosis)¹¹ achieves reverse remodeling through other novel devices under investigation such as the Edge to Edge Mitral Valve Clip (Evalve, Inc.) and the Accucinch System (Guided Delivery Systems), both of which provide annuloplasty percutaneously.

Percutaneous aortic valve replacement is not a new initiative, since the pioneer attempts to deliver catheter-based valves date back to the sixties. During the last few years, percutaneous heart valve (PHV) replacement and repair has emerged as an additional therapy to potentially avoid the reoperation in young patients with congenital heart disease or severely sick patients. Although a great deal of work remains to be done in the area of percutaneous aortic heart valve replacement, preliminary results indicate that the development of these devices for transluminal placement is feasible.

Conclusion:

New devices are on the foreground to treat patients with varying degrees of heart failure. From total artificial hearts, percutaneous heart valves and rings, to catheter-based devices for the transport of drugs, stem cells, sealants and other agents, there is no doubt that this field is moving quickly to develop minimally invasive tools that will reduce morbidity and mortality in individuals being diagnosed with heart failure. There is anticipation in the medical community that the effectiveness of these technologies will outweigh some of the pharmacologic approaches of the past in the treatment of congestive heart failure.

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