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Evaluation of Cardiac Function after VAD Implantation

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1. Introduction

Heart failure constitutes a major health problem with a current prevalence of over 5.8 million in the USA and over 23 million worldwide. (Lloyd-Jones, 2010) During the last decades a dramatic increase in the number of heart failure patients and hospitalizations was observed (Curtis et al., 2008) with an incidence of more than 550,000 annually in the USA and a lifetime risk of 20%. Although prevalence increases with age, heart failure can also affect young patients (Lloyd-Jones, 2010; Levy et al, 2002; Lloyd-Jones et al, 2002). It is also estimated that 10% from all HF patients have reached advanced stages of the disease, which is characterized by development of symptoms refractory to standard treatment, often requiring prolonged hospitalizations, intravenous vasoactive medication and diuretics and ultimately, consideration of mechanical support (Ammar et al., 2007).

Despite the therapeutic advances in the recent decades and the improvement in prognosis (drugs that counteract neurohormonal activation, devices that prevent or treat lethal arrhythmias and correct dyssynchrony), advanced heart failure remains a lethal clinical syndrome. Mortality rate for patients who had to be hospitalized due to heart failure deterioration is approaching 75% at 5 years; for end stage patients it is almost 80% (Ammar et al., 2007).

Cardiac transplantation is currently the best available treatment of advanced heart failure, but it is available to fewer than 2500 patients in the United States each year, when approximately 5–10 people are on the waiting list for each transplant taking place (Taylor et al., 2009). In addition, hundreds of thousands of patients who have severe end-stage heart failure are not eligible for a heart transplant due to concomitant multisystem disease, uncontrolled diabetes, continued tobacco use, or psychosocial limitations; however their condition continuously deteriorates.

The limitations of medical therapy in advanced stage heart failure, the lack of donor organ availability, and the large number of patients who do not qualify for transplantation due to contraindications, have spurred interest in mechanical circulatory support (MCS). Since the mid 1980s, for patients experiencing recurrent hospitalizations for heart failure decompensation despite optimal treatment and manifesting symptoms or signs of progressive end organ dysfunction, mechanical support of the circulation with Ventricular Assist Devices (VADs) has a well established and continuously expanding role (Stevenson & Rose, 2003). In addition to short term support of critically ill patients with appropriate devices, long term Left Ventricular Assist Devices (LVADs) have been approved for transplant candidates as bridge to transplantation or for patients suitable for destination

therapy as permanent treatment (Miller et al., 2007; Slaughter et al., 2009). There is now compelling evidence that prolonged unloading of the left ventricle with the use of an LVAD is associated with structural reverse remodeling (Mancini et al., 1998; Drakos et al., 2007) that can be accompanied by significant functional improvement (Dandel et al., 2005). Therefore, a new, although relatively rare indication for mechanical support is emerging, namely bridge to recovery (Hon & Yacoub, 2003).

However, before the use of ventricular assist devices as a "bridge to myocardial improvement" or complete recovery becomes feasible, reliable methods to detect complete recovery need to be developed. The optimal time for device removal in these cases need also to be determined, in order to guarantee safe and effective weaning from the device and long-term clinical stability without mechanical support. These tasks are by no means trivial, since the operation of the assist device makes evaluation of most of the currently available indices (echocardiographic parameters, biomarkers) difficult.

In addition, the continuously expanding role of LVADs as destination therapy mandates the evaluation of device and cardiac function at regular intervals, in order to detect system malfunction, thrombosis, or complications such as progression of valvular or right heart disease. Changes in patient symptoms or hemodynamics should prompt a thorough investigation of the function of both the pump and the supported heart. Knowledge of the underlying functional reserve of the patient's heart is necessary, in order to estimate the urgency of a device exchange procedure, in case of mechanical failure.

For these reasons, evaluation of cardiac function during mechanical support has emerged as one of the key factors for the optimal management of this group of patients. Many different approaches, involving both established clinical modalities such as echocardiography together with advanced techniques at the cellular and molecular level are being applied.

2. Remodeling: Potentially reversible alterations

It is important to recognize that HF is a syndrome rather than a primary diagnosis with many potential etiologies, diverse clinical features, and numerous clinical subsets. It is a progressive disorder with principal manifestation a change in the geometry and structure of the LV; the chamber dilates and/or hypertrophies and becomes more spherical—a process referred to as cardiac remodeling. Apart from the anatomic changes, the biology of the cardiac myocyte, and the structure and volume of myocyte and nonmyocyte components of the myocardium, are also affected.

There are two major categories of unfavorable alterations that occur in failing myocardium; these that occur in the volume and structure of cardiac myocytes and these that occur in the volume and composition of the extracellular matrix. As far as the first is concerned, increasing evidence suggests that progressive myocyte loss, through both necrotic and apoptotic cell death due to excessive adrenergic stimulation, (Josue et al., 1907) takes place in the myocardium of patients with advanced heart failure (Mann et al., 1992). The loss of functional myocardial tissue increases the work of the normal myocardial cells, leading to hypertrophy in an attempt to cope with the higher load, by increasing the number of sarcomeres. However, the chronically increased rate of energy consumption puts the cells of the hypertrophied and failing heart in an energy-starved state (Katz, 1988). Endomyocardial biopsies taken from the hearts of patients with congestive heart failure have shown a correlation between decreased ATP content and impaired contraction and relaxation. (Bashore et al., 1987). Abnormalities in calcium homeostasis were also found in failing cardiomyocytes leading to abnormal contractile function and force-frequency relationships.

In addition, there are several important changes that occur within the extracellular matrix of the myocardium (Thomas et al., 1998; Tyagi et al., 1996; Tyagi et al., 1996; Li et al., 1998), with fibrosis being the most widely recognized. Fibrosis due to excessive deposition of fibrillar collagen occurs around intramyocardial blood vessels and as replacement of lost myocytes. A family of collagenolytic enzymes, matrix metalloproteinases (MMPs), becomes also activated within the failing myocardium (Thomas et al., 1998; Tyagi et al., 1996; Li et al., 1998). Activation of MMPs leads to progressive degradation of the extracellular matrix, which in turn leads to realignment (slippage) of myocyte bundles and/or individual myocytes within the LV wall, and thus accounts for the LV wall thinning and the dilation that occurs in heart failure.

