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Interventional Therapies for Heart Failure

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Executive Summary

The use of interventional devices for the treatment of medically refractory heart failure is an emerging field. Several novel approaches are under development including strengthening of cardiac contraction with *cardiac contractility modulation*, modification of the heart rate with *vagal nerve stimulation*, reduction of ventricular size with *surgical ventricular restoration*, increasing renal perfusion with *targeted renal therapy*, decreasing fluid overload with *ultrafiltration*, and improving cardiac output with *continuous aortic flow augmentation*. *Ventricular assist devices*, which have been used as a bridge to transplantation and as destination therapy, are now being investigated as a bridge to recovery, as some observations show reverse remodeling of the heart with these devices. Advances in ventricular assist devices are decreasing the degree of invasiveness and improving device longevity and reliability. With a growing understanding of the hemodynamic fundamentals of heart failure and promising new interventional devices on the horizon, we can hope for continued improvements in the quality of life and survival of patients with this debilitating disease.

Introduction

Disease mechanisms and treatments for congestive heart failure (CHF) have been studied for decades. Still, the quest for therapies that favorably impact quality of life and prognosis is ongoing. Standard pharmacologic treatments include ACE inhibitors, angiotensin receptor blockers, β -blockers, aldosterone inhibitors, and diuretics. These treatments block key neurohormonal pathways and counteract salt and water retention, thus interrupting the vicious cycle responsible for

progressive cardiovascular remodeling, deterioration of renal function, and decreased exercise tolerance (Figure 1). Despite availability of these accepted therapies, most patients exhibit disease progression, experience repeated hospitalizations, and ultimately succumb to their disease. Evidence indicates that attempts at additional pharmacologic-based neurohormonal blockade may be detrimental and we may have reached the limit to which neurohormonal and cytokine mechanisms can

