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# Myocardial Recovery Following Left Ventricular Assist Device Therapy

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## 1. Introduction

Heart Failure (HF) represents an increasing clinical problem with a reported mortality (for either diastolic or systolic HF) of approximately 60% at 5 years after diagnosis (Shahar et al. 2004). The incidence of end-stage HF has increased four-fold in the last 20 years (Hubler et al. 2003; Terracciano et al. 2010). Symptomatic HF confers a worse prognosis than the majority of cancers, with mortality as high as 45% at one year (Cohn 1996; Jessup and Brozena 2003), and there are currently more than 16 million people in Europe and the United States (US) suffering from this disease. HF is also a major burden in the developing world (Mayosi 2007). Despite substantial medical advances in the treatment of HF, cardiac transplantation (CTx) remains the best long term therapy for patients suffering from end-stage disease, with 50 % survival at 10 years post CTx (Hunt, SA et al. 2009a; Trulock et al. 2007). A fixed and inadequate donor organ pool means that CTx is available to only a small proportion of eligible patients. In the US an estimated 100 000 patients are believed to be suitable for CTx (Maybaum et al. 2008), but only 2200 transplants are performed annually (Hunt, SA et al. 2009b). As a consequence the use of LVADs as Bridge-to-Transplantation (BTT) has increased steadily over the last few years and approximately 9000 CTx candidates, i.e. more than a third of all listed candidates in the US, have undergone LVAD implantation since 1999 (Mancini and Lietz 2010).

Initially, LVADs were utilised in the acute setting, in the management of post-cardiotomy cardiogenic shock (PCCS), a rare clinical scenario associated with high morbidity and mortality (Mehta et al. 1996). Despite improvements in LVAD technology, and the understanding of PCCS, the use of mechanical unloading (MU) in this acute setting is now minimal, with large studies showing survival of 23-52.4% (Sylvain et al. 2010).

The role of LVADs subsequently expanded to incorporate patients with severe drug-resistant HF, primarily as a BTT, with subsequent extension of the role to include “destination therapy” (DT) in those patients unsuitable for CTx (Kirklin et al. 2011).

In a small minority of patients a third application for chronic LVAD therapy, “Bridge-to-Recovery” (BTR) evolved, following the observation that MU appeared to coincide with cellular, molecular, electrophysiological and structural myocardial changes consistent with functional recovery (Altemose et al. 1997; Farrar et al. 2002; Heerdt, PM et al. 2000a; Hetzer et al. 2000; Ogletree-Hughes et al. 2001; Sylvain et al. 2010; Young 2001). Such observations allied with anecdotal examples of cardiac recovery in isolated patients following enforced device removal (mandated by the development of complications) (Frazier 1994; Frazier and

Myers 1999), alerted the world to the possibility that the remodelling of end-stage HF was reversible (“reverse remodelling”) (Klotz et al. 2008).

Within the context of an increasing incidence of HF, amongst a growing population of older patients (> 65 yrs) ineligible to receive CTx, inadequate organ availability and ever improving pump technology, the concept of BTR offers great hope as a potential treatment strategy to either replace, or work alongside that of CTx in years to come. However, BTR i.e. sufficient recovery of cardiac function to allow explantation of device, remains a controversial subject, with few successful reported cases worldwide (Birks et al. 2006; Birks et al. 2011; Maybaum et al. 2007). The Harefield protocol, a novel strategy in which LVAD is combined with pharmacotherapy including the  $\beta_2$ -AR agonist Clenbuterol, significantly increases the rate of explantation (Birks *et al.*, 2006; Birks *et al.*, 2011; see section 6 of this Chapter). In general, explantation rates vary considerably between studies but, with the exception of the Harefield protocol, remain universally low within the context of chronic HF (Dandel et al. 2005; Simon et al. 2005).

The purpose of this chapter is to review the effects of LVAD therapy, focussing on the mechanisms mediating functional recovery. We review clinical and experimental data supporting and opposing the concept of BTR. The first section of this chapter will focus on myocardial reverse remodelling followed by the clinical aspects of BTR.

## 2. Myocardial reverse remodelling

Myocardial remodelling associated with LVAD therapy is known to occur at structural, whole heart, cellular, molecular, metabolic, electrophysiological, cell survival and functional levels.