These alterations in the biochemical composition of the myocardium impose several de novo mechanical burdens on the failing heart. Perhaps the most obvious problem that occurs in the remodeled ventricle is the increase in LV end-diastolic volume, and hence end-diastolic wall stress. As the load on the ventricle at end-diastole contributes importantly to the afterload of the ventricle at the onset of systole, LV dilation by itself will increase the work of the ventricle, and hence the oxygen demand. The increase in wall thinning along with the increase in afterload created by LV dilation leads to a functional afterload mismatch that may further contribute to a decrease in forward cardiac output and shifts the end-diastolic pressure-volume relation (EDPVR) towards larger volumes (Burkhoff et al.; 1988) Moreover, the high end-diastolic wall stress may even lead to episodic hypoperfusion of the subendocardium with resultant worsening of LV function (Vatner et al., 1988, Shannon et al., 1993; LeGrice et al., 1995; Givertz et al., 1998).

Accordingly, there has been significant interest in developing therapeutic interventions to prevent and reverse these processes of adverse remodeling. Both angiotensin-converting enzyme inhibitors and nitroglycerin have been shown to attenuate ventricular enlargement after myocardial infarction, suggesting, at least in part, that reduction of wall stress may be an important factor for amelioration of remodeling (Jugdutt et al., 1988; Pfeffer et al., 1988). In addition, chronic ß-blocker therapy reduces ventricular mass and normalizes left ventricular shape in patients with heart failure (Hall S et al., 1994). Thus, evidence from pharmacological interventions that target neurohormonal activation and hemodynamic stress in heart failure suggested that the remodeling process may be reversed to some degree, although to a limited extent; this knowledge challenged the notion that ventricular dilation due to remodeling in advanced heart failure is an irreversible process. More importantly, this generated the hypothesis that ventricular assist devices, which have been used in critically ill patients awaiting heart transplantation, may reverse the remodeling changes to a greater extent, even up to the level of complete recovery, since they can provide profound hemodynamic unloading of the left ventricle, unparallel to the respective achieved by combination of drug treatment.

3. Principles of LVAD operation

The Artificial Heart Program of the National Heart, Lung, and Blood Institute, chartered in 1964, sponsored and initialized the development of mechanical cardiac-support devices (Hogness et al., 1991). The first goal was to develop a device for the temporary support of a patient with terminal heart failure until a donor organ could be found. This strategy has become a daily reality in transplantation centers worldwide since the approval by the Food and Drug Administration (FDA) of the pneumatically driven left ventricular assist devices as a bridge to transplantation in 1994 and of the self-contained, vented electric devices for the same purpose in 1998 (Mancini et al., 1998; McCarthy et al., 1998; DeRose et al., 1997).

Candidates for left ventricular or biventricular assist devices were patients eligible for transplantation with signs of near circulatory collapse, generalized debilitation, or end-organ deterioration, in order to improve their eligibility for transplantation and their chances for survival. The last decade, pulsatile left ventricular assist devices (LVADs) have been replaced by devices which continuously expel blood volume from within the failing left ventricle into the aorta. In 2008, the Food and Drug Administration approved the use of the continuous flow LVAD (HeartMate II) in patients who were candidates for bridge to transplantation and in 2010 for destination therapy (Thoratec, 2009).

4. Types of LVADs

The first LVADs were pulsatile volume displacement pumps. The main ones are the Heartmate I, the Thoratec paracorporeal VAD (PVAD, that can be used to support both ventricles), the Berlin Heart (paracorporeal, suitable for biventricular support), Novacor and the Cardiowest total artificial heart.

The Heartmate I has been widely used and inserted in over 5000 patients. It's flow pattern is pulsatile, similar to the normal circulation and can pump 4–10 l/min. Valves in the inflow and outflow cannulas ensure unidirectional flow through the system. A unique inner surface texture negates the use of anticoagulation and only antiplatelet therapy is needed. This device was used in the landmark REMATCH trial and was the first one to be approved as destination therapy.

Although pulsatile pumps provide excellent hemodynamic support, they have limitations, particularly their large size (hence needing extensive surgical dissection and patients with adequate body size), noisy operation, and importantly, limited long-term durability (Lahpor, 2009).

Continuous flow or second-generation axial flow pumps are being increasingly used during the last decade, as LVADs. These are continuous-flow rotary pumps that have only one moving part, the rotor, unlike the first-generation devices, and hence are expected to be more durable. The more frequently used ones are the Heartmate II, Berlin Heart Incor, the Jarvik 2000 and the MicroMed-DeBakey VAD.

The HeartMate II pump (Thoratec Corp.) is the only continuous-flow pump currently approved as a bridge to transplantation and destination therapy. This device can be operated at a pump speed between 8,000 to 12,000 revolutions/min (RPM), generating flow rates up to 10 l/min. In comparison to the first-generation Heartmate I device, it is one-seventh its size and one-quarter its weight. Over 3000 patients have had a Heartmate II implanted and is the most widely used second-generation device.

The mean duration of support reported for these continuous flow, rotary pumps is longer compared with the first-generation devices (166–236 vs. 50–60 days) (El-Banayosy et al., 2000). The incidence of thrombo-embolic events in HeartMate II patients is in most studies comparable with the Heart- Mate I with annual ischemic stroke rates ranging from 3 to 6% and for transient ischemic attacks from 1 to 4% (Strüber et al., 2008). Hemorrhagic stroke rates tend to be higher (2–3%), probably due to the need for anticoagulation. A somewhat higher neurologic complication rate has been reported with the use of another nonpulsatile device, the Micromed DeBakey VAD (stroke rate 15–18%).

Newer implantable (nonpulsatile with magnetic bearings) pumps, such as the VentrAssist, DuraHeart and HeartWare, currently under evaluation in clinical trials, may combine the advantages of even smaller size with longer durabilty.