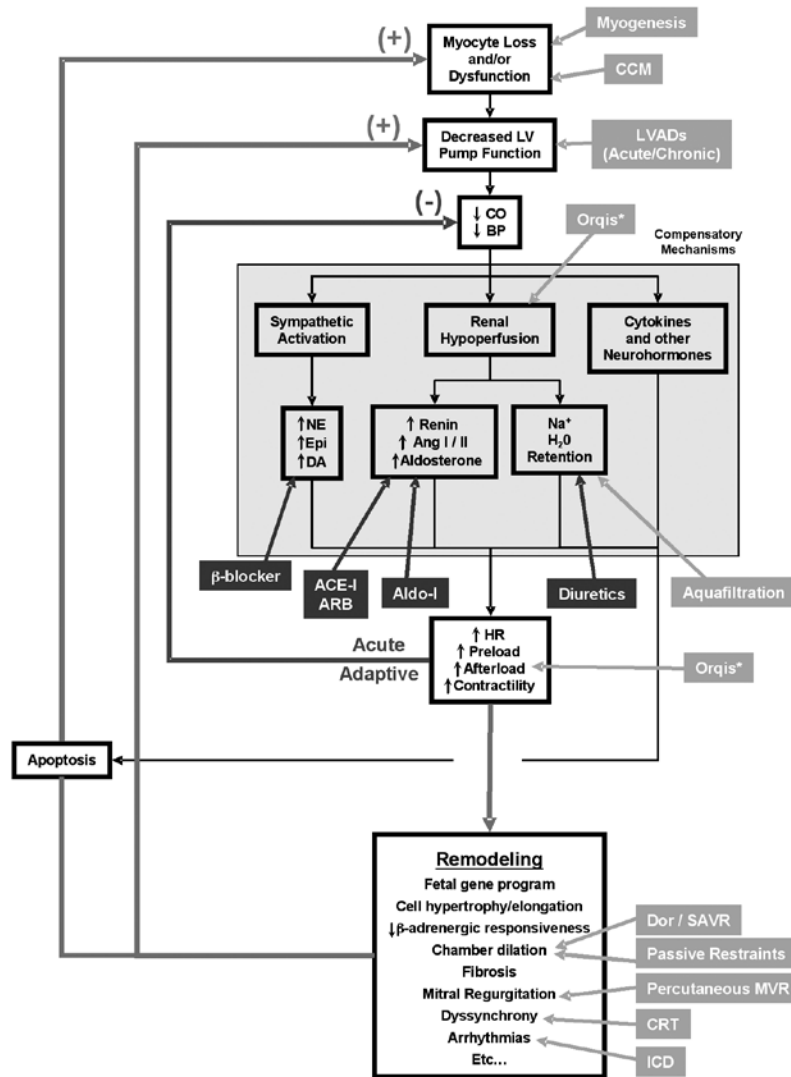


Figure 1 The Vicious Cycle of Ventricular Remodeling

Myocyte loss and/or dysfunction results in pump dysfunction. In the acute setting, neurohormonal activation attempts to restore cardiac output and blood pressure via mechanisms considered adaptive in the short term. If sustained, neurohormonal activation and increased mechanical stresses conspire in a maladaptive process to drive a multitude of abnormal processes including apoptosis. Blue boxes show pharmacologic treatments and where they block the cycle. Green boxes show device-based therapies and where they intervene.

Abbreviations: CO, cardiac output; BP, blood pressure; NE, norepinephrine; EPI, epinephrine; Dopa, dopamine; Ang I/II, angiotensin I and II.

*Orqis, continuous aortic flow augmentation with femoral-to-aorta blood shunting.

Reprint from Mancini D and Burkhoff D⁽²⁾

be blocked in CHF patients⁽¹⁾. Heart transplantation, considered as a final treatment option for patients with severely decompensated CHF, is also limited by the relatively small number of donor hearts.

These realities have fueled intensive efforts to develop and test device-based therapies for CHF. A comprehensive review of heart failure devices in various stages of development was published in 2005⁽²⁾. Since then, no new devices have been approved for the treatment of CHF, many of the devices under investigation at that time remain under investigation, and investigation has been halted on a few. This speaks to the relatively slow pace, long time horizon, and relatively high efficacy and safety standards required for gaining acceptance of new therapy. This chapter shall review some of the latest developments in interventional devices used in therapy of CHF. An overview of the devices under investigation, along with their proposed underlying pathophysiologic target, is summarized in Figure 1.

Electrical Therapies for Chronic Heart Failure

Implantable cardioverter defibrillators (ICD) and cardiac resynchronization therapy (CRT) are arguably the most important device-based treatments currently FDA approved for use in patients with CHF. It is well known that ICDs detect life threatening arrhythmias and deliver electrical therapy (e.g., anti-tachycardia pacing, direct-current cardioversion pulses, and back-up bradycardia pacing) to prevent sudden death. Likewise, CRT improves pump function in patients with mechanical dyssynchrony by using a biventricular pacemaker to restore the synchrony of myocardial contraction. Multiple studies show that CRT improves quality of life and exercise tolerance, while reducing hospitalizations and mortality. CRT is currently approved for CHF patients with New York Heart Association (NYHA) functional class III or IV symptoms and a QRS duration >120-130 ms. Studies are still underway to determine if CRT is effective in patients with a normal QRS duration, but evidence of mechanical dyssynchrony on tissue Doppler imaging (TDI) studies, or in preventing disease progression in patients with NYHA class II symptoms.

Cardiac Contractility Modulation Therapy

In order to enhance the strength of cardiac muscular contraction, non-excitatory electrical signals called cardiac contractility modulation (CCM) signals can be delivered during the absolute refractory period of the cardiac cycle^(3,4). The CCM signals are delivered by a device, the OPTIMIZER™ (Impulse Dynamics, Orange-

