Review

Impact of left ventricular assist device (LVAD) support on the cardiac reverse remodeling process

Stefan Klotz\textsuperscript{a,*}, A.H. Jan Danser\textsuperscript{b}, Daniel Burkhoff\textsuperscript{c}

\textsuperscript{a}Department of Thoracic and Cardiovascular Surgery, University Hospital Muenster, Albert-Schweitzer-Str. 33, 48149 Muenster, Germany
\textsuperscript{b}Department of Pharmacology, Erasmus Medical Center, Rotterdam, The Netherlands
\textsuperscript{c}Department of Medicine, College of Physicians and Surgeons, Columbia University, New York City, NY, USA

Abstract

With improved technology and expanding indications for use, left ventricular assist devices (LVADs) are assuming a greater role in the care of patients with end-stage heart failure. Following LVAD implantation with the intention of bridge to transplant, it became evident that some patients exhibit substantial recovery of ventricular function. This prompted explantation of some devices in lieu of transplantation, the so-called bridge-to-recovery (BTR) therapy. However, clinical outcomes following these experiences are not always successful. Patients treated in this fashion have often progressed rapidly back to heart failure. Special knowledge has emerged from studies of hearts supported by LVADs that provides insights into the basic mechanisms of ventricular remodeling and possible limits of ventricular recovery. In general, it was these studies that spawned the concept of reverse remodeling now recognized as an important goal of many heart failure treatments. Important examples of myocardial and/or ventricular properties that do not regress towards normal during LVAD support include abnormal extracellular matrix metabolism, increased tissue angiotensin levels, myocardial stiffening and partial recovery of gene expression involved with metabolism. Nevertheless, studies of LVAD–heart interactions have led to the understanding that although we once considered the end-stage failing heart of patients near death to be irreversibly diseased, an unprecedented degree of myocardial recovery is possible, when given sufficient mechanical unloading and restoration of more normal neurohormonal milieu. Evidence supporting and unsupporting the notion of reverse remodeling and clinical implications of this process will be reviewed.

© 2008 Elsevier Ltd. All rights reserved.

Keywords: Mechanical assist device; Heart failure; Reverse remodeling

Contents

1. Introduction ................................................................. 2
2. Different types of LVAD systems ........................................ 3
3. LVAD induced reverse remodeling .................................... 4
   3.1. Introduction .......................................................... 4
   3.2. Hemodynamic effects of LVAD support ......................... 5

\*Corresponding author. Tel.: +49 251 8347401; fax: +49 251 8348316.
E-mail address: Stefan.Klotz@ukmuenster.de (S. Klotz).

0079-6107/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.

Please cite this article as: Klotz, S., et al., Impact of left ventricular assist device (LVAD) support on the cardiac reverse remodeling process. Prog. Biophys. Mol. Biol. (2008), doi:10.1016/j.pbiomolbio.2008.02.002
1. Introduction

Nearly 5 million Americans suffer from heart failure, with 550,000 new cases diagnosed each year (American Heart Association, www.americanheart.org). It is estimated that about 250–500,000 people in the US, and approximately 2.2 million worldwide, are currently in the terminal phase of heart failure. For this population, annual mortality despite optimized medical therapy approaches 50% and heart transplantation is often the only therapeutic treatment option. However, limited donor availability has resulted in approximately 2400 transplants per year in the US, with about 4000 patients populating the transplant waiting list at any given time (United Network for Organ Sharing, www.unos.org). It is estimated that up to 50,000 patients per year in the US could benefit from heart transplantation if organs were available. Implantable left ventricular assist devices (LVADs) have emerged as a treatment option to improve survival and quality of life for patients with end-stage heart failure in two ways. The most common use of LVADs is to bridge critically ill patients to heart transplant. In addition, LVADs can be used as a temporarily support until native cardiac function recovers and the LVAD can be explanted (bridge-to-recovery, BTR) or in patients not eligible for transplant as destination therapy.

The growing importance of LVAD support in end-stage heart failure patients is demonstrated even by the data from The University Hospital of Muenster. While in the late 90s only a small percentage of end-stage heart failure patients needed to be bridged to cardiac transplantation by LVAD support, almost half of the patients receiving a transplant in the past 5 years have received LVAD support prior to transplant (Fig. 1).

Fig. 1. The percentage of transplanted patients with LVAD support prior to transplantation. Data from the Department of Thoracic and Cardiovascular Surgery, University Hospital Muenster.
Since it is believed that most of these patients would not likely have survived to transplant, this reflects a shift towards allocating hearts for transplant and salvaging an increasingly sicker group of patients.

Besides studies showing survival and other clinical benefits provided to patients by LVADs, studies on cardiac tissues and blood samples obtained from patients who have undergone LVAD support have yielded enormous insights into the pathophysiology of heart failure. In the past, it was generally believed that the massively dilated and dysfunctional hearts of patients with severe end-stage heart failure are irrevocably damaged. However, circulatory support with an LVAD leads to reversal of chamber enlargement, reduction in left ventricle (LV) mass and improved global pump function (Fig. 2A). This process has been termed reverse remodeling. It was originally proposed that such reverse remodeling could permit explantation of the device and once again allow the native heart to resume responsibility for the circulation. However, in most cases of LVAD explant, heart failure reoccurs rapidly (Fig. 2B). The purpose of this article is to review the clinical and basic evidence supporting the notion of ventricular reverse remodeling and the clinical implications of this process as they relate to the prospects of recovery of heart function. This paper shall focus on increments in understanding obtained since those prior reviews.