5. Alteration of cardiac hemodynamics by LVAD support

The primary action of an LVAD is to provide volume and pressure unloading of the LV, while simultaneously restoring systemic blood pressure and blood flow to the peripheral organs. At the same time, LVAD support eliminates the need for administration of potentially toxic pressors and inotropes (McCarthy et al., 1995; Frazier et al., 1996). With most LVADs , this is achieved by withdrawing blood from the left ventricle (most often) or left atrium and returning it to the arterial system, providing in this way profound LV pressure and volume unloading. This also results in reductions in pulmonary venous and arterial pressures and pulmonary vascular resistance (Klotz et al., 2004). The normalization of blood pressure and cardiac output, improves perfusion to all body organs, which results in improved autonomic function and normalization of the neurohormonal and cytokine milieu that is present in heart failure (McCarthy et al., 1995).

Heart failure is considered a systemic disease that affects many organs because of hypoperfusion and the abnormal neurohormonal and cytokine stimulation; normalization of the latter by LVADs promotes recovery not only of the heart but of all peripheral organs as well (Levine & Levine , 1990). Not all effects of LVAD support, however, are beneficial. LVADs provide pressure and volume unloading only to the LV. In the face of increased cardiac output, the right ventricle (RV) (often diseased due to a cardiomyopathy process or due to chronic pressure and volume overload) can become volume overloaded and unable to accommodate the resultant flow (Ochiai et al., 2002). In addition, excessive unloading of the LV provokes RV dysfunction, by shifting the interventricular septum to the left. This increases RV diameter, right ventricular wall stress and consequently RV afterload. As a result, RV distention and failure occur in as many as 20% to 30% of LVAD recipients (Ochiai et al., 2002). More specifically, RV and LV are connected in series and interact with each other hemodynamically, due to the anatomic coupling provided by the shared interventricular septum and common muscle fibers. The impact of LV support by an LVAD on RV geometry, hemodynamics and function can be complex. The reduction of LV filling pressures by the LVAD can decrease substantially RV afterload and in that way improve RV function. On the same time, the LVAD can increase venous return to the RV (by increasing cardiac output), therefore RV operates with a higher preload. An LVAD that excessively unloads the LV can produce a leftward septal shift. This can potentially improve RV filling, however at the same time it reduces substantially the systolic LV contribution to RV contraction, through dyscoordination of interventricular septal motion, and the overall effect may be a significant deterioration of RV function. RV failure occurring after LVAD implantation can be treated with inotropic agents and pulmonary vasodilators, while at the same time optimization of the LVAD function (adjustment of RPM in case of continuous flow devices) is mandatory. Despite these measures, simultaneous right ventricular support is required in many cases.

During the previous decade, pulsatile LVADs were dominating clinical use; however, in the recent years nonpulsatile devices are by far more frequently used in the clinical practice, and next-generation devices in development are also based on the same principal of continuous flow (axial or centrifugal). Although these novel devices are, as already mentioned, smaller, more durable and reliable, more energy efficient, less thrombogenic, and less surgically traumatic to implant, they do not generate normal pulsatile flow. Although there is considerable data that long term non-pulsatile flow does not have detrimental effects on end-organ function, little is known about the consequences of lack of pulsatility on reverse

remodeling. Klotz et al investigated the hemodynamic effects during long-term support with nonpulsatile and pulsatile LVADs; they found that LV pressure unloading was similar between these 2 types of LVADs, whereas LV volume unloading was significantly more pronounced with a pulsatile device (Klotz et al., 2004). The significance of this difference is not known.

Thohan et al showed that although there are differences between these two classes of devices with regard to magnitude of unloading, both forms of support were equally effective in normalizing cell size and tumor necrosis factor-alfa levels (Thohan et al., 2005).

Most recently, Bartoli et al studied the effect of continuous vs pulsatile devices on cardiac hemodynamics, in a bovine model of left ventricular heart failure. Their data revealed that continuous unloading diminished energy requirements during cardiac cycle to non-physiological levels, particularly at higher levels of support. During increasing levels of continuous unloading, the variation between end-systolic and end-diastolic pressures diminished significantly, volumes and pressures decreased to non-physiologically low values and resulted in chronic closure of the aortic valve. On the other hand, pulsatile flow during left ventricular support, despite similar reduction in left ventricular end diastolic volumes, preserved a normal range of physiologic pressures. Therefore, continuous unloading dramatically reduces cardiac metabolic demands to values that are not normally observed in mammals; the significance of this observation for cardiac function during long term support is still unknown (Bartoli et al., 2010).

However, there are also physiological limitations to the function of pulsatile VADs. Klotz et al. demonstrated that with pulsatile LVADs device ejection is not generally coordinated with ventricular contraction and this device–heart dyssynchrony may paradoxically increase afterload. This is a result of the fact that native left ventricular contraction can occur at a phase when both the inlet valve of the device and the native aortic valve are closed (the latter due to higher aortic than ventricular pressure). This results in isometric ventricular contraction, which is energy demanding and non-efficient and can cause excessive stretching of the myocardium, particularly in the presence of systemic hypertension, which can occur following left ventricular assist device insertion, particularly of the pulsatile type. Regurgitation of the inlet valve of the left ventricular assist device can also result in systolic and diastolic stretching of the myocardium. On the other hand continuous-type flow pumps, are not subject to such dyssynchrony. While the degree of pressure unloading is similar to pulsatile LVADs, systemic arterial pressure is not increased to the same extent with continuous flow LVADs. In addition, although flow across the aortic valve is evident in less than 40% of the patients with continuous flow LVADs, as already mentioned, the absence of inflow and outflow device valves allows forward flow during each left ventricular ejection, even if this occurs with low systolic pressures. In that way, the afterload of the native ventricle is kept low continuously.

These fundamental, functional differences between the pulsatile and nonpulsatile LVADs are crucial especially for the evaluation of cardiac function after device implantation, as it will be later shown.

6. Reverse remodeling

One of the earliest recognized changes of patients' hearts supported by an LVAD until transplantation was the reduction of the size of the cardiac silhouette on chest radiographs,

observed immediately before transplantation possibly due to the unloading of the dilated heart. In addition, retrospective analysis of echocardiograms showed that after a short term period of LVAD support, LV end diastolic diameter decreased significantly (6.81 to 5.39mm), with corresponding increases in ejection fraction (11% to 22%). Echocardiographic studies performed in the pre-implant period and at explantation at the time of transplantation in 20 patients, in order to further investigate the effect of unloading on left ventricular function, showed a significant decrease in LV end-diastolic volume, LV end-systolic volume, left atrial volume, and an increase in LV ejection fraction (Thohan et al., 2005).