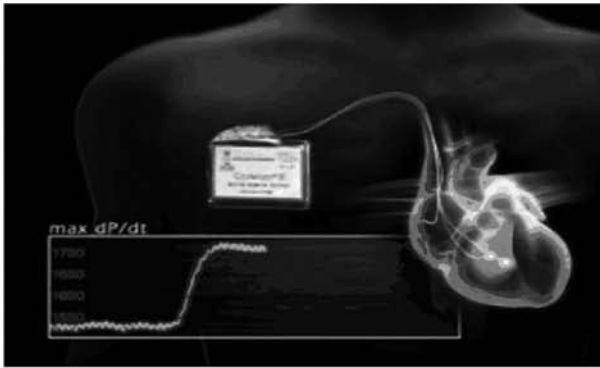
burg, NY) (Figure 2A), that resembles an ICD or pacemaker and delivers therapy via three standard transvenous pacing leads inserted into the right ventricular septum. The OPTIMIZER™ system was studied in the FIX-CHF-4 trial, a prospective, randomized, double-blind, crossover study that enrolled 164 subjects who were ineligible for CRT and had an EF <35%, as well as NYHA class II or III symptoms despite optimal medical therapy. Preliminary results of this study were reported at the 2006 Scientific Sessions of the Heart Failure Society of America in Seattle, WA⁽⁵⁾. Significant improvements were found in peak VO₂, Minnesota Living With Heart Failure scores, and the 6-minute hall walk test (6MW). Those with the device showed a trend toward fewer deaths and hospitalizations. FIX-CHF-5 is a pivotal trial underway at 50 sites in the United States that is enrolling 428 subjects with NYHA class III or IV symptoms despite optimal medical therapy. Because CCM signals are intended to improve the strength of muscle contraction, it is postulated to work equally well in patients with normal and abnormal QRS duration and also in combination with CRT. Acute hemodynamic studies have provided initial validation for this concept by showing that the impact of CCM and CRT on left ventricular contractile force are additive when applied at the same time⁽⁶⁾. Investigators are already starting to gather information on combining CCM with CRT in the chronic setting⁽⁷⁾.

Vagal Nerve Stimulation

The use of parasympathetic nerve stimulation to slow the heart rate is the basis for a new approach to CHF treatment⁽⁸⁾. The device called the CardioFit™ system (BioControl Medical, Israel) is implanted in the subcutaneous pocket in the chest and the electrode is positioned around the vagus nerve in the neck. By continuously monitoring an electrocardiogram, stimulation is adjusted to the patient's optimal heart rate. The vagus nerve is stimulated through a propriety tri-polar cuff electrode that provides accurate control over specific nerve fibers, thus avoiding cross activation of undesired fibers. It will be of interest to see if heart rate modulation beyond that which can be achieved with β -blockers can provide additional clinical benefit. The device is presently in early studies for treatment of class II and III heart failure patients.

Surgical Approaches to CHF

At least two surgical approaches for treating CHF have received significant attention in recent years, surgical ventricular restoration (SVR) and passive ventricular constraint.



A. Optimizer™



B. Mannequin™ Endoventricular Shaper



C. The Blue Egg



D. Corcap™



E. HeartNet™ Ventricular Support System



F. HeartMate® IP LVAS



H. HeartMate® II



I. Abiocor™ implantable TAH



G. HeartMate® XVE LVAS



J. Cardiwest™ TAH

Figure 2 Devices Used in Refractory Heart Failure

Surgical Ventricular Restoration

It has been postulated that reverse remodeling can be achieved by decreasing the radius of the curvature of the dilated heart, thereby decreasing myocardial wall stress and improving myocardial contraction. When achieved by surgical excision of infarcted, akinetic, or dyskinetic portions of the ventricular wall this is termed *surgical ventricular restoration*. The result is a smaller, more normal, elliptically-shaped chamber that theoretically has improved function. Dyskinetic scar (aneurysm) removal, called *aneurysmectomy*, is already a clinically accepted procedure. Akinetic scar removal, via a procedure popularly known as the *Dor Procedure*, is under investigation in a National Institutes of Health-sponsored trial, Surgical Treatment of Ischemic Heart Failure Trial (STICH). This study is comparing medical therapy with coronary artery bypass surgery and/or surgical ventricular restoration for patients with CHF and coronary artery disease.

The limitations of surgical ventricular restoration include the lack of a uniform method of performing the procedure and the lack of agreement on the ultimate size and geometry of the reconstructed chamber, as well as the surgical technique for reconstructing the chamber. Two devices studied outside of the STICH trial, the Blue Egg device (Bioventrix, CHF technologies) (Figure 2C) and the Mannequin™ Endoventricular Shaper (Chase Medical) (Figure 2B), are inserted into the chamber to provide a guide for reshaping and resizing the left ventricle. This may help standardize the results of these procedures. The acute hemodynamic effectiveness of surgical ventricular restoration has also been challenged⁽⁹⁾, and the results of the STICH trial will be pivotal in determining whether this procedure will gain widespread acceptance.

