Clinical Perspective

A novel strategy to maximize the efficacy of left ventricular assist devices as a bridge to recovery

Introduction

Heart failure is one of the major causes of morbidity and mortality in both developed and developing countries[1,2]. Despite advances in the medical management of heart failure the only real effective form of therapy for patients with advanced heart failure is cardiac transplantation. Heart transplantation is, however, becoming increasingly limited by the shortage of donor organs. There is, therefore, a pressing need for the development of alternative therapies for these patients.

Left ventricular assist devices are being used in patients with advanced heart failure, generally as a bridge to transplantation. A small number of these patients have shown a significant improvement in myocardial function[3], which has been sufficient in some cases to allow explantation of the device[4,5]. The exact proportion of these patients is still unknown, but is thought to be very small[6]. In addition, the mechanisms involved are largely unknown. Maximizing the rate of recovery depends on understanding the cellular, molecular and biophysical changes and the mechanisms responsible for progression and/or regression of heart failure in these patients. Although heart failure is known to be a multifactorial disease, there is now compelling evidence that a process of progressive hypertrophy or remodelling[7–16] plays a major part. Although hypertrophy starts as a physiological adaptive response to increased load from a variety of causes, it becomes maladaptive and results in a self perpetuating pathological process of remodelling, ending in terminal heart failure. An intriguing aspect of this process is that it is not unidirectional, but can be traced back through a process of ‘reverse remodelling’[17,18] towards normality.

As the initial stimulus is almost invariably stretching of the myocardium, it follows that unloading with a left ventricular assist device plays an important role in reverse remodelling. However, on its own, unloading appears to be inadequate. We therefore evolved a strategy of combination therapy, aiming at inducing maximal regression of pathological hypertrophy, followed by induction of physiological hypertrophy[19] of both cardiac and skeletal muscle[19–21]. In this article, the rationale and early results of this strategy are presented.

The process of remodelling

Remodelling involves different components of the myocardium which include the cardiomyocyte, the matrix, endothelial cells and fibroblasts.

The cardiomyocytes change their phenotype with marked enlargement in their size which is more pronounced in the long axis as compared to the width or depth[13–16] (Fig. 1). This is associated with a deterioration in contractile function[22,23] (Fig. 2) (both contraction and relaxation and a response to catecholamine)[24], and induction of a specific gene programme involving several groups of genes[25–28]. These include genes encoding sarcomeric and cytoskeletal proteins, calcium handling proteins, metabolic enzymes, ion channels, secreted cytokines and growth factors and enzymes involved in the apoptotic pathway. Abnormalities in the cytoskeletal proteins and their regulators appear to play an important role in familial and acquired[29,30] forms of dilated cardiomyopathy. Of particular interest in this context are the LIM proteins[31] which mediate interaction between the cytoskeleton and multiprotein transcription factors. Mice deficient in muscle LIM (MLP knock-out mice) develop dilated cardiomyopathy with almost all the characteristics of human dilated cardiomyopathy[32]. It is of interest that a recent study has reported decreased MLP expression in patients with dilated and ischaemic cardiomyopathy[33]. A link between changes in cytoskeletal proteins and calcium handling is suggested by the fact that an animal model combining deficiency of MLP and the calcium handling protein phospholamban did
not develop cardiomyopathy\textsuperscript{34}. This is supported by early observations in our bridge to recovery programme, that haemodynamic recovery is associated with a reduction in expression of phospholamban and an increase in \textit{SERCA}$_2$ (Fig. 3) and sarcoplasmic reticulum calcium content (Fig. 4).

The extracellular matrix is in a dynamic equilibrium regulated by a family of enzymes termed metalloproteinases and their inhibitors (tissue inhibitors of metalloproteinases). Differential changes in these enzymes have been reported in the myocardium of patients with dilated cardiomyopathy and heart failure\textsuperscript{35} and are thought to play an important role in the process of remodelling\textsuperscript{36} and possibly recovery.

Pathological hypertrophy is associated with increased fibrosis and collagen remodelling of the myocardium secondary to the proliferation and

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Isolated ventricular myocytes from patients at the time of insertion of a left ventricular assist device (LVAD) (middle horizontal panel) showing severe hypertrophy as compared to normal controls (top horizontal panel). Bottom panel shows ‘normalization’ of the size of the myocytes post left ventricular assist device.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Sample traces from contraction of left ventricular trabeculae prior to and after 8 months of left ventricular assist device (LVAD) support combination. Time to 90\% relaxation (R$_{90}$) was slower prior to left ventricular assist device, R$_{90}$=0.925 vs 0.46 after left ventricular assist device. Preparations were stimulated at 0.5 Hz at 32 °C.}
\end{figure}
increased secretory activity of cardiac fibroblasts\textsuperscript{37}. The renin angiotensin aldosterone system is thought to play an important role in this process of fibrosis\textsuperscript{38,39}. Currently high throughput analysis of gene expression through gene chip technology\textsuperscript{26} and the use of proteomics\textsuperscript{27} is being used to expand our knowledge of the changes in gene expression associated with ‘remodelling’ and heart failure. Such knowledge could help in monitoring molecular markers of recovery and possibly stimulate novel targets for pharmacological interventions.