2. Different types of LVAD systems

The typical LVAD is comprised of three primary components: a pump which receives blood through an inflow cannula and pumps blood through an outflow cannula; a wearable controller which powers the pump and permits adjustment of system operating parameters and a power source which typically allows switching between a base station powered by alternating current and a rechargeable battery pack. With the typical implantation, the inflow cannula draws blood via an LV apical inflow cannula and returns blood to the ascending aorta. With this configuration, the native aortic valve remains shut much of the time and it can almost be considered that the LV acts as a low-pressure atrium for the LVAD.

Two different classes of LVADs are currently in use. The first group, the so called pulsatile LVADs, have pusher plates which change the volume of a pumping chamber to propel blood from the LV to the aorta in a pulsatile manner. Valves in the inflow and outflow ensure unidirectional flow through the system. The flow
pattern is pulsatile, similar to the normal circulation. The other group of devices, the so-called continuous flow LVADs, are axial or centrifugal pumps which produce a non-pulsatile nearly continuous flow pattern. The rate of flow depends on the pressure gradient across the pump, so flow generally varies slightly during the cardiac cycle. These LVADs are much smaller; they do not have valves because there is no possibility of backflow and therefore produce almost no noise.

LVADs are also classified as being implanted either intra- or extracorporeally. LVADs with intracorporeally placed pumps and pulsatile pump flow are the HeartMate (Thoratec Corporation, Pleasanton, CA), the Novacor VAD (WorldHeart Corp., Ottawa, Canada) and the Thoratec IVAS (Thoratec Corporation, Pleasanton, CA). Extracorporeal systems are the Thoratec device (Thoratec Corporation, Pleasanton, CA), the ExCor BerlinHeart (BerlinHeart AG, Berlin, Germany) and the Abiomed AB5000 (Abiomed, Danvers, MA). The InCor BerlinHeart (BerlinHeart AG, Berlin, Germany), the DeBakey VAD (Micromed Cardiovascular Inc., Houston, Tx), the Jarvik 2000 (Jarvik Heart Inc., New York, NY) and the HeartMate II (Thoratec Corporation, Pleasanton, CA) are non-pulsatile axial flow pumps (Fig. 3).

3. LVAD induced reverse remodeling

3.1. Introduction

Untreated, heart failure is characterized by progressive ventricular dilatation and dysfunction. This ventricular remodeling results from abnormal mechanical stress on the myocardium (increased preload and afterload) and chronic neurohormonal activation. Loss of myocytes (as occurs following infarction) or reduced myocardial contraction (e.g., idiopathic cardiomyopathies) reduces overall ventricular pump function. This leads to reduced blood pressure and cardiac output which activates autonomic reflexes that again lead to increased circulating levels of neurohormones. In parallel with autonomic reflex activation, decreased systemic blood pressure and renal hypoperfusion, aldosterone, renin and angiotensin I increase, which leads to angiotensin II production. These factors attempt to restore cardiac output and blood pressure.
via mechanisms that are initially considered adaptive. However, if sustained, neurohormonal activation and increased mechanical stresses conspire in a maladaptive process to drive cellular hypertrophy and elongation, global recapitulation of a fetal gene program, apoptosis, myocardial fibrosis and ventricular enlargement and dysfunction. These in turn establish a milieu for dyscoordinated myocardial contraction (e.g., conduction defects), ventricular arrhythmias and mitral regurgitation. In addition, a systemic inflammatory response with increases of a multitude of cytokines contribute importantly to myocyte loss and disease progression (Mann, 2003). It is known that this process of ventricular remodeling, at a minimum, involves molecular, biochemical, metabolic, cellular, extracellular matrix (ECM) and ventricular structural characteristics. After the introduction of LVADs, it was appreciated that many of these abnormalities seen in end-stage heart failure were not permanent, but could be reversed, at least to some degree. The primary action of LVADs is to provide volume and pressure unloading of the LV while simultaneously restoring total systemic blood pressure and blood flow. However, one important indirect effect of LVAD support is normalization of the neurohormonal and cytokine milieu (McCarty et al., 1995). Importantly, while the neurohormonal milieu is determined largely (though not entirely) by the blood perfusing the myocardium and is therefore common to the LV and RV, the hemodynamic benefits of LVADs are provided only to the LV. Consequently, comparisons of effects on the RV and LV further allowed for identification of whether the primary mechanism responsible for reverse remodeling relate to mechanical factors or neurohormonal factors.

3.2. Hemodynamic effects of LVAD support

LVADs unload the LV and essentially replace the work of the heart while maintaining peripheral pulses. Two different aspects of hemodynamic unloading have to be acknowledged: volume and pressure unloading. Volume unloading is demonstrated by the echocardiograms shown in Fig. 4 and is associated with decreased stretch on muscles. In addition, there is marked pressure unloading as evidenced by a reduction in pulmonary pressures (Table 1). Reduced pressure and volume translate to decreased stress on the muscles. Another piece of evidence showing systolic pressure unloading of the LV by the LVAD is obtained from echocardiography which reveals that during normal LVAD operation, the aortic valve almost always remains closed; this implies that peak LV pressure generation is generally less than diastolic aortic pressure (Klotz et al., 2004). These hemodynamic effects are realized immediately after LVAD implantation and are maintained for the duration of LVAD support.