Passive Ventricular Restraint

The Corcap™ (ACORN Cardiovascular Inc) (Figure 2D) and HeartNet™ (Paracor Medical Inc) (Figure 2E) devices are two passive ventricular restraint devices that evolved from an earlier investigational approach called *cardiomyoplasty*. In this technique, a passive material wrap is placed around the heart to provide gentle, permanent restraint in order to prevent or even reverse pathological ventricular dilation. This approach has been shown to reduce the myocardial wall stress and thereby promote reverse remodeling in animal models of heart failure. A multicenter randomized study from ACORN Cardiovascular has suggested that this approach improves NYHA class and reduces the requirement for subsequent major cardiac procedures such as cardiac transplantation and ventricular assist device (VAD) insertion⁽¹⁰⁾. These products are still not approved pending more clinical data.

In evaluating the effectiveness of surgical CHF

treatments, the need for mitral valve repair or replacement is an important, yet potentially confounding factor during clinical trials. Numerous efforts are underway to develop devices that allow for percutaneous repair of the mitral valve. If this goal is achieved, the reduction in risk compared to surgical therapy may allow percutaneous repair to be performed as a sole therapy to treat symptoms of heart failure. Mitral valve repair as a stand alone surgical procedure is not currently the standard of care for patients with dilated cardiomyopathy (ischemic or idiopathic) due to poor outcomes in CHF patients compared to standard degenerative mitral regurgitation patients. Availability of less invasive percutaneous devices may lead to evidence that treating mitral regurgitation in patients with CHF can impact favorably on quality of life, exercise intolerance, and even mortality. Percutaneous valve repair is discussed elsewhere in this publication.

Devices to Treat Acutely Decompensated Heart Failure

Renal Artery Vasodilator Drug Delivery

In severe decompensated CHF, reduced renal perfusion is common secondary to relative hypotension and renal artery constriction. These patients become increasingly diuretic resistant and fluid overloaded. With this problem in mind, devices like Targeted Renal Therapy™ (Flowmedica Inc) have been developed, which can deliver medication, such as short-acting vasodilator, directly into the renal artery. Selective delivery of vasodilators can enhance renal perfusion without the side effect of further reducing systemic arterial pressure. In conjunction with standard diuretic therapy, significant natriuresis and diuresis can be achieved. One example of such a therapy is the investigator-sponsored study of fenoldapam to reduce the nephrotoxicity of catheterization dye⁽¹¹⁾. The concept is also proposed that the kidneys may eliminate a substantial amount of any drug infused directly into the renal arteries, limiting the amount of medication in the systemic circulation.

Ultrafiltration

Another device-based system that deals directly with the problem of fluid overload is the Aquadex™ system (CHF solutions) (Figure 4C). This device works on the principle of aquapheresis through a venous access that removes isotonic salt and water at an average rate of approximately 150cc/hr without clinically significant changes in serum electrolytes, heart rate, and blood pressure⁽²⁾. The UNLOAD trial, a randomized multicenter study, shows greater weight and fluid loss, as well as reduced rehospitalizations among patients receiving ultrafiltration therapy⁽¹²⁾.

Continuous Aortic Flow Augmentation

The use of continuous aortic flow augmentation is an investigational approach for acute CHF exacerbations in patients who are inotrope dependent or refractory. The CACION[®] System (Orquis Medical) (Figure 4A) consists of an extracorporeal, magnetically-levitated centrifugal pump that withdraws blood from both femoral arteries and returns it to the descending thoracic aorta in a continuous, nonpulsatile manner at rates between 1.1 and 1.5 L/min. This device showed an increase in overall cardiac output, improved renal function, additional diuresis, and reduced pulmonary artery pressures in experimental animals. Initial clinical evaluation has shown that in patients with heart failure and persistent hemodynamic derangements despite intravenous inotropic and/or vasodilator therapy, this approach improves hemodynamics and renal function⁽¹³⁾. A multicenter clinical trial (MOMENTUM) based on this approach has started recently. In addition to the short-term CACION device, a totally implantable augmentation system called EXELERAS[®] (Orquis Medical) (Figure 4B) is now under review as a long-term option.