LV pressure-volume relationships were also evaluated in LVAD supported hearts after explantation and a shift towards normal was observed, suggesting that multiple favorable alterations at the cellular, tissue and whole organ level had occurred, described with the general term reverse remodeling (Levin et al., 1995). Although the hearts did not return to completely normal size, an average time of 30.8 days was needed in order for the reverse remodeling to be observed, while at 90 days most of the process was completed in this patient cohort (Madigan et al., 2001). In contrast, reverse remodeling of RV in LVAD supported hearts was not observed, suggesting that reverse structural remodeling is primarily mediated by the profound hemodynamic unloading and not only by normalized neurohormonal milieu, as previously already mentioned (Barbone et al., 2001). Another explanation of this discrepancy in favorable outcome between the LV and the RV might be the RV dysfunction induced by excessive LV unloading, as previously explained. It is of interest that when an RVAD is implanted in the RV, changes in the RV End Diastolic Pressure - Volume relationships are comparable with those observed in the LV of LVAD supported hearts (Klotz et al., 2005).

In addition to the effects on structure, the LVAD supported hearts on average exhibited reduced left ventricular trabeculae length, diameter, and mass as compared to the medically managed hearts. LVAD support, led also to increased contractile strength, faster time to peak concentration and reduced time to 50% relaxation in isolated cardiomyocytes (Dipla et al., 1998). Myocytes also exhibited improved contractile responses to increased frequency of stimulation, an effect blunted in end-stage heart failure. This was paralleled by normalization of b-adrenergic receptor density and reversal of RyR2 hyperphosphorylation (Marx et al., 2000). In addition, Klotz S et al. showed that LVAD support was associated with a significant increase in total and especially cross linked collagen deposition in LV myocardium (Klotz et al., 2005). The levels and activity of matrix metalloproteinases tended to decrease following LVAD support. Again, a similar structural reverse remodeling was not generally observed in the RV (Barbone et al., 2001).

7. Bridge to recovery

Even in the first Bridge to Transplantation trials, a small but increasing number of cases was noted where after a certain time of support the ventricular function improved sufficiently to allow consideration of removal of the device. Some patients, after explantation, were discharged without requiring heart transplantation and the idea of bridge to recovery emerged (Levin et al., 1994). In 1996, Levin et al. described for the first time the explantation of an LVAD in a 19-year-old man who had advanced heart failure caused by idiopathic dilated cardiomyopathy. Following LVAD support for 183 days the device was explanted but unfortunately, the heart redilated soon after the explantation procedure; ejection fraction worsened, and the patient died of heart failure (Levin et al., 1996).

In 1998 Mancini et al published a retrospective review of a total of 111 LVAD patients, evaluated for cardiac recovery. Only 5 successful explantations were identified (Mancini et al., 1998).

Low rate of recovery (9%) was published from Maybaum et al. in a study that included 67 patients supported by LVAD. Simon et al reported recovery in 11% of the non ischemic patients and only 2.5% in the ischemic population in a study of 154 LVAD patients (Simon et al., 2005).

However, in other series results have been more promising. In patients with acute myocarditis, it is well known that the combination of profound mechanical cardiac unloading and the appropriate therapy allows complete recovery and weaning from LVAD support in many cases (Farrar et al., 2002; Grinda et al., 2004). Muller et al reported a higher percentage of recovery and explantation in 17 patients with dilated cardiomyopathy; In 5 out of the 17 (29%) patients after 160 days of mechanical support the LVADs were successfully explanted and patients maintained normal cardiac function for 51 to 592 days (Muller et al., 1997)

The most promising results were reported by Yacoub and co-workers, with the use of a protocol combining mechanical unloading of the left ventricle with an optimum medical treatment at maximal tolerated doses, including β2-receptor stimulation. With this approach, in a carefully selected patient population of dilated cardiomyopathy patients, 11 of 15 (73%) demonstrated cardiac recovery sufficient to undergo successful device explantation, with 100% and 89% cumulative rates of freedom from recurrent HF at 1 and 4 years, respectively (Birks EJ et al., 2006). This study was conducted using the first-generation, pulsatile HeartMate XVE device. Interestingly, the same group demonstrated better results for quality of life in the bridge to recovery group 3.6 years after the LVAD removal, compared to the bridge to transplantation patients and even to transplanted patients (George et al., 2008).

Recently, the same investigators presented data supporting the feasibility of sustainable myocardial recovery using a continuous flow LVAD. They published the results of 19 non ischemic cardiac failure patients, who underwent implantation of a HeartMate II pump as a bridge to recovery. The successful explantation rate was 63.2% at 2 years. Estimated survival without heart failure recurrence was 83.3% at 1 and 3 years (Birks et al., 2011).

Nevertheless, results from other, larger series of DCM patients were not similarly encouraging, either as far as explantation rates or sustainability of recovery is concerned. All these studies should be interpreted with caution, since patient selection, devices and pharmacological protocols varied considerably. However, if bridge to recovery ever becomes an acceptable indication for LVAD therapy, the need for validated protocols for left ventricular function assessment during support will become even more pressing.

8. Destination therapy

After the landmark REMATCH trial, LVAD use as destination therapy became an accepted indication, for patients with advanced stage heart failure and contraindications to cardiac transplantation. Recently, even better results have been achieved with the new generation continuous flow pumps. Although destination therapy is considered permanent, there are many reasons why assessment of cardiac function should be performed regularly. Right ventricular failure can manifest even many years after LVAD implantation. Aortic valve disease can also progress after many years of support and can have important hemodynamic consequences.

9. Evaluation protocols

Despite these promising results, the clinical reality shows that the actual percentage of true complete myocardial recovery leading to successful weaning and device explantation is low. Therefore, identification of these patients is a challenging but absolutely necessary task, in order to avoid inappropriate device explantations and risking significant patient morbidity and mortality.

Several groups have used protocols to assess functional performance of the native heart, under reduced levels of support.