There are several potential consequences of prolonged complete LV unloading that need to be considered. One potential consequence is cuspal fusion of the aortic valve. If the ventricle recovers and device explant is considered in this setting, aortic valve replacement will be indicated. The presence of outflow tract obstruction may lead to myocardial ischemia, at times, when there is synchronous contraction of a recovered LV and the LVAD due to supra-systemic pressure, resulting in reduced coronary blood flow and subendocardial ischemic damage (Bellotto et al., 1992). In addition, with pulsatile LVADs, device ejection is not generally coordinated

![Fig. 4. Echocardiograms of a patient 1 week after left ventricular assist device (LVAD) surgery taken at end diastole. (A) LVAD operation was temporarily suspended (for ~45 s) during a routine venting procedure. End-diastolic dimension is >6 cm, indicating a dilated ventricular cavity. (B) This image showing internal dimension of ~3 cm with thickened LV wall was taken within 1 min after LVAD operation was restored. The LVAD provides substantial volume unloading of the heart. Inflow, LVAD inflow conduit; LV, left ventricle; RV, right ventricle; Ao, aorta; LA, left atrium. Adapted from reference Levin et al. (1995).](image)
with ventricular ejection and this device–heart dysynchrony may paradoxically increase afterload. Continuous-type flow pumps, on the other hand, are not subject to such dysynchrony. While the degree of pressure unloading is similar to pulsatile LVADs, systemic arterial pressure is not increased as much with continuous flow LVADs (Table 1). In addition, flow across the aortic valve is evident in about 50% of the patients with continuous flow LVADs (Klotz et al., 2004).

The tremendous reductions of pulmonary pressures are useful in patients with pulmonary hypertension. Pulmonary hypertension associated with “fixed” increased pulmonary vascular resistance (PVR) is a severe problem in candidates for orthotopic heart transplantation. High PVR cannot always be handled by donor hearts’ RVs, leading to a high risk of lethal right ventricular failure after transplantation (Klotz et al., 2003). Mechanical support by an LVAD appears to be an effective approach to reversing high PVR before cardiac transplantation (Etz et al., 2007).

3.3. Reverse structural remodeling

Ventricular structure is characterized by LV muscle mass and the end-diastolic pressure–volume relationship (EDPVR) (Burkhoff et al., 2005). Pfeffer et al. (1979) demonstrated that the EDPVR shifts rightwards towards larger volumes in chronic heart failure, a phenomenon they called ventricular remodeling. Shifts of the EDPVR in human heart failure were soon confirmed in both ischemic and idiopathic cardiomyopathies (Burkhoff et al., 1988). However, EDPVRs from LVAD-supported hearts were shifted back towards normal (Fig. 5A). In contrast, LVAD induced structural reverse remodeling is not generally observed in the RV (Barbone et al., 2001). However, if the RV is supported by an assist device, changes in the RV-EDPVRs are comparable with those observed in the LV of LVAD supported hearts (Klotz et al., 2005c). Since central venous pressure remains elevated during LVAD support (Kavarana et al., 2002; Ochiai et al., 2002) the lack of reverse structural remodeling in the RV (at the same time when reverse structural remodeling is strongly present in the LV) signifies that reverse structural remodeling is primarily mediated by hemodynamic unloading and not by normalized neurohormonal milieu.

The reason is, that there are two basic ways in which the RV and LV interact: hemodynamic interactions (also referred to as indirect interactions), and mechanical interactions (also referred to as direct or anatomic interactions) (Farrar, 2000). Hemodynamic ventricular interactions are due to the RV and LV ventricles being in series, connected by the SVR and PVR. Mechanical interactions are due to the anatomic coupling provided by the shared interventricular septum and common muscle fibers of the RV and LV. LVAD support in parallel with the LV can increase RV venous return and reduce RV afterload by shifting blood volume from the pulmonary to the systemic vascular systems. An LVAD that unloads the LV can produce a leftward septal shift by reducing the transseptal pressure gradient, potentially improving RV filling but decreasing the systolic

Table 1
Pressure unloading during LVAD support

<table>
<thead>
<tr>
<th></th>
<th>Pre-LVAD (mmHg)</th>
<th>During LVAD (pulsatile)</th>
<th>During LVAD (non-pulsatile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPA</td>
<td>33.7±8.0</td>
<td>18.3±7.5*</td>
<td>18.6±5.1*</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>23.1±7.6</td>
<td>8.0±7.0*</td>
<td>8.9±4.4*</td>
</tr>
<tr>
<td>PVR (WU)</td>
<td>2.7±1.3</td>
<td>2.0±0.9*</td>
<td>2.0±1.0*</td>
</tr>
<tr>
<td>TPG (mmHg)</td>
<td>10.3±3.0</td>
<td>10.4±3.7*</td>
<td>9.7±4.1</td>
</tr>
<tr>
<td>SVR (dynes⁻¹ cm⁻⁵)</td>
<td>1251±363</td>
<td>1579±550*</td>
<td>1215±363</td>
</tr>
<tr>
<td>mAP (mmHg)</td>
<td>76.7±11.5</td>
<td>104.6±13.6*</td>
<td>77.7±6.2</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>4.3±1.4</td>
<td>5.6±1.3</td>
<td>4.1±2.0</td>
</tr>
</tbody>
</table>

mPA, mean pulmonary pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; TPG, transpulmonary gradient; SVR, systemic vascular resistance; mAP, mean systemic arterial pressure and CO, cardiac output. Adapted from reference Klotz et al. (2004).

*p<0.05 vs. pre-LVAD.
LV contribution to RV contraction. Only if the pulmonary artery and RV pressures are also reduced during LVAD support, then both ventricles can become dimensionally unloaded.