### 2.1 LVAD induced reverse structural remodelling

#### 2.1.1 Restoration of cardiac geometry and regression of myocyte hypertrophy

LVAD therapy has been shown to reduce left ventricular dimensions (Frazier et al. 1996) and to restore the end-diastolic-pressure volume relationships (EDPVR) towards normal values (Levin et al. 1995). In addition, regression of both cardiac and myocyte hypertrophy has been consistently demonstrated to occur during LVAD treatment (Madigan et al. 2001; Zafeiridis et al. 1998).

Pharmacotherapy alone has proved effective in retarding the negative remodelling associated with HF (Yancy et al. 2001), but is unable to induce profound reverse remodelling to the extent of LVAD therapy (Levin et al. 1995). The structural changes described have not been documented in the right ventricle (RV) of LVAD supported patients, suggesting that the predominant factor driving remodelling to be haemodynamic (Klotz et al. 2008), rather than the normalization of neurohumoral and cytokine environment known to occur during support (Birks et al. 2001; Delgado, III et al. 1998; Klotz et al. 2009; McCarthy et al. 1995).

#### 2.1.2 Cytoskeletal proteins

Sarcomeric and skeletal protein changes have been consistently shown to occur in association with MU. De Jonge *et al.* demonstrated improvements in distorted cytoskeletal architecture involving a number of proteins including actin, tropomyosin, troponin T and troponin C (De et al. 2002). Reversal of disruption of the amino terminus of dystrophin (Vatta et al. 2004), and upregulation of dystrophin gene expression (Mohapatra et al. 2010) occur in LVAD supported patients. Work conducted at Harefield hospital demonstrated a

specific collection of protein expression alterations that coincided with functional recovery and device explantation, involving a variety of proteins such as myosin heavy chain, sarcomeric actin, troponin C, troponin T, lamin A/C, spectrin, integrins beta1, beta6, alpha-tropomyosin, alpha1-actinin, and vinculin (Birks et al. 2005; Latif et al. 2007).

### 2.1.3 Extracellular matrix

The ECM constitutes approximately 3 % of normal myocardium, and is largely made up of collagen. Type 1 collagen, type 1: type 3 collagen ratio, collagen cross linking and fibrosis have been shown to be elevated in a variety of clinical as well as experimental disease states (Avendano et al. 1999; Badenhurst et al. 2003; Marijjanowski et al. 1995; Mukherjee and Sen 1991; Porter and Turner 2009; Woodiwiss et al. 2001).

Reports of LVAD-induced ECM changes have been conflicting, with some revealing increased myocardial fibrosis and ECM volume following unloading (Klotz, S. et al. 2005b; Li et al. 2001; Matsumiya et al. 2005; Saito et al. 2010), and others showing a reduction (Akgul et al. 2004; Bruckner et al. 2001; Maybaum et al. 2007; Thohan et al. 2005; Thompson et al. 2005). Bruggink *et al.* demonstrated a biphasic response with initial expansion of ECM and then a subsequent regression with prolonged MU (Bruggink et al. 2006). This discrepancy is thought to arise from differences in HF aetiology, duration of MU, pharmacotherapy employed during MU (Klotz, S. et al. 2007a), as well as the varying and often semi-quantitative methods utilised for analysis (Bruckner et al. 2000).

Matrix metalloproteinases (MMPs) are a group of enzymes responsible for collagen degradation and are tightly regulated by tissue inhibitors of metalloproteinases (TIMPs). HF is associated with large changes in MMP and TIMP action and thus ECM composition (Li et al. 2001; Matsumiya et al. 2005), and it is understood that altered regulation in their expression contributes to “negative” ECM remodelling in HF (Mann and Spinale 1998; Spinale et al. 2000; Wilson and Spinale 2001). Normalisation (decrease) of MMP1:TIMP1 ratio has been reported with LVAD use in a DCM population and coincides with increased LV collagen cross linking, type 1: type 3 ratio and increased ventricular stiffness (Klotz, S. et al. 2005b). A study conducted at Harefield hospital showed that all but one (TIMP4) of the MMPs and TIMPs studied, displayed a change in expression during LVAD therapy (Felkin et al. 2009). TIMP4 expression decreased in this study in contrast to previous studies showing unchanged/decreased MMP and augmented TIMP levels to coincide with LVAD support (Klotz, S. et al. 2005b; Li et al. 2001). Levels of cardiac fibrosis (Matsumiya et al. 2005; Saito et al. 2010) and profibrotic marker gene expression (Felkin et al. 2009) at time of LVAD implantation demonstrate predictive power with regards to likelihood of subsequent functional recovery, device explantability and durability of recovery. Negative ECM remodelling may represent a potentially important modifiable barrier to recovery in HF patients (Klotz, S. et al., 2007b).