Mancini et al. attempted to define criteria in order to identify potential candidates for LVAD explantation. They analyzed a retrospective cohort of 111 LVAD supported patients. They were able to find 5 patients that successfully underwent explantation of the LVAD. However, in 4 heart failure recurred, 2 died and 2 underwent new LVAD implantation (interestingly, in one of them recovery was again observed). Only one patient remained clinically stable with good LV function at 15 months after explantation. Subsequently, they applied strict criteria in a prospective cohort of 39 patients, supported by the pulsatile HeartMAte XVE system. They used cardiopulmonary exercise testing, right heart catheterization, echocardiographic, and data from the LVAD sensor. Measurements were obtained during stress in the automated mode of the device (full support), during down titration of the level of support, and during exercise at a fixed low rate (20bpm). Adequate peak VO2 (>20ml/kg/min) and cardiac output (10 l/min), the presence of an open aortic valve during each cardiac cycle and maintenance of normal-size left ventricle with normal fractional shortening after completion of the exercise protocol at low support levels were criteria for LVAD explantation. Significant clinical recovery occurred in only one of the prospectively studied patients. Limitations of this protocol were the relatively short period of support and the rapid weaning protocol used, that may have not allowed adaptation of patient's hemodynamics and neurohormonal status to the higher demands of the low-support status (Mancini et al., 1998b).

Other studies have confirmed the results of low rates of ventricular recovery, as well as the recurrence of heart failure frequently with the need of LVAD re-implantation, a process often referred to as recurrent remodeling (El-Banayosy et al., 2001; Helman et al., 2000). A common finding in these studies was the higher rate of recovery in patients with idiopathic dilated cardiomyopathy.

Muller et al used a more progressive and prolonged weaning procedure in order to identify truly recovered patients. They evaluated 17 patients with IDC under support with pulsatile pumps (Novacor or HeartMate XVE). They used echocardiography after 4 minutes of complete withdrawal of support to assess complete myocardial recovery (stable EF and ventricular dimensions at normal or nearly normal levels). Subsequently, they put patients with signs of substantial recovery on fixed, asynchronous mode of support for 3 consecutive weeks, in order to test the stability of cardiac function. The fixed-rate mode leads to a dissociation in the coordination between cardiac ejection and optimum filling of the pump, a discrepancy that tends to increase left ventricular afterload. When this occurs, synchronization between heart and pump is random at best. Investigators were able to identify 5 patients who underwent successful LVAD explantation. All remained clinically stable for a period of 51 to 592 days. The approach of keeping patients at increased demands (high afterload) before removal is intriguing, because it could potentially identify those at risk for rapid deterioration. Unfortunately no data about hemodynamics, echocardiography

parameters or exercise tolerance at the completion of this testing period were provided. Nevertheless, 29% of the IDC patients were successfully weaned. Importantly, all patients in this study were under maximum pharmacological treatment. Another interesting observation was that, according to the findings of this study, longer periods of support (ventricular unloading for more than 100 days) may have actually been detrimental to recovery and may have contributed to myocyte atrophy (Muller et al., 1997).

Maybaum et al. in a prospective, multicenter, observational study used a slightly different clinical protocol for the evaluation of recovery in 67 patients supported by pulsatile pumps. Monthly assessments were performed including resting echocardiogram at full and reduced (output of 4 l/min) LVAD support, and cardiopulmonary exercise testing in ambulatory patients. Patients with LV ejection fraction (LVEF) 40% at reduced device support underwent dobutamine echocardiography with simultaneous hemodynamic monitoring. Complete recovery leading to LVAD explantation was observed only in the 9% (6/67) of the patients enrolled. Some interesting observations were made in this study. All patients that were successfully weaned demonstrated high contractile reserve on the dobutamine echocardiogram (mean EF of 60±10% at peak dobutamine dose), suggesting that contractile reserve may be a valid clinical tool for studying LV function under LVAD support. At the lowest rate of support, recovered patients had a wedge pressure of 8.5±4.5 versus 15±5.7 mm Hg of those that did not demonstrate similar improvement, indicating that a normal wedge pressure under partial support can be an important indicator of genuine recovery. Four out of 6 of the recovered patients had a short history of heart failure (2 acute myocarditis, 1 recent myocardial infarction, one IDC of recent onset) and they all remained stable post-explantation. The remaining two had chronic IDC and experienced a reduction of EF shortly after explantation, without clinical consequences. On the other hand, all supported patients improved their exercise tolerance and there was no discrimination of this parameter with genuine recovery. It should be noted that exercise tests were performed under maximal support. However, improvement of skeletal muscle function may act as a confounding factor for interpretation of the results of cardiopulmonary stress test in patients with LVADs.

In 2006, the Harefield group, led by Magdi Yacoub, reported the most intriguing data, as far as bridge to recovery protocols are concerned. They proposed and evaluated a combination therapy involving LVAD support to achieve maximal unloading of the myocardium, together with pharmacological therapy at the maximal tolerated doses, aiming at reversal of remodeling, followed by addition of pharmacologic stimulation of the β2 receptors by clenbuterol, for the development of physiological hypertrophy of the cardiac muscle. More specifically, ACE inhibitors, angiotensin 1 receptor antagonists, spironolactone and beta blockers with their well established effect on reverse remodeling were administered to the mechanically supported patients. Once maximal reverse remodeling had been achieved, a program of inducing physiological hypertrophy was instituted. This consisted of administration of the beta-2 agonist clenbuterol which is known to induce skeletal muscle hypertrophy (Petrou et al., 1995) and improve performance, as well as to stimulate physiological 'myocardial hypertrophy' (Wong et al., 1998). Evidence of recovery was monitored by repeated echocardiographic measurements and a '6 min walk' test with the device (pulsatile HeartMate XVE) switched off (on heparin). Patients also underwent cardiopulmonary exercise stress test, right and left heart catheterization (including left and right heart pressures, cardiac output with the device on and off, left ventricular angiography and left ventricular biopsies). Explantation was considered if the following criteria were met