In addition, univentricular effects are observed on regression of free wall mass and cellular hypertrophy (de Jonge et al., 2001; Rivello et al., 2001). Fig. 5B shows the normalization of LV myocyte cross-sectional area during LVAD support. The time course of change of LV myocyte cell dimension paralleled changes in mass (Madigan et al., 2001), but no such changes were observed in the RV (Barbone et al., 2001). Finally, in addition to normalized myocyte diameter, LVAD support induces normalization of the cytoskeleton as evidenced by normalization of sarcomeric proteins, vinculin, desmin and \(\beta\)-tubulin (Aquila et al., 2004; de Jonge et al., 2005; Latif et al., 2007; Vatta et al., 2004). Reduction of myocyte damage is also evident, as indicated by reduction of coagulative necrosis, contraction bands and myocytolysis (Rose and Park, 2005).

3.4. Reverse functional remodeling

In addition to the effects on structure, studies of trabeculae and myocytes isolated from LVAD supported hearts also demonstrate improved intrinsic myocardial contractile properties. LVAD support leads to increased contractile strength, faster time to peak concentration and reduced time to 50% relaxation in isolated cardiomyocytes (Dipla et al., 1998). It was demonstrated that myocytes also exhibited improved contractile responses to increased frequency of stimulation (normalized force–frequency relationship, FFR) and to \(\beta\)-adrenergic stimulation. These findings were subsequently confirmed in isolated trabeculae (Fig. 6A) (Heerdt et al., 2000; Ogletree-Hughes et al., 2001). Recovery of the FFR correlated with improved expression of calcium cycling genes and improved calcium accumulating efficacy of the sarcoplasmic reticulum (Heerdt et al., 2000; Terracciano et al., 2004). We observed that the FFR improved in the LV, not in the RV, which also correlated with chamber-specific normalized expression of genes involved in calcium cycling (Barbone et al., 2001). However, mechanical unloading with an RVAD significantly improves the FFR of the RV (Klotz et al., 2005c).

Similarly, the response of isolated trabeculae to \(\beta\)-adrenergic stimulation with isoproterenol demonstrated similar recovery following LVAD supported. While the effect of \(\beta\)-adrenergic stimulation on peak force...
generation is blunted in end-stage heart failure, the response following LVAD support is normalized (Fig. 6B). This was paralleled by normalization of β-adrenergic receptor density and reversal of RyR2 hyperphosphorylation (Marx et al., 2000). Despite the differential hemodynamic and structural remodeling effects of LVAD support as described above, we observed equal recovery of β-adrenergic myocardial responsiveness, β-adrenergic receptor density and reversal of RyR2 hyperphosphorylation in the RV and LV. This suggested that reverse remodeling of the β-adrenergic pathway during LVAD support is primarily mediated by systemic factors (such as biochemical milieu) and is not directly mediated by hemodynamic factors (Klotz et al., 2005a). This was expected, given the strong dependence of regulation of β-adrenergic signaling on circulating catecholamine levels and evidence showing that LVAD support normalizes neurohormonal milieu (including circulating norepinephrine levels) (Morawietz et al., 2000), restores β-adrenergic receptor density, and improves the ability of cardiac muscle to respond to β-adrenergic stimulation (Ogletree-Hughes et al., 2001). Importantly, because structural and other key aspects of reverse remodeling occur only in the LV, these findings indicate that restoration of β-adrenergic pathway function is not sufficient to reverse all of the abnormalities of end-stage failing hearts requiring transplantation.

3.5. Reverse molecular remodeling

As already mentioned to above, the structural and functional improvements in myocytes and in the ventricular chamber have as their basis normalized expression of certain genes and post-translational regulation of certain proteins that improve cellular functions and metabolism. The influence of LVAD support on gene expression, protein content and protein function has been studied by several groups. One of the first publications demonstrated by northern blot analysis of paired pre- and post-LVAD samples, that gene
expression for sarcoplasmic endoreticular \( \text{Ca}^{2+} \)-ATPase subtype 2a (SERCA2a), the ryanodine receptor (RyR), and the sarcolemmal \( \text{Na}^+ \)-\( \text{Ca}^{2+} \) exchanger were upregulated following LVAD support (Heerdt et al., 2000) (Fig. 7A). In addition, myocardial protein content of SERCA2a, measured by western blotting, increased significantly after LVAD support. Most of these changes were independent of the etiology of the underlying heart failure (Heerdt et al., 2006) (Fig. 7B).

Early studies showed normalization of expression and function in the LV (not the RV) of proteins involved with calcium handling known to be abnormal and contribute to contractile dysfunction in heart failure. Many studies have also focused on expression of genes involved with hypertrophy, cell cycling and apoptosis. A majority of studies suggest that these all shift towards normal during LVAD support and indicate a regression of hypertrophy and reduction in the amount of apoptosis. However, not all such gene expressions are normalized by LVAD support. The PKB/Akt/GSK-3beta pathway is not activated during LVAD support (Razeghi et al., 2003). Therefore, other signaling pathways must be responsible for the improvement of cellular function and cell survival.