Left Ventricular Assist Devices

Due to limited availability of donor organs and urgency of cardiac support in severe decompensated CHF, ventricular assist devices (VADs) have the potential to play an important role as a bridge-to-transplantation (BTT). Since the results of the REMATCH (Randomized Evaluation of Mechanical Assistance in the Treatment of Congestive Heart Failure) trial⁽¹⁴⁾, VADs are also being considered as destination therapy (DT) in patients ineligible for heart transplant and even as an alternative to transplant. VADs are classified into extracorporeal and intracorporeal devices. Extracorporeal devices are mainly used as short-term BTT in very emergent situations and are not generally considered for DT or BTT when an intracorporeal device can be inserted electively in a patient already known to be a good candidate for transplantation. The extracorporeal devices that are used as a full support VAD include Abiomed BVS 5000[™] and Thoratec[®] VAD. Those that are used for short-term hemodynamic support include the Tandem Heart[®] (clinically-available) and the Impella[®] (in clinical trials). Intracorporeal devices most commonly used for DT and BTT are the HeartMate[®] and Novacor[®]. Detailed descriptions of most VADs have been provided on many occasions⁽²⁾ and were also reviewed in the SIS Yearbook from 2006⁽¹⁵⁾. Below is a discussion of new developments.

Thoratec HeartMate[®] LVAD

There are 3 forms of Thoratec available, namely the *IP* (Implantable pneumatic) (Figure 2F), the *XVE*

(extended-lead vented electric) (Figure 2G) and the *SNAP-VE* (suture-not-applied vented electric). These devices use pusher plate technology with a polyurethane diaphragm to propel blood in a pulsatile fashion up to 10 L/min. The Thoratec HeartMate[®] II (Figure 2H) is a high speed (6,000 to 15,000 rpm) non-pulsatile axial flow rotary pump which uses electromotive force to provide blood flow up to 10L/min. Clinical trials are underway evaluating its safety and efficacy for both BTT and DT.

World Heart's Novacor[®] LVAS

Novacor[®] II VAD (World Heart Inc) (Figures 3B and 3C) is currently an investigational device and is the next generation to the already available Novacor[®] VAD (Figure 3A). The Novacor[®] II is based on a similar principle of unloading the left ventricle and propelling the blood to the aorta through a pusher plate system, but it has a smaller size and improved technology. It is an abdominal implant, and has a magnetically-driven pulsatile VAD consisting of two chambers, namely a pre-chamber, which fills the blood from the left ventricle through an inflow conduit, and a pumping chamber, which pumps blood into the aorta through an outflow conduit. The chambers are partitioned by a pusher plate. When the pusher plate is driven to the right (the pumping stroke), the pre-chamber expands, filling from the left ventricle. Simultaneously, the pumping chamber is compressed, ejecting blood into the body. When the pusher plate returns to the left (transfer stroke), the pre-chamber is compressed while the pumping chamber expands; blood transfers from the pre-chamber to the pumping chamber, with no inflow or outflow. Because the total volume of the two chambers remains constant as one fills and the other empties, the system can operate without a volume compensator or venting through the skin, thereby reducing the risk of complications by eliminating the need to perforate the skin.

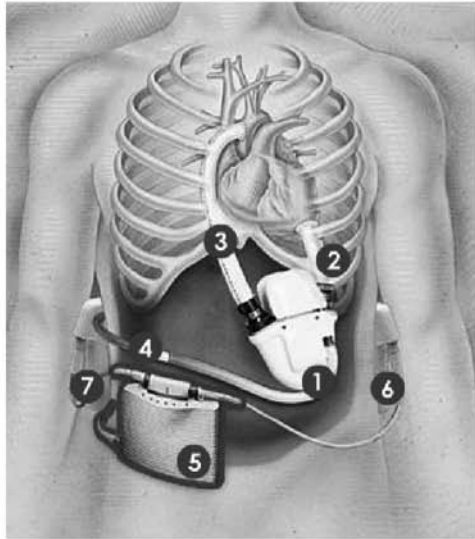
World Heart's Levacor VAD

The Levacor VAD (WorldHeart Inc) (Figure 3D) is a compact, pulsatile centrifugal pump with an impeller that is completely magnetically levitated, optimizing blood flow around the impeller while eliminating dependence on the patient's blood for suspension. This device is intended for destination therapy and is currently under investigation. Potential advantages to this technology include a smaller size, a simpler mechanism, a lack of valves, and improved durability.