Pharmacological blockade of the Renin-Angiotensin-Aldosterone-System (RAAS) in HF therapy is known to decrease cardiac fibrosis, collagen content and ventricular dilatation, with significant improvements in mortality (Arnold et al. 2003). Similar effects on ECM have also been seen in several different experimental models of HF (Bartha et al. 2008; Ibrahim et al. 2009; Meng et al. 2009). Klotz et al. have shown that ACE inhibition (ACE-I) reduces the increase in LV myocardial Angiotensin II/noradrenaline (NA) (Klotz et al. 2009), total collagen levels and collagen crosslinking associated with LVAD therapy, leading to their suggestion that pharmacological manipulation of the ECM represents a critical target in improving the frequency and extent of recovery during LVAD therapy (Klotz, S. et al. 2007b).

No changes in RV chamber size, mass or collagen content were noted despite normalisation of MMP:TIMP ratio and myocardial Ang II levels, inferring that neither haemodynamic unloading nor pharmacotherapy alone were sufficient for positive structural ECM remodelling to occur, and that complex dual regulation (neurohumoral and haemodynamic) of fibrotic mechanisms is likely to exist. All patients were bridged to CTx in this retrospective study and hence the impact of these structural ECM changes on whole heart cardiac functional recovery was not assessed.

## **2.2 LVAD effects on $\text{Ca}^{2+}$ regulation and signaling pathways**

### **2.2.1 $\text{Ca}^{2+}$ regulation**

HF is associated with alterations in a multitude of  $\text{Ca}^{2+}$  regulatory mechanisms, the balance of which varies with stage and aetiology of disease (Bers 2006). Mishandling of cytoplasmic  $\text{Ca}^{2+}$  causes deranged myocyte excitation-contraction (EC) coupling, abnormal systolic and diastolic function, as well as arrhythmogenesis in clinical and experimental HF (Gwathmey et al. 1987; Pieske et al. 1996). LVAD therapy is associated with reversal or alteration in expression and function, of many  $\text{Ca}^{2+}$  handling elements known to be adversely remodelled during HF, with a clear correlation with functional recovery being observed with certain parameters. Despite this, the true functional relevance of many of the LVAD-associated changes in  $\text{Ca}^{2+}$  cycling remains unclear.

Reverse electrophysiological remodelling occurs during LVAD therapy, demonstrated by reduction of QT interval and myocyte action potential duration (APD) (Harding et al. 2001). Mechanisms regulating APD involve alteration in function and expression of ion transporters with changes in depolarising and hyperpolarising currents. Detrimental effects of APD prolongation in HF on EC coupling, cellular relaxation and contraction are recognized (Gaughan et al. 1999; Wickenden et al. 1998), as well as positive effects such as augmentation of intracellular  $\text{Ca}^{2+}$  via alteration in L-type  $\text{Ca}^{2+}$  and NCX currents, presumed to be compensatory adaptive mechanisms (Bouchard et al. 1995; Weber et al. 2002; Wickenden et al. 1998). APD reduction has been associated with functional clinical recovery during LVAD support (Terracciano et al. 2004), but delineation of a precise contributory role of APD to functional recovery is difficult as the specific role of APD changes in HF itself remains unclear.

### **2.2.2 Sarcoplasmic reticulum $\text{Ca}^{2+}$ content**

A key determinant of effective  $\text{Ca}^{2+}$  release and myocyte contractility is the sarcoplasmic reticulum (SR)  $\text{Ca}^{2+}$  content and this parameter has been shown to be decreased in HF (Bers 2006) although increased SR  $\text{Ca}^{2+}$  content is noted to occur in some models during compensated HF (Soppa et al. 2008). 3 main mechanisms are thought to be responsible for the diminished SR  $\text{Ca}^{2+}$  content in HF : a) depressed Serca 2a function b) enhanced NCX function and c) enhanced SR  $\text{Ca}^{2+}$  leak (Bers 2006). Increased SR  $\text{Ca}^{2+}$  uptake has been shown to occur in response to LVAD support (Dipla et al. 1998; Frazier et al. 1996), and together with augmented  $\text{Ca}^{2+}$  transient amplitude correlate with improved myocyte contractility (Chaudhary et al. 2004; Dipla et al. 1998). Importantly, recovery of diminished SR  $\text{Ca}^{2+}$  content and L-type fast inactivation (most likely secondary to increased SR  $\text{Ca}^{2+}$  release) correlated with myocardial recovery and device explantation (Terracciano et al. 2004).