![Diagram showing gene expression changes before and after LVAD support](image)

Fig. 7. (A) Representative Northern blot depicting normal hearts and CHF hearts pre- and post-LVAD support and (B) mRNA values of individual CHF patients pre- and post-LVAD support. Adapted from reference Heerdt et al. (2000).
Studies of the influence of LVAD support on myocardial metabolism have also yielded mixed results. On one hand, improvement of overall myocardial mitochondrial function (Heerdt et al., 2002), normalized expression of uncoupling protein 3 (Razeghi et al., 2002) and enhanced caveolin expression (Uray et al., 2003) have been reported. On the other hand, gene expression of other proteins involved in metabolism that are down regulated in heart failure (e.g., glucose transporter 1 and 4 and muscle carnitine palmitoyl transferase-1) are not normalized during mechanical unloading (Razeghi et al., 2002). Thus, it appears that LVAD support only partially reverses depressed metabolic gene expression in the failing human heart.

Microarray GeneChip platforms have been used to survey changes in transcription patterns in response to LVAD support. Genes involved in regulation of myocardial hypertrophy and vascular signaling were significantly downregulated (Hall et al., 2004). Using this technique, our group showed that calcium-handling genes were upregulated, while genes involved with regulation of myocardial fibrosis did not change on the transcription level (Rodrigue-Way et al., 2005). Other studies identified that of 3088 transcripts that exhibited abnormal abundance in heart failure, only 11% exhibited partial recovery and only 5% showed true normalization (Margulies et al., 2005). This latter study in particular reinforced the notion that although normalized expression of specific genes of interest can be identified following LVAD support, the normalization is not ubiquitous and expression of many genes is still abnormal. This may provide clues as to why function is not completely normalized in a majority of patients undergoing LVAD support. Studies of protein content and protein function currently lag studies of gene expression in identifying the number of proteins that are either present in abnormal quantities or whose function is abnormal.

3.6. Reverse electrical remodeling

Electrophysiologic abnormalities observed in failing myocytes from humans or animal models are manifested by a distortion of myocyte action potential shape and duration. Prolongation of the action potential delays myocyte repolarization and cellular relaxation. Because the QT interval is an index of ventricular repolarization on the surface electrocardiogram, it is not surprising that many patients who have heart failure exhibit a prolonged QT interval. Moreover, both QT prolongation and conduction abnormalities, reflected by an increased QRS duration, have been associated with increased mortality among patients who have chronic heart failure (Shamim et al., 1999). Regarding LVAD induced reverse electrical remodeling early and sustained changes have to be differentiated. Harding et al. (2001) could show that the immediate effects of mechanical unloading (directly following LVAD implantation) leads to a significant decrease in QRS duration, an increase in absolute QT duration and in the heart rate-corrected QT interval (QTc). This might reflect acute increases in myocyte action potential duration immediately after cardiac decompression rather than a defect in cardiac conduction. In addition, changes of the Na⁺–Ca⁺⁺ exchanger might produce an inward current that would prolong QT and QTc with immediate unloading. Acute unloading of the ventricle, reflected by intraoperative hemodynamic measurements, is likely associated with a decrease in overall sarcomere length during the cardiac cycle. However, such mechanisms for immediate changes in QT and QTc after LVAD placement are speculative at this point. Harding et al. (2005) could also show, that the increase in QTc interval predisposed LVAD patients to ventricular arrhythmia. Other studies confirmed these findings with a higher risk of de novo monomorphic ventricular tachycardia which was a predictor for mortality in the early stage following LVAD implantation (Bedi et al., 2007; Ziv et al., 2005). A week after LVAD placement the QRS duration was still decreased, while the QTc interval showed a biphasic pattern with a decrease to values below the initial values before LVAD implantation. In a study from Xydas et al. (2006) the QRS duration decreased linear with prolonged time of unloading. However, they could not show a biphasic pattern of the QTc interval. Studies in isolated cardiac myocytes showed that delayed decreases in heart rate-adjusted QTc were the result of decreases in action potential duration after LVAD support. Therefore, the shortening of the action potential duration likely contributes to the improved cellular contractile performance observed after sustained LVAD support.

3.7. Remodeling of the extracellular matrix and the renin-angiotensin-aldosterone-system

Remodeling of the ECM and especially collagen metabolism plays a major role in adverse LV remodeling and dysfunction in chronic end-stage heart failure. Changes in collagen content, the relative content of

Please cite this article as: Klotz, S., et al., Impact of left ventricular assist device (LVAD) support on the cardiac reverse remodeling process. Prog. Biophys. Mol. Biol. (2008), doi:10.1016/j.pbiomolbio.2008.02.002
different collagen subtypes and cross-linking are important features of ECM remodeling and each has specific implications for changes in passive myocardial properties. The main fibrillar collagens of the ECM are types I and III. In dilated cardiomyopathy increased collagen type I, type I/III ratio and cross-linking associated with fibrosis cause LV stiffening and impaired contraction and relaxation, whereas newly synthesized collagen type III, being immature, contributes to LV dilation. However, there is controversy concerning how collagen content changes following LVAD support. Some groups reported a decrease in total collagen after mechanical unloading towards normal values (Akgul et al., 2004; Thohan et al., 2005; Thompson et al., 2005), while other groups reported an increase in collagen content (Bruggink et al., 2006; Li et al., 2001; Liang et al., 2004; Matsumiya et al., 2005; Milting et al., 2006; Oriyanhan et al., 2007). In our own studies, we found that myocardial stiffness increased significantly following LVAD support to values significantly above normal. In addition, collagen content and in particular cross-linked collagen, increased tremendously following LVAD support (Klotz et al., 2005b). A more detailed analysis of extracellular collagen matrix composition revealed that the absolute content of type I and type III collagens as well as the collagen type I/III ratio were increased. In a recent study from Bruggink et al. (2007) the collagen type IV content of the basement membrane was negative affected following LVAD unloading.