**Mechanisms of remodelling**

Although the exact molecular mechanisms of remodelling are still not fully known, several mediators amenable to pharmacological interventions have been implicated. These include the renin-angiotensin-aldosterone system\textsuperscript{38–41}, the $\beta_1$-receptor system\textsuperscript{19–43}, endothelins and cytokines\textsuperscript{43,44}. Most of these are closely linked to the process of loading or stretching of the myocardium. The renin-angiotensin-aldosterone system has been shown to have potentially harmful effects on the myocytes, fibroblasts, and endothelial cells. Similarly, several studies have shown that increased sympathetic activity, particularly those involving $\beta_1$-receptor function, are maladaptive and involved in the progression of human heart failure\textsuperscript{42,45}. This is supported by the proven beneficial effects of beta-blockers\textsuperscript{45} especially those which are $\beta_1$ specific, such as metoprolol. In animal models, administration of $\beta_1$ agonists produces pathological hypertrophy associated with fibrosis and can produce apoptosis of cardiac myocytes\textsuperscript{19,46}. In contrast, $\beta_2$ agonists can produce physiological hypertrophy\textsuperscript{19} and do not cause apoptosis\textsuperscript{46}. In addition, transgenic mice over expressing $\beta_1$ receptors die prematurely while those over expressing $\beta_2$ receptors (25 fold) have enhanced myocardial function with a normal survival\textsuperscript{47}.

Activation of the immune system with increased myocardial expression and circulatory levels of several cytokines, such as TLR\textsuperscript{48}, interleukin 6 and tumour necrosis factor\textsuperscript{43,44}, have been implicated in the progression of heart failure through their direct effects on the myocardial cells producing contractile dysfunction and possibly apoptosis\textsuperscript{28}. In the current bridge to recovery programme we have used a combination of mechanical support with pharmacological manipulation of two of the four putative mechanisms mentioned above.

**Combination therapy**

The rationale of the combination therapy is to achieve maximal unloading of the myocardium
combined with pharmacological therapy, aimed at remodelling reversal, followed by stimulation of the development of physiological hypertrophy.

Although pusher-plate implantable left ventricular assist devices produce significant unloading of the left ventricle by drawing blood from the apex, their function is not co-ordinated with native left ventricular contraction, which can occur at a phase when both the inlet valve of the device and the native aortic valve are closed. This results in isometric ventricular contraction, which is energy consumptive and can cause excessive stretching of the myocardium, particularly in the presence of systemic hypertension which can occur following left ventricular assist device insertion. Regurgitation of the inlet valve of the left ventricular assist device can also result in systolic and diastolic stretching of the myocardium. The latter is known to induce Brain Natriuretic Peptide (BNP)[49] which is only expressed in hypertrophied or failing myocardium. Several drugs currently in use for the treatment of heart failure can help the process of unloading and actively produce reverse remodelling. These drugs include beta-blockers and drugs known to modulate the renin-angiotensin-aldosterone system. Beta-blockers have multiple beneficial effects: slowing heart rate, lowering blood pressure, as well as a direct effect on the myocardium by reversing remodelling and upregulating β-receptors. The combination of ACE inhibitor and angiotensin I receptor antagonists has the advantage of full blockade of the receptors, together with enhanced endothelial function due to increased concentrations of bradykinin produced by ACE inhibition[41]. The beneficial effect of combining these drugs is supported by clinical and experimental studies[41,50,61]. Apart from the effect on reverse remodelling, these drugs have a direct effect on the sarcoplasmic reticulin[61], which improves calcium handling and diastolic function. The addition of spironolactone has been shown to enhance survival in heart failure[52] and reduce myocardial fibrosis in these patients[53].

Once maximal reverse remodelling has been achieved, a programme of inducing physiological hypertrophy is instituted. This consists of administration of the β2 agonist clenbuterol which is known to induce skeletal muscle hypertrophy and improve performance[21] and also to stimulate physiological ‘myocardial hypertrophy’[19,20]. As explained earlier, β2 agonist do not cause apoptosis[46] or increased mortality in animal models[47]. During administration of clenbuterol, β1 receptor antagonist therapy is continued. The action of clenbuterol on the structure and function of skeletal muscles[21] could be particularly valuable in patients with heart failure who are known to have significant skeletal muscle abnormalities. During this period, an active exercise programme is administered, again to help the process of physiological hypertrophy.