### **2.2.3 Serca 2a**

Sarcoplasmic Endoreticulum  $\text{Ca}^{2+}$  ATPase 2a (SERCA 2a) is the principal protein responsible for the reuptake of  $\text{Ca}^{2+}$  into the SR, which allows for sufficient replenishing of  $\text{Ca}^{2+}$  stores

for the subsequent heartbeat. Effects on Serca 2a gene expression and protein levels vary. Clinical and experimental studies have shown recovery (Takaseya et al. 2004), as well as no change (Chaudhary et al. 2004) to occur with MU, in addition to a biphasic response, i.e. initial recovery followed by subsequent decline coinciding with contractile function deterioration (Oriyanhan et al. 2007). Similarly, phospholamban (PLB) PLB:Serca2a ratio a key determinant of contractile function (Koss et al. 1997), known to be elevated in HF, displays a similar short term recovery (decreased ratio), with later resurgence of ratio coinciding with prolonged support and decline in contractile function (Ogletree et al. 2010).

### **2.2.4 Na<sup>+</sup>-Ca<sup>2+</sup> exchanger (NCX)**

Enhanced NCX activity / gene expression and protein levels are known to occur in most but not all models of HF (Bers 2006) with certain studies showing no change (Hasenfuss et al. 1999; Komuro et al. 1992) or even a reduction (Heerdt, PM et al. 2000b). In an environment of high intracellular Na<sup>+</sup>, prolonged APD and diminished Ca<sup>2+</sup> transients, enhanced NCX activity promotes Ca<sup>2+</sup> entry, a probable inotropic action. Reported LVAD-induced NCX changes are equivocal, improved Ca<sup>2+</sup> extrusion has been associated with increased NCX gene expression and functional recovery (Terracciano et al. 2007). However, partial restoration of positive force frequency relationship (FFR) (Chaudhary et al. 2004), as well as enhanced contractile strength in non-recovered patients (Heerdt, PM et al. 2000a), occurs in the absence of alterations in NCX protein levels. The well documented discordance between gene expression and protein levels, as well as regional LV expression heterogeneity, may be responsible for such discrepancies.

### **2.2.5 Ryanodine receptor (RyR)**

Diastolic Ca<sup>2+</sup> leak secondary to deranged RyR function is also an important contributor in Ca<sup>2+</sup> mishandling in HF (Marx et al. 2000). Chronic PKA mediated hyperphosphorylation of RyR2 promoting a “leaky” receptor is just one of the proposed mechanisms thought to lead to SR Ca<sup>2+</sup> depletion and disease progression in HF (Kushnir and Marks 2010; Shan et al. 2010), and normalisation of this parameter has been seen to occur with LVAD support (Marx et al. 2000).

### **2.2.6 Beta-adrenergic signalling**

Improvement of beta-AR (β-AR) responsiveness and density occurs during LVAD therapy (Dipla et al. 1998; Klotz, S. et al. 2005a; Milting et al. 2006; Ogletree-Hughes et al. 2001), as well as mechanically unloaded failing rat hearts (Oriyanhan et al. 2007). LVAD induced β-AR “recovery” is independent of cessation of systemic β-AR agonist therapy (Ogletree-Hughes et al. 2001), of greater magnitude than that caused by pharmacotherapy alone (Klotz, S. et al. 2005a), and unrelated to duration of support (Ogletree-Hughes et al. 2001). Mechanisms promoting such recovery remain unclear and direct haemodynamic unloading and/or normalisation of cytokine and neurohumoral environment are likely to be important. Support for the latter as the predominant governing factor is derived from results showing LVAD associated β-AR recovery to occur in both RV and LV, despite isolated LV haemodynamic unloading (Klotz, S. et al. 2005b). Alteration in the specific expression of genes involved in β-AR signalling such as phosphodiesterase 1A, 3B, calcineurin A and Rap guanine nucleotide exchange factor 4 RAPGEF4 (EPAC2) has been shown to coincide with functional myocardial recovery in patients undergoing device explantation (Hall et al. 2007).