Matrix metalloproteinases (MMPs) are a family of functionally related enzymes that cleave matrix components and are responsible for collagen denaturation and degradation. Therefore, MMPs and the tissue inhibitor of metalloproteinases (TIMPs) play an important role in regulating ECM turnover. In particular, it is now appreciated that an imbalance between MMPs and TIMPs drives adverse ECM and LV remodeling. In end-stage heart failure, increased MMP-1, -2 and -9 and decreased TIMP-1, -3 and -4 have been implicated in adverse ECM and LV remodeling, and the abnormal MMP-1/TIMP-1 and MMP-9/TIMP-3 ratios modulate ECM turnover. Following LVAD support MMP-1 and MMP-9 trended to decrease with a normalization of the MMP-1/TIMP-1 ratio. This suggests that there is a high rate of collagen breakdown in end-stage heart failure which is reduced following LVAD support resulting in the overall increase in collagen content (Fig. 8). In contrast to the LV, the RV showed little signs of ECM remodeling. The different effects on RV and LV properties initially identified in this study suggested that the primary mechanism by which LVAD influences ECM properties relates to reduced mechanical stretch by mechanical unloading. Furthermore, it was tempting

---

Fig. 8. Changes of the extracellular collagen matrix (ECM) in end-stage heart failure and LVAD induced adverse ECM remodeling, which leads to myocardial fibrosis and stiffness. See text for details.

Please cite this article as: Klotz, S., et al., Impact of left ventricular assist device (LVAD) support on the cardiac reverse remodeling process. Prog. Biophys. Mol. Biol. (2008), doi:10.1016/j.pbiomolbio.2008.02.002
to question whether the deleterious changes of the ECM during LVAD support could be a factor in the extremely low observed rate of full ventricular functional recovery or for the high rate of recurrent remodeling (i.e., progressive deterioration of pump function) that typically occurs following LVAD removal.

Another important factor in end-stage heart failure is the up-regulation of the renin-angiotensin-aldosterone-system (RAAS). Circulating and tissue angiotensin II (Ang II), and other neurohormones (e.g., aldosterone, norepinephrine, endothelin, vasopressin and cytokines) all contribute to adverse LV remodeling and dysfunction. Myocardial tissue levels of angiotensin I and II, known regulators of myocardial collagen synthesis, showed trends towards further increased levels in the LV following LVAD support (Klotz et al., 2005b). Therefore, increased collagen cross-linking following LVAD support could be attributed to decreased degradation of immature collagen coupled with ongoing production of new collagen.

These findings prompted us to perform another hypothesis driven study that related to the impact of angiotensin-converting enzyme inhibition (ACE-I) use on the ECM and recovery during LVAD support (Klotz et al., 2007). It is known that RAAS inhibition with ACE-I is able to reduce collagen synthesis and inhibits myocardial fibrosis in end-stage heart failure (Fig. 8). We therefore tested whether ACE-I use during LVAD support lead to an improvement in myocardial stiffness, ECM normalization and myocardial function. In a retrospective analysis of patient on LVAD support, we observed that ACE-I therapy during LVAD support indeed reduced tissue levels of angiotensin II significantly compared to an increase in the control patients who did not receive ACE-I during similar periods of LVAD support. In addition, ACE-I therapy prevented the tremendous increase in collagen and cross-linked collagen deposition as described above.

3.8. Indirect effects during LVAD support

As noted above on several occasions, by normalizing blood pressure and cardiac output, LVAD support results in normalization of tissue and circulating neurohormons (Delgado et al., 1998; Thompson et al., 2005) and cytokine milieu (Birks et al., 2001; Itescu and John, 2003) which are imbalanced in heart failure. This includes significant reductions of plasma atrial and brain natriuretic peptide, epinephrine, norepinephrine, plasma renin, angiotensin and endothelin-1. The potential significance of these secondary effects may have been unanticipated by early LVAD designers, but their profound importance is now widely recognized. Heart failure is considered a systemic disease that affects many organs because of the abnormal neurohormonal and cytokine milieu; normalization of this milieu by LVADs promotes system-wide recovery.

3.9. Influence of different LVAD flow patterns on reverse remodeling

In the 1990s patients with end-stage heart failure were usually treated with pulsatile LVADs. The continuous flow LVADs, which are now coming into more common use, provide a non-pulsatile flow which is not physiological. The debate regarding the effect of non-pulsatile flow on organ function and the hormonal situation is extensive and remained controversial in the 1980s. However, the use of non-pulsatile assist devices showed good clinical results for bridge-to-transplant (Haj-Yahia et al., 2007; Miller et al., 2007). In particular, concerns regarding the quality of life with non-pulsatile blood flow were dismissed. However, nearly all studies demonstrating LVAD induced reverse remodeling were conducted in the 90s using pulsatile LVADs, and only a few studies are available measuring the degree of reverse remodeling comparing non-pulsatile continuous with pulsatile flow devices. Both types of devices reduce levels of biochemical markers of brain injury (protein S-100b and neuron specific enolase) to the same degree (Potapov et al., 2001). Loebe et al. (2001) demonstrated that non-pulsatile LVAD support was associated with an increased stimulation of one part of the inflammatory system (interleukin 6), while tumor necrosis factor alpha, C3a, C5a and neutrophil elastase were not affected. Vatta et al. (2004) demonstrated that both device types significantly reverse the disruption of the N-terminus of dystrophin, but the extent was greater with a pulsatile device. However, no explanation or hypothesis as to these effects was offered in either of these studies. Other studies reported similarity of both LVAD types regarding right ventricular structure and end organ perfusion (Eya et al., 2005; Kucuker et al., 2004). We showed that the degree of left ventricular pressure unloading was similar with pulsatile and non-
pulsatile LVAD support (Klotz et al., 2004). However, the degree of volume unloading was significantly higher with a pulsatile LVAD. Echocardiographic parameter confirmed these results. Regular opening of the aortic valve occurred in only 10% of the patients with a pulsatile device, while it was evident in 50% of the patients with a non-pulsatile device. While these differences had no impact on mortality before or after cardiac transplantation, differences in myocardial recovery with these two different device types is currently not clear and is the topic of ongoing research.