**Monitoring recovery**

Evidence of recovery is monitored by echocardiography (with measurement of left ventricular dimensions, posterior and septal wall thickness in systole and diastole, left ventricular long axis function, aortic and mitral valve opening and closing). These measurements are then repeated (on heparin) with the device switched off for 5 then 10 then 15 min. If this is well tolerated, the echo is repeated after a ‘6 min walk’ with the device switched off and the distance covered is measured. If a 6 min walk distance of 300 m is achieved with no deterioration in echo parameters, exercise capacity with measurement of VO2 max is determined with the device off after an appropriate period of rest (>6 h). MUGA scans are performed (for left ventricular and right ventricular ejection fractions and response to exercise) if there is echocardiographic evidence of maintained left ventricular function off the machine for 15 min. Patients also undergo 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). Myocardial biopsies taken at cardiac catheterization are examined by light microscopy and analysis is performed to investigate the molecular mechanisms that may be involved in remodelling and reverse remodelling using quantitative real time polymerase chain reaction, Western blotting and immunocytochemistry. Myocytes are isolated from left ventricular core tissue at the time of implantation and from biopsies taken during follow-up. Single cells are prepared for size and force–frequency contraction patterns and the change with offloading is studied. Explantation of the device is considered if, with the device off, ventricular dimensions are normalized, ejection fraction is ≥45%, left ventricular end-diastolic pressure is ≤8 mmHg, cardiac index is more than 2.8, and most importantly VO2 max is ≥20, and VE/VO2 <3.4[54].

**Clinical experience**

To date we have used the combination therapy in 17 patients. Of these, 14 were prospectively recruited, while three were included from a previous programme of bridge to transplantation. At the time of
insertion of the device (Thermocardiodynamics vented electric Heart Mate I). All patients were in class IV of NYHA classification, with a deteriorating haemodynamic state and varying degrees of end stage organ failure, precipitated by the low cardiac output and thought to be reversible. All patients had essentially normal coronaries, and were on inotropic support, and/or intra-aortic balloon counterpulsation. There were three peri-operative deaths due to multi-organ failure, and one late from infection. The remaining patients have been followed-up for periods ranging from 1–30 months, and all are clinically well. Of the 12 patients who were followed up for more than 2 months, all showed evidence of improved cardiac function without the support of the left ventricular assist device (Fig. 5). This was accompanied by consistent diminution in left ventricular volumes and improvement in exercise capacity. Four patients underwent successful explantation of the device and remained in class I NYHA for periods of 1–9 months. One patient, who had to have the device explanted before instituting the clenbuterol therapy, has a dilated ventricle but no exercise limitation and no clinical evidence of failure. The remaining patients have normal left ventricular dimensions. Serial examination of blood and myocardial biopsies showed progressive ‘normalization’ of the neurohumeral, cellular, molecular and functional changes (Figs 1–6) known to be present in end-stage heart failure and malfunctioning donor hearts with acute heart failure\[55,56\].

**Conclusion**

A strategy of combined mechanical and pharmacological therapy of end-stage heart failure appears to result in fairly consistent ‘normalization’ of cardiac structure and function. Further studies are required to determine the longer term efficacy of this strategy and elucidate further the concepts of ‘reverse remodelling’ and ‘physiological hypertrophy’. It is hoped that this will contribute to the management of

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**Figure 5** Left ventricular ejection fraction (off pump) before and after left ventricular assist device insertion and the combined Harefield regime.

**Figure 6** Changes in serum interleukin 6 following left ventricular assist device (LVAD) and pharmacological therapy in two patients a & b.

**Figure 7** Relative expression of atrial (*---*) and brain (**---**) natriuretic peptide) after insertion of a left ventricular assist device.
these patients and possibly identify new targets for therapy of heart failure.  

M. H. YACOUB  
Heart Science Centre,  
Royal Brompton and Harefield Hospital,  
Harefield, Middlesex, U.K.

The author gratefully acknowledges the contribution of members of the LVAD research group for data included in this article. These include Drs Patrick Tansley, Emma Birks, Chris Bowles, Maren Koban, Cesare Terracciano, Virginia Owen, Rahat Warraich and Paul Barton.

This work was supported by the Harefield Research Foundation, the Royal Brompton and Harefield Charitable Trustees, the British Heart Foundation and Thermocardiodynamics Inc.

References