### 2.2.7 Neurohumoral effects

LVAD support is known to decrease plasma adrenaline, noradrenaline (NA), renin, aldosterone and vasopressin (Klotz et al. 2009) as well as Atrial and B-type natriuretic peptide plasma levels (Thompson et al. 2005), myocardial gene (Kuhn et al. 2004) and protein (Wohlschlaeger et al. 2008) expression. Occasional correlation between measured biomarkers and functional improvement raises the possibility of the potential use of such markers in guiding therapy and prediction of recovery (Thompson et al. 2005). However, LVAD effects on the RAAS have recently been shown to be complex, with actual increased myocardial Ang II and NA levels, occurring despite reductions in plasma renin and aldosterone levels (Klotz et al. 2009). Such changes are postulated to arise from an LVAD induced recovery of depleted angiotensinogen levels, leading to enhanced generation of myocardial Ang II with subsequent sympathetic stimulation causing elevated NA levels, and shown to correlate with increased fibrosis and ventricular stiffness (Klotz et al. 2009), structural changes that were prevented by ACE-I. The negative effects of NA and Ang II on ECM remodelling and apoptosis are well known (Bonnetfont-Rousselot et al. 2002; Klotz, S. et al. 2007b), and such findings emphasise the importance of possible pharmacological manipulation of specific neuroendocrine pathways in combination with LVADs in promoting positive remodelling.

## 2.3 Cell survival and regeneration

### 2.3.1 Apoptosis

LVAD therapy appears to have beneficial effects on cell survival and apoptotic pathways although results are not uniform amongst studies. There are several distinct apoptotic pathways and their regulation is complex. Human HF is generally characterised by loss of cardiomyocytes (Narula et al. 2006) but rarely and inconsistently the presence of abundant apoptosis is demonstrated (Francis GS 1999). LVAD support causes normalisation and augmentation of anti-apoptotic proteins FasExo6Del (Bartling et al. 1999), BCL-XL levels (Milting et al. 1999), BCL-2 (Francis et al. 1999), decreased myocardial TNF- $\alpha$  levels (Razeghi et al. 2001; Torre-Amione et al. 1999), a cytokine believed to possess apoptotic regulatory properties, decreases in markers of DNA fragmentation (Bartling et al. 1999), cellular repair (PCNA) (Francis et al. 1999) and markers of cellular apoptosis (Baba et al. 2000).

### 2.3.2 Cardiomyocyte regeneration

LVAD-induced recovery of pro-apoptotic pathways activated in HF seemingly infers a potential for increased cell survival and augmentation of myocyte number, a mechanism that easily lends itself to promoting improved cardiac function and recovery. Previously held assumptions that cardiomyocytes are terminally differentiated, with severely limited, if any, potential to undergo mitotic division have now been challenged (Anversa and Kajstura 1998). Evidence showing that in response to injury cardiomyocyte division occurs (Beltrami et al. 2001; Engel et al. 2006), coupled to work demonstrating the existence of endogenous cardiac stem pools (Hosoda et al. 2010; Leri et al. 2005; Urbanek et al. 2005) naturally leads to the idea that together with the “anti-apoptotic” effects of LVAD therapy, the favourable biochemical and haemodynamic environment afforded by MU may also promote cardiac regeneration via increased cardiomyocyte division, or endogenous stem cell proliferation, thus reversing HF myocyte loss.

Evidence in support of such an LVAD role is limited (Wohlschlaeger et al. 2010). Wohlschlaeger et al. recently showed a dramatic 2 fold reduction in mean cardiomyocyte DNA and a 2 fold increase in number of diploid cardiomyocytes, together with significant decrease in the number of polyploid cardiomyocytes, a characteristic of human cardiac hypertrophy (Adler and Sandritter 1980; Sandritter and Adler 1976; Wohlschlaeger et al. 2010). The authors propose that these findings can be explained by a single unifying theory, hypothesising LVAD support to a) ameliorate hypertrophic stimuli that promote the transition of “mitotically arrested” cardiomyocytes into the S phase of DNA replication (Busk et al. 2002) (reduction in polyploidy), as well as b) promote real cell division or progenitor cell proliferation (increase in diploidy and reduction of DNA content per cardiomyocyte). Such findings require further mechanistic study, but clearly demonstrate the plasticity and reversibility of the cardiomyocyte DNA phenotype in HF, and raise the attractive possibility of LVAD-induced cardiac regeneration.

## 2.4 Myocardial metabolism and energetics

Myocardial metabolism and energetics have been shown to be consistently altered in HF (Neubauer 2007), resulting in an energy deficient mechanically inefficient heart, characterised by diminished ATP and phosphocreatine levels (Ingwall and Weiss 2004; Starling et al. 1998). The exact mechanisms remain unclear, but altered carbohydrate metabolism and myocardial insulin resistance have been proposed as key determinants of deranged energetics in HF and a potential therapeutic target (Ashrafian et al. 2007). LVAD therapy has been associated with improved mitochondrial metabolic function (Lee et al. 1998), and normalisation of mitochondrial cardiolipin constitution in ICM (Heerdt et al. 2002).. In addition, normalisation of raised myocardial Arginine:glycine amidinotransferase (AGAT) mRNA levels, occurs in patients successfully undergoing LVAD explantation as part of the Harefield protocol (Hall et al. 2007), reinforcing the importance of altered metabolic pathways in HF pathogenesis and future therapy.