3.10. Bridge-to-recovery and clinical marker for myocardial recovery

In recent years the term of “bridge-to-recovery” emerged. With all the positive findings regarding the reverse remodeling process described above explantation of the device after a certain time of support seemed to be a promising and desirable alternative to transplantation as well as a feasible strategy to reduce the organ shortage. It was appreciated relatively early that with the combination of profound mechanical cardiac unloading and the appropriate therapy it was possible to wean patients with acute myocarditis from LVAD support (Farrar et al., 2002; Grinda et al., 2004). These patients had an almost normal life expectancy following LVAD explantation. However, LVAD implantation due to acute myocarditis represents the minority of all LVAD implantations and the relevance of all the promising LVAD recovery data noted above to the major groups with ischemic or idiopathic dilated cardiomyopathy (ICM, DCM) difficulties unclear. Indeed, there is a major gap in the many positive findings of reverse remodeling illustrated above, and the reality of a low rate of LVAD weaning and explantation. As early as 1996, Levin et al. showed for the first time the clinical course of a 19-year-old man who had fulminate heart failure caused by an idiopathic dilated cardiomyopathy. Following LVAD support for 183 days the device was explanted. Unfortunately, the heart redilated soon after explant, ejection fraction worsened, and the patient died of heart failure (Levin et al., 1996). Mancini et al. attempted to identify potential LVAD explant candidates by the use of exercise testing with reduced LVAD flow. They showed that significant clinical recovery occurred in only 5 out of 111 patients (Mancini et al., 1998b). Also, in these patients, symptoms frequently returned and many died of consequences of heart failure. Other reports confirmed these results with low rates of ventricular recovery or with the need of LVAD reimplantation following explanation, a process that is termed recurrent remodeling (El-Banayosy et al., 2001; Helman et al., 2000). Reasons for these poor results with lack of sustained myocardial recovery following LVAD explantation are not known. However, in the study from Birks and Yacoub they were able to wean 11 out of 15 patients with idiopathic dilated cardiomyopathy with the use of β-blocker, ACE-inhibitor and aldosterone inhibitor followed by the β2-adrenergic-receptor agonist clenbuterol (the so called “Harefield” protocol) (Birks et al., 2006). In contrast, in a smaller group of patients, many with ischemic cardiomyopathy, treated less rigourously with background CHF medications for shorter durations prior to starting clenbuterol, George et al. (2006) from Columbia University found significant increase in skeletal muscle mass, but no change in cardiac function and they were not able to wean any patient from the device. In addition, in the latest larger studies, clinical recovery was only observed in a very small percentage of LVAD supported patients (Liden et al., 2007; Maybaum et al., 2007). Table 2 gives an overview LVAD weaning studies.

In addition to these discrepancies, clinical markers of myocardial recovery are often missing. The most promising tools for identifying potentially weanable LVAD patients were exercise testing and echocardiography during a short term trial of reduced LVAD flow or even complete pump stop (Khan et al., 2003). However, both tests could not definitely prove which patient is a good candidate for weaning and LVAD removal. Another experimental approach was to find certain plasma levels as a marker for myocardial recovery during LVAD support. For example, it was suggested that significantly reduced natriuretic hormones (ANP and BNP) might identify good candidates for weaning (Thompson et al., 2005). However, despite a significant reduction in ANP and BNP levels during LVAD support, sympathetic nerve activity, measured by iodine-125-metaiodobenzylguanidine (125I-MIBG) scintigraphy, remained below normal even 2 months after the LVAD implantation (Miyagawa et al., 2001). In addition, TNFα did not correlate with the clinical indices of heart failure during LVAD support (Razeghi et al., 2001). Thus, no reliable clinical or biochemical marker has yet been identified to predict good LVAD weaning candidates.
4. Conclusion

Shifts of ventricular and myocardial properties back towards normal observed during LVAD support are collectively referred to as reverse remodeling. While many properties exhibit profound reverse remodeling during LVAD support, this is not a ubiquitous process. Important examples of myocardial and/or ventricular properties that do not regress towards normal during LVAD support include abnormal ECM metabolism, increased tissue angiotensin levels, myocardial stiffening and partial recovery of gene expression involved with metabolism. In addition, LVAD support cannot correct an inherited genetic defect that may underlie an idiopathic cardiomyopathy (Towbin and Bowles, 2002). For the case of ischemic cardiomyopathy, LVAD support cannot lead to repopulation of the infracted tissue with contracting myocytes. Several clinical studies could unfortunately not demonstrate a high rate of weaning from the device, as anticipated form the basic research studies. These realities may serve to establish theoretical as well as practical limits to the extent and sustainability of LVAD-induced reverse remodeling.