Myocardial Responses to LVADs

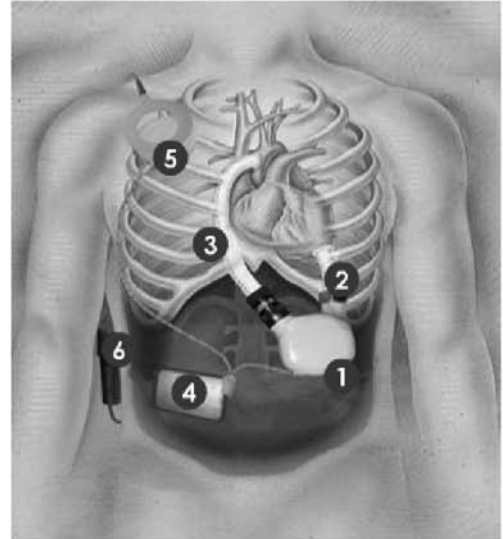
One very important and interesting biological byproduct of VAD use in patients with end-stage heart failure is the phenomenon of reverse remodeling. The

Figure 3 Additional Devices Used in Refractory Heart Failure



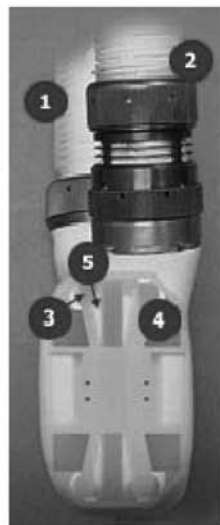
A. The Novacor® LVAS

1. Pump, 2. Inflow conduit with valve, 3. Outflow conduit with valve, 4. Percutaneous lead, 5. Controller, 6. and 7. Power pack



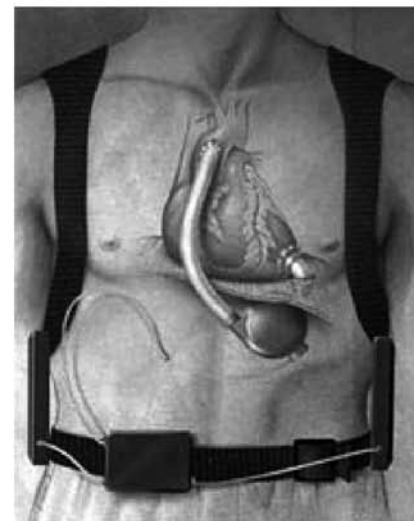
B. Novacor® II LVAS

1. Pump, 2. Inflow conduit, 3. Outflow conduit with valve, 4. Implanted controller, 5. Transcutaneous Energy Transmission System (TETS), 6. Power pack/External controller



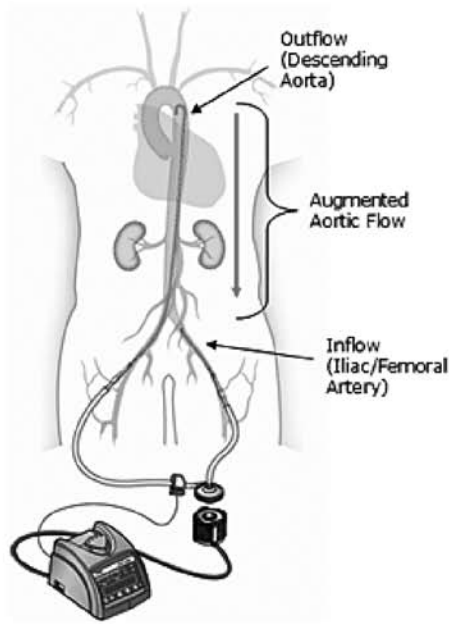
C. Pump/ Drive unit technology of Novacor® II LVAS