## 2.5 IGF-1

Insulin growth factor (IGF-1) has been shown to possess favourable cardiac effects in experimental models of HF, with both early and delayed short term IGF-1 administration causing cardiac hypertrophy and improvement in function (Duerr et al. 1995; Duerr et al. 1996). IGF-1 displays anti-apoptotic (Li et al. 1997) as well as regenerative properties in both skeletal (Musaro 2005; Pelosi et al. 2007) and cardiac muscle (Santini et al. 2007; Welch et al. 2002), with cardiac specific IGF-1 expression attenuating disease progression in a mouse model of DCM (Welch et al. 2002).

IGF-1 mRNA levels are elevated at time of explantation of LVAD in patients treated with the Harefield protocol, suggesting elevated IGF-1 levels maybe important for the recovery process (Barton et al. 2005). 2 clearly defined groups were identified: those in which IGF-1 mRNA was high at implantation in which it remained high, and those in which IGF-1 mRNA was low at implantation and increased significantly during recovery. It is highly likely that the increase in IGF-1 mRNA seen in this study is induced by the combination therapy used in the Harefield protocol, and not MU alone, as previous studies have shown no change in IGF-1 expression or IGF pathway activation during isolated LVAD support in patients bridged to transplantation (Hall et al. 2004; Razeghi et al. 2003).

Mechanisms governing the increase in IGF-1 and the subsequent role played in recovery are unclear. Findings of positive correlation between IGF-1 levels and MMPs 11, 14, TIMPs 1

and 2 as well as stem cell recruitment factor SDF-1 expression, advocate modulation of the ECM and cellular regeneration to be important (Barton et al. 2005; Hall et al. 2004). Clenbuterol treatment of cultured cardiomyocytes has been shown to increase fibroblast-derived IGF-1, causing myocyte hypertrophy via paracrine signalling (Bhavsar et al. 2010; Hall et al. 2004). This suggests that IGF-mediated prevention of myocardial atrophy may also be involved in promoting functional recovery.

### **3. Clinical aspects of recovery**

#### **3.1 Pharmacological enhancement of myocardial recovery**

The evidence presented so far suggests that LVAD support can induce significant reverse remodelling in end stage HF, but on its own these changes rarely result in clinical recovery. However, combined pharmacological and LVAD therapy has been shown to achieve greatly improved rates of functional recovery (Birks et al. 2006; Birks et al. 2011) with the greatest rates of explantation being achieved using the Harefield protocol.

#### **3.2 Harefield protocol**

A clinical study at Harefield hospital in 2006 achieved an explantation rate of 73% using a novel pharmacological regimen involving the use of the drug clenbuterol, a  $\beta_2$ -AR agonist, in combination with aggressive high dose conventional medical therapy (lisinopril, carvedilol, spironolactone and losartan) (Birks et al. 2006) and pulsatile support. The purpose of this novel treatment strategy, was to enhance LVAD induced myocardial remodelling with high dose “conventional” pharmacotherapy (Phase 1), and prevent LVAD induced myocardial atrophy with high dose (up to 720 mcg tds) clenbuterol (Phase 2). Despite the fact this study was a single centred, small, non-randomised study only involving a small number of patients (n=15), all with non-ischaemic cardiomyopathy, the unprecedented high rates of recovery generated the notion that pharmacological  $\beta_2$ -AR stimulation may enhance myocardial recovery during LVAD therapy, and that future success in making BTR a widespread reality may rest, at least partially upon manipulation of this hitherto overlooked pathway. Support for this rationale has been further strengthened by recent results showing achievement of a 63.2% explantation rate, amongst a DCM cohort (n=20), utilising the same protocol in combination with non-pulsatile mechanical support (Birks et al. 2011).

