Gene expression profile of the recovering human heart

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This editorial refers to 'Molecular signature of recovery following combination left ventricular assist device (LVAD) support and pharmacologic therapy'⁷ by J.L. Hall et al., on page 613

Heart failure is a disease of increasing prevalence and poor prognosis. Current data indicate that 5-year survival following the diagnosis of heart failure is 50%, and patients with end-stage disease face a 1-year survival rate of 50%. Recent predictions suggest that heart failure will become the leading cause of all disability by 2020. For patients with refractory end-stage heart failure, there are few options for effective treatment. Although cardiac transplantation provides the best therapeutic outcome for end-stage HF, substantial limitations of this surgical intervention include an extremely limited supply of acceptable donor hearts, having reached a plateau of less than 3000 per year worldwide.

Left ventricular assist device (LVAD) support of end-stage heart failure patients was originally approved as a bridge to cardiac transplant, and recent reports suggest improved outcomes in transplant recipients supported by LVAD in comparison with those treated with chronic inotropes.¹ Improved morbidity and mortality were found in the REMATCH trial of long-term LVAD support compared with optimized medical management in severe HF patients ineligible for transplant, leading to the approval of LVAD as destination therapy.

Unloading the left ventricle in end-stage heart failure patients with LVAD support can lead to partial normalization of myocardial structure and function, termed reverse remodelling. Reverse remodelling has been associated with changes in gene expression following LVAD support⁵-⁶ or pharmacological therapy.⁷ In select patients, LVAD support in conjunction with pharmacological therapy may result in sufficient reverse remodelling to allow explant of the device. LVAD-associated reverse remodelling provides the unique opportunity to obtain myocardial tissue in humans in end-stage heart failure at the time of LVAD implant and subsequent explant upon myocardial recovery or transplantation. This allows for the serial analysis of gene expression profiles in the same patient that may provide important insights into both the progression and regression of heart failure.

Hall et al.⁸ report global analysis of gene expression changes in heart failure patients they have recently described,⁹ who were supported with LVAD, the β2-adrenergic receptor (β2-AR) agonist clenbuterol, and additional pharmacological management. Using a pathway analysis strategy, the authors identified several changes in the integrin pathway associated with recovery, supporting their previously reported single gene findings in these same patients.¹⁰,¹¹ Less compelling alterations were found throughout the cAMP pathway with a similar approach, although the authors discovered down-regulation of a newly identified member of this pathway named EPAC2. They suggest these specific changes occurred uniquely in the recovery patients, and were not found in their prior analyses of non-recovery patients. Finally, the authors utilized software that can identify potentially unrecognized interactions between the diversity of genes that were associated with the recovery process. It is interesting to speculate regarding the functional contribution of alterations in the genes and pathways identified by the authors in the recovery process. However, the human recovery model only allows for speculation regarding their functional role. Although the authors indicate some skepticism of animal models, such models will be required to evaluate the functional role of newly identified genes and pathways in the development and regression of heart failure.

Interpretation of the current results should be approached with caution due to extremely limited sample size. While microarray studies are a powerful method to investigate global changes in gene expression, they also require sufficient sample size and appropriate statistical analysis. There are numerous approaches to normalize microarray data and verify its quality prior to analysis, accompanied by several methodologies to assess the false discovery rate among genes identified in subsequent statistical analyses. Perhaps due to sample size, neither data normalization nor false discovery rates are reported, both of which would be important to evaluate the significance of the results. In an attempt to reduce error, the authors combine results from paired and un-paired t-tests, and utilize only genes that overlap both lists for further study. Unfortunately, t-tests, in particular, are statistically weak in small samples with abnormal distribution. The major benefit of studying the recovery patients is the ability to perform paired statistical analysis on the same patients before and after recovery. However, even paired statistics

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LVAD/clenbuterol-mediated recovery from heart failure in a limited patient population. This should provide the impetus for large multi-centre trials with controlled medical interventions to understand the biology of cardiac remodelling with mechanical support. Study of gene expression, genetics, and genome-wide associations in such a trial could provide further mechanistic insights into the recovery process and potentially identify therapeutic and diagnostic targets. Expansion of sample size in larger, controlled trials and a combination of clinical, genetic and genomic information could one day identify both therapeutic targets as well as a prediction paradigm for individual patient response to mechanical support with targeted pharmacological therapy. Hall et al. provides a launching point for such studies.

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References