(with the device off for 15 minutes): a) left ventricular end-diastolic diameter < 60 mm; left ventricular end-systolic diameter <50mm; LVEF >45%; left ventricular end-diastolic pressure (or pulmonary-capillary wedge pressure) < 12 mm Hg; a resting cardiac index > 2.8 l/m², maximal oxygen consumption (VO2 max) with exercise > 16 ml/kg/min and a VE/VCO2 slope < 34. Explantation of the device was feasible in 73% of the patients with idiopathic dilated cardiomyopathy who could be enrolled in the study (or in 46% of all the IDC patients that underwent implantation of an LVAD at this period in their center), with 100% and 89% cumulative rates of freedom from recurrent HF at 1 and 4 years, respectively (Birks et al., 2006). It should be noted that patients who could be weaned from LVAD support, not only fulfilled the above mentioned criteria, but achieved values within the normal range on these tests: LVEF of 64±8% before explantation (12±6% before implantation, P=0.001), left ventricular end-diastolic diameter of 55.9±8.3 mm (compared with 75.1±16.3 mm, P=0.002), mean left ventricular end-systolic diameter 39.6±6.5 mm (compared with 66.9±16.3 mm, P=0.002). Before explantation, VO2 max (with the pump off) was 20.7±6.1 ml/kg/min and VE/VCO2 slope 32.5±7.9. Pulmonary-capillary wedge pressure before explantation (with the device off for 15 min) was 9.0±4.1 mm Hg and cardiac index 2.8±0.7 l/m². Interestingly, the same group demonstrated better results for quality of life in the bridge to recovery group 3.6 years after LVAD removal, compared to bridge to transplantation patients and even to transplanted patients (George et al., 2008). These impressive data proved that in carefully selected patients, long term, stable myocardial recovery can be achieved and this may be a legitimate treatment target for IDC patients requiring mechanical support, in order to improve not only their prognosis and quality of life but also donor organ allocation, particularly in the era of donor organ shortage. However, selecting the appropriate candidates for this treatment remains a formidable task, since there are no criteria to predict which patient will experience recovery and if this improvement is going to be sustained for a long enough period to justify the risks of withdrawing mechanical support.

Extremely important data became also available from Hetzer's group in Berlin. They were able to wean 24.4% of 131 DCM patients from LVAD support (pulsatile devices in the vast majority) (Dandel et al., 2005). They also used off-pump tests in order to obtain echocardiographic measurements. An LV diastolic diameter < 55 mm and and LVEF> 45% were considered criteria for complete recovery, however they proceeded to device explantation in some patients with evidence of partial recovery. When patients were considered for device removal, an off-pump right heart catheterization was performed and normal right atrial and capillary wedge pressures were mandatory before proceeding to explantation. Twenty two / 32 patients experienced clinical stability for at least 3 years, whereas in 10 patients heart failure recurred and 8 of them required cardiac transplantation. Partial recovery in the echocardiogram as well as a history of IDC for more than five years was predictors of heart failure recurrence.

The same investigators also reported results about long term clinical stability of 35 IDC patients successfully weaned from LVAD support (Dandel et al., 2008). Decision for LVAD explantation was made based on off-pump echocardiographic assessment. For pulsatile devices, a complete cessation of LVAD operation was induced, under full heparinization. For continuous flow devices, echocardiography was performed after reduction of pump rate (revolutions per minute) at the lowest levels where retrograde flow (from the aorta to the LV) through the device was not observed. In addition to the above mentioned criteria, geometry of the LV was also assessed and LV relative wall thickness (RWT) >0.30 and

sphericity index < 0.8 were considered favorable indices. Recurrence of heart failure was observed in 16/35 of the patients and again evidence of partial recovery in the echocardiogram as well as a history of heart failure of more than 5 years and a required LV support duration of more than 6 months for induction of recovery.

Recently, the Harefield group, using the same medical treatment protocol published data from 19 patients with non ischemic cardiomyopathy, who received a continuous flow LVAD (Thoratec HeartMate II) as a bridge to recovery. LV function was monitored with monthly postimplantation echocardiographic measurements of the LV diameters and LVEF. As already mentioned, no real off-pump test can be performed with continuous flow pumps, because cessation of rotor function would result in backflow of blood from the aorta to the LV through the device, and therefore it would impose a tremendous volume overload on the LV. Therefore, the investigators performed echocardiograms, as well as 6-minute walk and cardiopulmonary exercise tests both with the device at optimal speed and after reduction of the level of support at 6000 rpm, where no regurgitation would occur. Right and left heart cardiac catheterizations were performed before explantation, again with the device at optimal speed and at 6000 rpm for at least 15 minutes. Using the same criteria for explantation as in their original study, complete recovery that allowed device explantation was achieved in 12/19 patients (63.2%), after 286±97 days. Estimated survival without heart failure recurrence was 83.3% at 1 and 3 years. Before explantation, at low flow for 15 minutes, ejection fraction was 70 ± 7%, left ventricular end-diastolic diameter was 48.6 ± 5.7 mm, left ventricular end-systolic diameter was 32.3 ± 5.7 mm, VO2peak was 21.6 ± 4 mL/kg/min, pulmonary capillary wedge pressure was 5.9 ± 4.6 mm Hg, and cardiac index was 3.6 ± 0.6 L/min/ m², indicating again that complete normalization of LV function and hemodynamics is associated with clinical stability and better long term outcome after explantation.

Importantly, this group thoroughly investigated methods to assess cardiac function under support with a continuous flow LVAD (Thoratec HeartMate II). They performed echocardiography at gradually lower rates of pump rotor speed and confirmed that at a fixed rate of 6000rpm, no forward or backward flow through the device could be identified. Therefore, pump speed at 6000rpm can induce physiologic loading on the LV and can be used for valid off-pump evaluations (George et al 2010). The same investigators also tried to clarify the role of optimal pump speed function on cardiopulmonary exercise stress test parameters. They were able to demonstrate that a rapid reduction of pump speed from optimal to 6000 rpm resulted in a reduction of VO2peak of 23% and of exercise duration of 18%. Despite the fact that multiple factors can influence exercise tolerance, and therefore a single value of VO2peak that can be considered threshold discriminating recovered patients probably does not exist, the relative change of this parameter between a test performed at optimal pump speed and at 6000 rpm is very important. Although this issue has never been addressed directly, ideally for a patient to be considered eligible for device explantation, these two values should not be significantly different (Jakovljevic et al., 2010).