#### **3.3 Clenbuterol**

Clenbuterol is classified as being a selective  $\beta_2$ -AR agent (Baronti et al. 1978) with partial agonist activity, displaying a high affinity for both  $\beta_1$ -ARs and  $\beta_2$ -ARs in a variety of tissues (Cohen et al. 1982).  $\beta_2$ -AR stimulation by various agonists has been shown to cause skeletal muscle hypertrophy in several animal species (Kim et al. 1991). Subsequent results showing clenbuterol to possess a direct “physiological” cardiac hypertrophic effect (Hon et al. 2001) prompted its inclusion in Harefield protocol, primarily as an agent to prevent myocardial atrophy thought to occur with prolonged MU.

#### **3.4 Prevention of myocardial atrophy by clenbuterol**

Myocardial atrophy has been widely proposed as one of the mechanisms thwarting myocardial recovery during LVAD treatment of HF, and a plausible explanation for low

explantation rates. As part of the Harefield protocol, after stable regression of left ventricular end diastolic dimensions is confirmed echocardiographically over a 2 week period, phase 2 (duration at least 6 mths), consisting of carvedilol being switched to a specific  $\beta_1$ -AR bisoprolol, and the addition of high dose (titrated up to maximum dose of 720 mcg tds) clenbuterol, is commenced.

Lack of echocardiographic measures such as left ventricular posterior wall thickness or relative wall thickness (RWT: interventricular septum thickness + posterior wall thickness/LVEDd), a known predictor of cardiac stability after explantation (Dandel et al. 2008), coupled with the absence of a control group, make it difficult to assess whether “prevention of atrophy” actually occurred in this study. Recovery does not seem to correlate with myocyte size, suggesting that this is not the most important target promoting BTR (Terracciano et al. 2004). Evidence regarding an anti-atrophic action of clenbuterol is equivocal, with experimental studies both supporting (Soppa et al. 2008) as well as opposing (Tsuneyoshi et al. 2005) this effect. A separate small single centre clinical study showed clenbuterol therapy (maximum dose 720mcg od) during MU was effective in preventing cellular atrophy, despite no echocardiographic change in wall thickness (George et al. 2006).

### 3.5 Other clenbuterol effects

The exact mechanisms through which clenbuterol acts remains unclear, but extensive work undertaken over the last decade, has clearly established that beyond the purely hypertrophic or “anti-atrophic” effects, originally advocating clenbuterol’s inclusion in the Harefield protocol, clenbuterol possesses a wide range of other positive actions. Clenbuterol administration for 1 week in normal rats has been shown to cause physiological hypertrophy, increased  $\text{Ca}^{2+}$  transient amplitude, increased SERCA 2a, PLB, NCX protein levels, and increased SR  $\text{Ca}^{2+}$  content (Soppa et al. 2005). Clenbuterol (1 week) has also been shown to enhance both whole heart and cellular function in chronically failing rodent myocardium, either alone or in combination with MU, with normalisation of myofilament sensitivity and APD duration and improved NCX activity (Soppa et al. 2008). Increased RyR2, SERCA2a protein expression and decreased apoptosis have been demonstrated in a similar model of HF after long term (9 weeks) clenbuterol therapy (Xydas et al. 2006). In addition, a clear cardioprotective inhibitory G protein dependent anti-apoptotic effect of acute clenbuterol administration has been recently shown during ischaemia reperfusion (Zhang et al. 2010). Clenbuterol modulation of IGF-1 dependent regenerative and hypertrophic pathways, as well as ECM effects may also be responsible for promoting functional recovery (Barton et al. 2005; Bhavsar et al. 2010; Hall et al. 2004).

### 3.6 Assessment of recovery

#### 3.6.1 Explantation criteria

Echocardiographic, haemodynamic and exercise testing criteria form the foundation on which explantation decisions are made, but specific assessment methods and criteria vary between institutes. At the Berlin Heart Institute LVEF >45%, LVEDd <55mm in the presence of normal central pulmonary pressures, during reduced support (Dandel et al. 2008; Muller et al. 1997) mandates explantation, whereas Harefield hospital employs the criteria of LVEF >45%, LVEDd < 60 mm, LVEDs <50mm, pulmonary capillary wedge pressure <12mm Hg, cardiac index >2.8 l min<sup>-1</sup> as well as exercise testing criteria,  $\text{VO}_2$  max of > 16ml kg<sup>-1</sup> min<sup>-1</sup> during “off pump” testing (Birks et al. 2011). Dobutamine stress testing has also been successfully utilised at the Texas Heart Institute (Frazier and Myers 1999).