Nevertheless, studies of LVAD-heart interactions have led to the understanding that although we once considered the end-stage failing heart of patients near death to be irreversibly diseased, an unprecedented degree of myocardial recovery is possible, when given sufficient mechanical unloading and restoration of more normal neurohormonal milieu. Comparison of effects on RV and LV have provided mechanistic insights by implicating hemodynamic unloading as primarily regulating certain aspects of reverse remodeling, neurohormonal factors as regulating other aspects and joint regulation of still other aspects. As such these observations have driven a paradigm shift of thinking of chronic heart failure as a progressive irreversible disease process to a potentially treatable entity.

A possible alternative would be to unravel the long sought after, highly elusive, molecular links between mechanical stress and the regulation of cell growth, and target these through pharmacologic means. Clinically, current experience would suggest that for patients with long standing cardiomyopathy only few will demonstrate substantial and sustained cardiac recovery during LVAD support. Future efforts to understand why this recovery is neither complete nor permanent, especially when the heart is re-exposed to hemodynamic stress, will continue to reveal new insights and could result in development of more effective, potentially curative treatments for this growing population of suffering patients. Approaches in which LVAD support is combined with one or more other treatment modalities, such as a drug therapy (Hall et al., 2007) or cell therapy (Gojo et al., 2007) to prevent post-LVAD explant remodeling, may prove particularly fruitful. At this point, clinical trials are ongoing to assess the efficacy of combining LVAD support with other therapeutic interventions.

Table 2
LVAD weaning in the clinical setting

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Disease</th>
<th>LVAD type</th>
<th>Mean LVAD—duration (weeks)</th>
<th>Weaning rate (%)</th>
<th>Recurrent CHF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levin et al. (1996)</td>
<td>1</td>
<td>DCM</td>
<td>Pulsatile</td>
<td>26</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Mancini et al. (1998a)</td>
<td>111</td>
<td>ICM</td>
<td>-</td>
<td>13</td>
<td>4.5</td>
<td>100</td>
</tr>
<tr>
<td>Helman et al. (2000)</td>
<td>2</td>
<td>MCD</td>
<td>Non-pulsatile</td>
<td>24</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Ueno et al. (2000)</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>3</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Hetzer et al. (2001)</td>
<td>95</td>
<td>-</td>
<td>Pulsatile</td>
<td>20</td>
<td>29.5</td>
<td>43</td>
</tr>
<tr>
<td>El-Banayosy et al. (2001)</td>
<td>13</td>
<td>-</td>
<td>Non-pulsatile</td>
<td>20</td>
<td>7.7</td>
<td>-</td>
</tr>
<tr>
<td>Khan et al. (2003)</td>
<td>16</td>
<td>-</td>
<td>Pulsatile</td>
<td>33</td>
<td>56.3</td>
<td>33</td>
</tr>
<tr>
<td>Dandel et al., 2005</td>
<td>131</td>
<td>-</td>
<td>Non-pulsatile</td>
<td>32</td>
<td>24.4</td>
<td>31</td>
</tr>
<tr>
<td>Simon et al. (2005)</td>
<td>154</td>
<td>-</td>
<td>Non-pulsatile</td>
<td>14</td>
<td>6.5</td>
<td>20</td>
</tr>
<tr>
<td>Birks et al. (2006)</td>
<td>15</td>
<td>-</td>
<td>Pulsatile</td>
<td>46</td>
<td>73.3</td>
<td>9</td>
</tr>
<tr>
<td>(George et al., 2006)</td>
<td>7</td>
<td>-</td>
<td>Pulsatile</td>
<td>23</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Liden et al. (2007)</td>
<td>18</td>
<td>-</td>
<td>Pulsatile</td>
<td>28</td>
<td>16.7</td>
<td>67</td>
</tr>
<tr>
<td>Maybaum et al. (2007)</td>
<td>67</td>
<td>-</td>
<td>Non-pulsatile</td>
<td>19</td>
<td>9.0</td>
<td>0</td>
</tr>
<tr>
<td>Own data 2007</td>
<td>104</td>
<td>-</td>
<td>Non-pulsatile</td>
<td>29</td>
<td>4.8</td>
<td>40</td>
</tr>
</tbody>
</table>

DCM, idiopathic dilated cardiomyopathy; ICM, ischemic cardiomyopathy and MCD, myocarditis.

Please cite this article as: Klotz, S., et al., Impact of left ventricular assist device (LVAD) support on the cardiac reverse remodeling process. Prog. Biophys. Mol. Biol. (2008), doi:10.1016/j.pbiomolbio.2008.02.002
point, the results of Birks et al. (2006) with intensive pharmacologic treatment are most promising. Our own basic studies of the impact of ACE-inhibition on the ECM are complimentary in that they show definitively that pharmacologic agents can significantly and beneficially impact on the biologic responses to LVAD support. It would be of interest to understand the specific contributions of other agents, at a myocardial level, to the overall process of recovery. A systematic approach, backed by sound basic investigation, may lead to new approaches of enhancing recovery during LVAD support.

References


Please cite this article as: Klotz, S., et al., Impact of left ventricular assist device (LVAD) support on the cardiac reverse remodeling process. Prog. Biophys. Mol. Biol. (2008), doi:10.1016/j.pbiomolbio.2008.02.002


Please cite this article as: Klotz, S., et al., Impact of left ventricular assist device (LVAD) support on the cardiac reverse remodeling process. Prog. Biophys. Mol. Biol. (2008), doi:10.1016/j.pbiomolbio.2008.02.002