Recently, stress echocardiography has been used in order to establish echocardiographic criteria for better evaluation of the native heart. In exercised patients, the systolic mitral annular motion increases significantly in parallel with cardiac output and the ratio of peak mitral E-wave velocity to early mitral annulus velocity (E/e'), has been demonstrated as a good approximation of LV filling pressures during exercise. These two parameters can be used as indices of cardiac output and pulmonary pressures in mechanically supported patients, even during off-pump tests.

In conclusion, although more or less similar methods are being used for LV function assessment during LVAD support, by most of the expert groups, criteria to diagnose recovery and results concerning the possibility for weaning from mechanical support vary considerably. There are no universally accepted patient selection criteria, as well as parameters that will safely predict adequate recovery and long term clinical stability after device explantation. Currently used criteria by most of the experienced groups for detection of recovery, as well as appropriate evaluation tests for pulsatile and non-pulsatile devices are summarized in Tables 1, 2 and 3.

	LVEF	LVIDd	PCWP	RAP	VO2max
Dandel et al., 2005	≥45%	≤ 55mm	≤10mmHg	≤8mmHg	-
Maybaum et al., 2007	≥40%	-	-	-	-
Mancini et al., 1998	-	≤ 55mm	≤10mmHg	-	20ml/kg/min
Yacoub et al., 2006, 2011	≥45%	≤ 60mm (LVESD<50mm)	≤12mmHg	-	>16ml/kg/min (VE/VCO2slope< 34)
Muller et al., 1997	≥41%	≤58mm	-	-	-

Table 1. Criteria for LVAD explantation, in different studies

On- pump	Off-pump
echocardiography (LVEF, LVEDD, LVESD, mitral E/A ratio, tricuspid regurgitation velocity, pulmonary valve acceleration time)	
doboutamine echocardiography (same parameters as above)	
cardiopulmonary exercise testing (VO2max, VE/VCO2slope)	
right heart catheterization (PCWP, RAP)	
6 min walking test	

Table 2. Tests used for recovery detection during support with pulsatile mechanical assist devices

Optimal speed (≈ 9000-10000rpm)	Reduced level of support (revolutions per minute: 6000rpm)
echocardiography (LVEF, LVEDD, LVESD, mitral E/A ratio, tricuspid regurgitation velocity, pulmonary valve acceleration time)	
doboutamine echocardiography (same parameters as above)	
cardiopulmonary exercise testing (VO2max, VE/VCO2slope)	
right heart catheterization (PCWP, RAP)	
6 min walking test	

Table 3. Tests used for recovery detection during support with non- pulsatile mechanical assist devices

10. Assessment of cardiac function during LVAD support as bridge to transplantation or destination therapy

Although recovery during support with an LVAD is an intriguing concept that merits further investigation, in everyday clinical practice, there are several more common reasons why native LV function should be monitored, despite the presence of an LVAD. During the recent years, data have accumulated about the long term problems that can manifest in patients supported by an LVAD, even many years after the implantation.

10.1 Determine optimal settings of LVAD function
Currently, continuous flow (axial or centrifugal) pumps are by far the most frequently used ones in the clinical practice, for long term patient support. Although maintaining adequate cardiac output to preserve end organ function and allow patients to be completely asymptomatic in their daily activities is an obvious need, optimal rotor speed of these pumps has not been determined yet, and seems to be a highly individualized parameter. For this decision, echocardiography provides the most easily accessible and valuable information. Many echocardiographic parameters should be taken into account, including LV and RV dimensions, the presence of mitral or tricuspid valve insufficiency, the shape of the interatrial or interventricular septum. At optimal pump interventricular and interatrial septum are at neutral position or slightly shifted to the left, whereas mitral and tricuspid valve regurgitation are minimal. Although, it is sometimes difficult to obtain good echocardiographic images in these patients, due to the apical cannula that often interferes with image acquisition, echocardiography remains the modality of choice for this kind of assessment, since it is noninvasive and widely available.

10.2 Aortic valve function
As far as the aortic valve is concerned, pulsed-wave Doppler can be used to assess flow across this valve. In patients with continuous flow mechanical support, aortic valve closure during the entire cardiac cycle has been found in up to 83% of patients, whereas a minority has intermittent opening with no detectable flow across the valve (Topilsky et al., 2011). This happens because at high pump speeds, the device unloads the LV at a point where LV systolic pressure is lower than aortic pressure and thus the aortic valve remains closed. On the other hand, with lowering of the revolutions per minute (RPM), the percentage of cardiac cycles where opening of the aortic valve occurs increases substantially. A continuously closed valve can have leaflet fusion as a consequence. This is commonly observed in patients with continuous flow LVADs and can have severe implications. Blood stasis and eventually thrombosis increases the risk of thromboembolic events and therefore more intense anticoagulation is needed. Aortic insuffiency can also develop or worsen (if preexisting) when the valve is constantly closed. The cause of this type of insufficiency is multifactorial; loss of pulsatility and chronically elevated aortic root pressure (the smaller device outflow diameter requires higher velocities to maintain the appropriate flow) produce high radial aortic root sheer stress, valve malcoaptation and finally aortic insufficiency. In addition, lack of regular aortic valve opening may independently promote valve thickening and fusion.

Recently it was reported that 6% of the patients with HMI will develop aortic insufficiency after a mean duration of 50 days of mechanical support and 11% after 1 year; 14% of the patients with HMII after 90 days of mechanical support and 25% after 1 year. This fact

points out the importance of pre-operative evaluation of the aortic valve in order to detect valve insufficiency and address it surgically during implantation. Moreover, since HMII is being increasingly used for destination therapy, it is important to exercise vigorous postoperative surveillance of these patients for aortic insufficiency development. In this direction frequent evaluation with echocardiography of the aortic root is mandatory, since aorta often dilates during mechanical support, especially in HMII patients who have closed aortic valves. In patients who can tolerate lower pump speeds without developing symptoms or signs of low cardiac output and end organ hypoperfusion, setting device function at a level that allows aortic valve opening every 3rd to 5th cardiac circle may ameliorate the problem.