### 3.6.2 “Off pump” testing

Off pump testing protocols have been developed relatively recently, and effectively involve cessation of pump flow (> 15 minutes) after systemic heparinisation, followed by assessment of haemodynamic and echocardiographic parameters at rest and after exercise. Turning off of pulsatile devices is acceptable, however turning off non-pulsatile devices leads to retrograde flow across the aortic valve, making functional assessment extremely difficult. This is avoided during testing by decreasing pump speed to 6000 RPM, resulting in zero forward or back flow, effectively ceasing haemodynamic support, or turning the pump “off”. Such “off pump” testing has been shown to be safe and well tolerated in both types of device (Birks et al. 2011).

### 3.6.3 Predictors of recovery

Identification of factors favouring recovery has historically been extremely difficult. Molecular, histological and biochemical markers associated with functional improvement and with recovery have been identified (discussed earlier), but to date no recognised marker is featured in weaning criteria, which remains largely determined by echocardiographic and haemodynamic parameters. Short duration of HF has commonly but not always been shown to favour recovery (Birks et al. 2011), however, recovery of patients with long durations of HF has also been achieved. Echocardiographic parameters at time of LVAD implant are not predictive of recovery, although sustained improvement, as opposed to progressive deterioration in EF, fractional shortening and LV dimensions during LVAD therapy is associated with greater likelihood of explantation (Birks et al. 2011).

### 3.6.4 Durability of myocardial recovery

The potential therapeutic value of identifying predictors of relapse in preventing LVAD re-implantation has attracted huge interest. Dandel *et al.* identified support duration >6 months, LVEF <45% and LVEDd >55mm at final pre explant echo, as well as a >10% worsening of either of these parameters compared to best obtained value, to be highly predictive of early relapse (Dandel et al. 2008). These findings support the idea that prolonged MU beyond the “optimal point” results in redilatation and functional deterioration (Maybaum et al. 2007). In addition, > 10% decrease in relative wall thickness (RWT: interventricular septum thickness + posterior wall thickness/LVEDd), RWT of <0.38 and duration of HF >5 years, also displayed positive predictive power for post LVAD cardiac instability. Post weaning deterioration in EF and LVEDd within the first 6 months increases risk of HF recurrence, highlighting the importance of early, regular functional surveillance of recovered patients.

### 3.6.5 Factors opposing recovery

It is proposed that as well as positive remodelling LVADs can induce negative remodelling. Negative remodelling of the ECM, and myocardial atrophy associated with prolonged MU are two potential barriers, thought to be opposing BTR, and pharmacological targeting of these components has yielded some clinical success. Regular and precise functional cardiac assessment during LVAD therapy is essential in promoting BTR. The increasing proportion of new generation devices being implanted as a means of DT in the US (Kirklin et al. 2011), in which functional recovery is neither expected, promoted, nor assessed may represent a significant new barrier to BTR. Consequently the fraction of LVADs being implanted in the

US as a means of BTR is decreasing (Kirklin et al. 2011) , and a lack of belief in, as well as desire to pursue BTR may mean potentially “recoverable” patients will not be optimised or even assessed for device explantation in the future.

#### 4. Conclusions

Constantly improving technology, the advent of even smaller pumps allowing less traumatic implantation and explantation with fewer complications has already, and will continue to improve LVAD associated morbidity, mortality and quality of life (Rogers et al. 2010). Further use of this unique research vehicle to better understand the reversible mechanisms involved in HF pathogenesis, will identify new therapeutic targets amenable to manipulation. It is probable that if BTR is pursued in future years, recent success suggests it should be (Birks et al. 2006; Birks et al. 2011), combination therapy i.e. LVAD + pharmacotherapy (existing or novel), gene or stem cell therapy, and even a combination of these will yield enhanced rates of recovery. Desires to implant smaller devices in patients with less advanced disease, and implement novel partial unloading, or intermittent ventricular reloading strategies may further improve the BTR strategy and the results of such studies are eagerly awaited.

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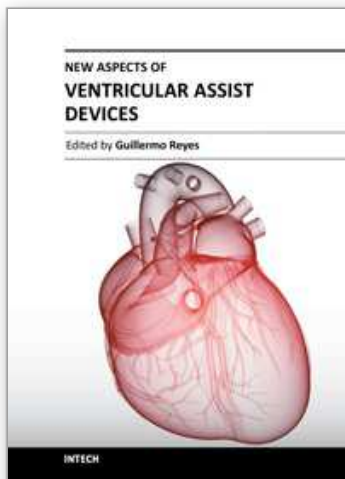
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Ventricular assist device has become one of the standard therapies for the support and the management of the failing heart. Updating our knowledge about these devices is mandatory in order to improve patient outcomes. In this book we can read the efforts 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.

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