1. Inflow conduit, 2. Outflow conduit with valve, 3. Pre-chamber, 4. Pumping chamber, 5. Pusher plate

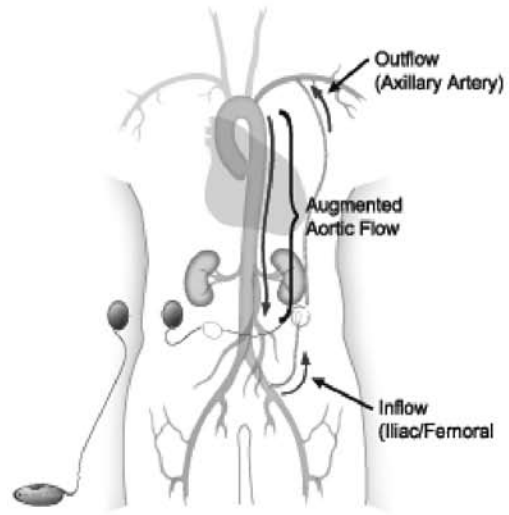


D. Levacor VAD

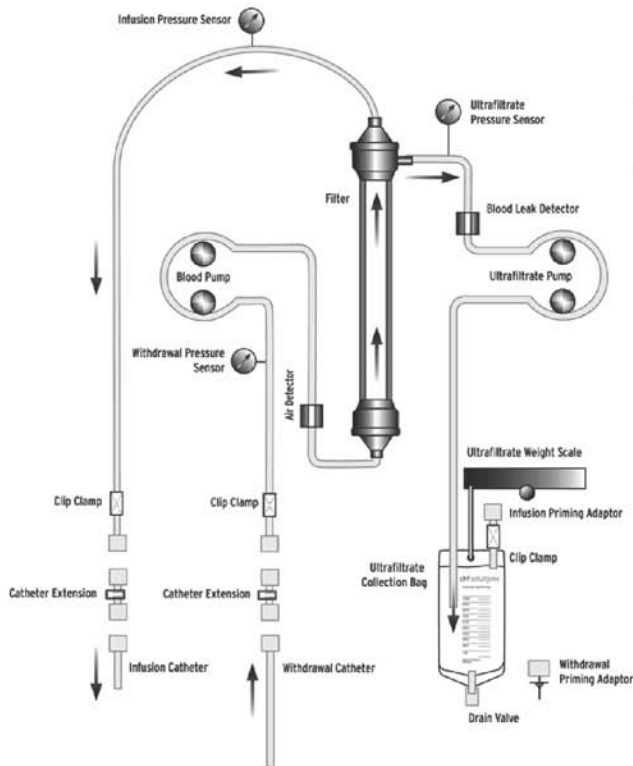
Figure 4 Devices Used in Acute Decompensated Heart Failure



A. CACION® System



B. EXELERAS® System



C. Ultrafiltration – Aquadex™ System

degree of normalization of many different characteristics is impressive and includes reversal of structural, cellular, extracellular, biochemical, and molecular factors. However, despite near normalization of these characteristics, few patients exhibit overall recovery of left ventricular function to the point where the device can be removed and the native heart once again able to support normal circulation. Observations from a handful of centers indicate that a small, but significant proportion of patients undergoing long-term mechanical assistance can be weaned from mechanical circulatory support after significant functional recovery. Use of VADs in this “bridge to recovery” (BTR) mode⁽¹⁶⁾ has yet to be reproduced outside these centers. This has led many investigators to believe that BTR is not a viable goal unless supplemented by other, as yet to be identified, treatments that can improve the extent and permanence of global ventricular recovery.

Total Artificial Hearts (TAH)

The Cardiowest™ total artificial heart (TAH) (Syncardia systems Inc) (Figure 2J) was approved by the FDA in 2005 as a BTT for patients in need of biventricular support. This device is implanted in an orthotopic position and consists of a biventricular pneumatic pump that replaces the native ventricles and all four cardiac valves. The Abiocror™ System (Abiomed Inc; Fig. 2I) is another device that is implanted in the orthotopic position. It has two main components: the implantable parts and the external parts. The implantable parts consist of the thoracic unit (replacement heart), as well as a battery and controller. The external parts consist of the console and the patient-carried electronics such as the battery, bag, and control module. A smaller version of the device named Abiocror™ II is being developed with a goal of five-year reliability.