10.3 Right ventricular function

Monitoring right ventricular function not only before but also after LVAD implantation is also crucial. As already mentioned right ventricular failure develops in about 20-30% of the patients supported with an LVAD. Under normal conditions, after LVAD implantation, the unloading of the LV reduces left atrial and mean pulmonary pressure improving right ventricular function. However, abnormal interventricular septum shift towards the left during unloading of the LV reduces the efficiency of RV contraction and additionally the elevated RV preload can deteriorate even more RV function leading to RV failure, which is associated with very high post-LVAD morbidity and mortality rates. RV failure after LVAD implantation increases the perioperative mortality rate from 10%–15% for those without RV failure to 38%–43% (Matthews et al., 2008).

Preoperative evaluation of RV and intraoperative and postoperative protection of RV function and management of RV failure are beyond the scope of the present manuscript. However RV failure may develop even late after LVAD implantation, as a cause of chronically increased RV preload (due to the increased cardiac output by the LVAD and parallel increased venous return), increased wall stress, changes in geometry of the RV in case of excessive leftward shift of the intraventricular septum and progressive tricuspid annular dilatation, which results in reduced tricuspid valve coaptation and increased RV preload due to tricuspid regurgitation. It must be emphasized that the RV is diseased in most of the times (cardiomyopathy, prior right ventricular myocardial infarction) and therefore poorly tolerates chronically elevated preload. Periodical echocardiographic assessments after LVAD implantation should be performed and if RV failure is detected appropriate therapeutic measures should be applied, i.e. reduction of pump speed if possible, in order to reduce preload and avoid excessive IVS leftward shift and diuretics to decrease RV preload. The role of RV afterload reducing agents, such as sildenafil, that can selectively reduce pulmonary vascular resistance, has not been studied in this clinical setting, but in theory appears as an attractive option.

10.4 Mitral valve function

MV regurgitation is rarely a problem in LVAD patients. LV unloading during LVAD support reduces LV size and filling pressures, improves coaptation of the MV leaflets and significantly reduces MR. In case mitral regurgitation appears after continuous LVAD implantation, inadequate LV decompression should be suspected and the possibility of increasing LVAD speed should be considered. Pulsatile LVADs by operating in a full-to-empty mode reduce the mitral regurgitation more than continuous-flow LVADs.

10.5 Assessment of device function-malfunction

Since device malfunctions may appear at any time after implantation (17% of deaths in REMATCH trial), if the patient's cardiac function is known to be severely compromised, emergency device exchange may be required even before symptomatic heart failure develops. The most common cause of continuous LVAD dysfunction is impeller thrombosis, which leads to reduced LVAD flow, and increased power use by the device. In this case, left ventricle is not fully unloaded and the increase in LV end diastolic volume will cause significant functional mitral regurgitation, right sift of the interventricular and interatrium septum and opening of the aortic valve in every LV contraction. In addition to these echocardiographic findings, laboratory analysis in patients with intravascular hemolysis will reveal increased LDH, plasma hemoglobin, bilirubin and D-dimers.

11. Conclusion – Future perspectives

Although the role of left ventricular assist devices as a bridge to transplantation or destination therapy is well established and high success rates have been achieved, the active monitoring of these patients for possible recovery is desirable for many reasons. For bridge to transplant patients, shortage of donor organs mandates the best allocation possible and removal from the list even of a small number of patients would increase the chances for a transplant of those who don't have other options. For patients initially selected for destination, recovery and device explantation would relieve them from risks of device related morbidity and mortality (device malfunction, thrombosis, bleeding and infection).

In order to materialize this very ambitious target, several prerequisites need to be satisfied:

- Criteria for optimal patient selection should be developed. These will rely on accurate diagnosis of the underlying disease that led to heart failure as well as disease duration.
- Optimal pharmacologic management of bridge to recovery patients needs to be established. Drug regimen should probably include all the available anti-remodeling substances, at maximal tolerated doses, and possibly β2-stimulation, but the efficacy of this approach needs to be demonstrated in randomized trials.
- Reliable protocols for evaluation of cardiac function under mechanical support need to be applied. These should be based on some type of off-pump test, depending on device type, and involve echocardiography, right heart catheterization and exercise stress test. It is not only the presence of good function of the native left ventricle that needs to be detected, but also long term stability that needs to be predicted. The latter remains the most challenging task currently. More prolonged in duration evaluation tests (than the ones used in most of the studies until now), using operation of the pump at the lowest possible rates in terms of safety, need to be tested in future studies.
- Histological, cellular and molecular indices of genuine recovery (as opposed to simple markers of unloading) are the subject of intense research and are expected to greatly contribute to the accurate diagnosis of significant ventricular recovery during mechanical support (Drakos et al., 2007).

LVADs designed specifically for recovery (easily implantable and explantable, atraumatic to the myocardium, operating in coordination with the native heart) are currently under development and may find a place in clinical practice in the future (Nanas et al., 1996). The principal of counterpulsation appears particularly promising for this purpose, since the LV can be very effectively unloaded, while at the same time it maintains adequate function for atrophy to be prevented. In addition, using different levels of support (every cardiac cycle, or 1-2, 1-3 etc) cardiac function can be easily assessed and monitored. Implantable

counterpulsation devices may be used in carefully selected candidates for recovery; if there is successful outcome, they can easily be removed, otherwise, they can serve as bridge to a permanent device implantation or transplantation.

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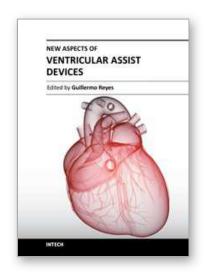
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New Aspects of Ventricular Assist Devices

Edited by Dr. Guillermo Reyes

Ventricular assist device has become one of the standard therapies for the support and the management of the failing heart. Updating our knowledge about these devices is mandatory in order to improve patient outcomes. In this book we can read the efforts made by many physicians concerned with the treatment of heart failure with mechanical devices. We all hope that the information compiled by experts in ventricle assist devices in this book will help us all to do better our main task - heal patients.

How to reference

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John Terrovitis, Eleni Tseliou, Stavros Drakos and John Nanas (2011). Evaluation of Cardiac Function after VAD Implantation, New Aspects of Ventricular Assist Devices, Dr. Guillermo Reyes (Ed.), ISBN: 978-953-307-676-8, InTech, Available from: http://www.intechopen.com/books/new-aspects-of-ventricular-assist-devices/evaluation-of-cardiac-function-after-vad-implantation

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