Implantable Pumps

Despite major advances in development of VADs, there are several factors that currently limit their widespread use. Among these are the invasive nature of the procedure, the high rate of morbidity including infection, bleeding, thromboembolic events, device reliability issues, and high costs. In order to address these obstacles, Circulite™ Inc (Hackensack) is developing a microVAD that is ultimately intended to be inserted by an interventional cardiologist in the catheterization laboratory. The pump, which is about the size of a AA battery, can pump 2.5-3.0 L/min (less than the standard VADs described above, which are designed to pump >5 L/min). It is intended to be placed subcutaneously in the right subclavian region. The device will draw blood from the left atrium via a cannula placed transeptally through the right subclavian vein. The blood will be

pumped into the right subclavian artery; the outflow cannula will be surgically anastomosed with the subclavian artery via a cutdown procedure. The rationale for this approach is that by making a permanently implanted device that can provide substantial circulatory support and can be inserted in the catheterization laboratory with less morbidity than a surgical procedure, the device can be used in patients that are less sick than those who ordinarily receive a VAD. Since these patients will be less sick, their requirements for ventricular support in terms of L/min blood flow will be substantially less than for patients requiring full VAD support. The initial clinical trials with this new type of device are expected around 2007 or 2008 and will be implanted in a small number of patients by a minimally invasive surgical procedure to prove viability of the pump and other system components.

Cellular Cardiomyoplasty

Intramyocardial implantation of cells aimed at repopulating scar with new contractile elements has spawned the field of cellular cardiomyoplasty. These approaches are frequently included in reviews of device-based therapies for heart failure since the therapies are usually implemented by interventional cardiologists using catheter-based delivery systems. Cell therapy for heart failure has been studied for nearly a decade. A wide range of cell types, doses, and delivery techniques have been studied. Early clinical investigations were small, single center, nonrandomized studies that showed favorable effects on left ventricular ejection fraction and end-diastolic volume. More recent studies have expanded to multicenter, double-blind, placebo-controlled trials in increasingly larger numbers of patients. These studies have shown less impressive results. Pivotal to advancing this important field is basic research that will lead the way to a robust therapy to repopulate the infarcted heart with long lasting myocardial cells. Stem cell therapy is discussed elsewhere in this publication.

Conclusion

Multiple device-based approaches to treating medically refractory CHF are available or on the horizon. Understanding the fundamentals of CHF, including the hemodynamic and neurohormonal aspects, has led to invention of specific devices that have shown promise in improving prognosis and quality of life for patients with this epidemic disease. The profound reverse remodeling routinely associated with VAD use further validates device-based approaches and should inspire research into ways of making this recovery more complete and permanent.

Interventional Devices in Heart Failure – An Overview

1. Approaches in Medically Refractory Chronic Heart failure
 - ICD
 - Cardiac resynchronization therapy
 - Cardiac contractility modulation
 - Vagal nerve stimulation
 - Surgical approaches
 - i. Ventricular Reduction Surgery (VRS) – Aneursymomorphy, SAVR
 - a. STICH trial
 - b. Mannequin endoventricular shaper
 - c. Blue egg device
 - ii. Passive ventricular restraint devices
 - a. Corcap
 - b. Paracor device
 - iii. Transventricular struts
 - iv. MV repair or replacement

2. Devices to treat acute decompensated heart failure
 - Renal artery vasodilator drug delivery
 - i. Targeted Renal Therapy™
 - Aquapheresis – ultrafiltration
 - i. Aquadex (UNLOAD trial)
 - Continuous aortic flow augmentation
 - i. Cancion® system
 - ii. Exeleras® system

3. Catherter based pumps for acute cardiogenic shock (acute hemodynamic support)
 - IV inotropes and IABP
 - Centrifugal pump
 - i. Tandem Heart Pc VAD
 - Axial flow pumps
 - i. Impella cardiosystem
 - ii. A-med system/Hemopump

4. Devices for chronic decompensated heart failure

LVADs – REMATCH trial

 - Extracorporeal devices
 - i. Abiomed BVS 5000
 - ii. Thoratec VAD
 - Intracorporeal devices
 - i. HeartMate LVAD – IP,XVE,SNAP-VE
 - ii. Novacor LVAS, Novacor II LVAS
 - iii. Arrow Lion heart - discontinued
 - iv. Jarvik
 - v. Micromed
 - vi. Kriton
 - vii. Levacor VAD (Rotary blood pumps)
 - Total Artificial Heart (Biventricular)
 - i. Abioco Artificial Heart
 - ii. Cardiowest Total Artificial Heart

5. Cellular therapies
 - Myocell Implantation --- Myocath delivery catheter system
 - Autologous progenitor stem cell therapy

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