The Holy Grail of LVAD-induced reversal of severe chronic heart failure: the need for integration

Magdi H. Yacoub* and Cesare M. Terracciano

Imperial College London, National Heart & Lung Institute, Harefield Heart Science Centre, Harefield, Middlesex UB9 6JH, UK

Online publish-ahead-of-print 1 April 2011

This editorial refers to ‘Heart failure reversal by ventricular unloading in patients with chronic cardiomyopathy: criteria for weaning from ventricular assist devices’, by M. Dandel et al., on page 1148

For a long time conventional wisdom had it that chronic severe heart failure is a unidirectional progressive disease which invariably results in death. This paradigm has dramatically changed with the demonstration that ‘prolonged’, near-complete unloading of the left ventricle (LV) with or without pharmacological therapy can result in sufficient clinical recovery in a variable percentage of patients to allow removal of the device with stable, normal or near-normal function over many years.1,2 This strategy avoids or delays transplantation and provides an innervated heart capable of providing normal power output3 and an improved quality of life. Surprisingly, this paradigm has been actively pursued in only very few centres, with varying rates of success in terms of both the percentage of patients who ‘recover’ and the period of sustained recovery.2,4 The field has been hampered by the availability of cardiac transplantation programmes in most centres performing left ventricular assist device (LVAD) implantations. Cardiac transplantation constitutes a validated form of treatment which obviates the need for repeated close observations to monitor recovery and evolve innovative methods.

In spite of these difficulties, the field is progressing steadily. Dandel and colleagues, from the pioneering German Heart Centre, who made important contributions in this field, have reported a retrospective analysis of the predictors of survival as recurrence of heart failure in a homogeneous group of 47 patients with idiopathic cardiomyopathy or myocarditis, who have been followed up for up to 15 years after explantation.5 They identified several risk factors for recurrence of heart failure which include older age, longer history of heart failure, and larger LV dimensions pre-operatively. In addition, they identified parameters just before or just after explantation which predict stability of recovery. As the authors mention, explantation of the device can sometimes be dictated by complications such as infection or thrombo-embolism in patients who have not achieved the pre-determined criteria for explantation. Surprisingly, in their series and some other studies,4 some of these patients continue to do very well after explantation, showing that the clinical and echo criteria used were not sufficient to guide therapy and that additional parameters such as load-independent haemodynamic parameters, inotropic reserve, or biomarkers are needed. As the authors rightly point out, in their series, the analysis is hampered by the relatively small number of patients, highlighting the importance of ‘integration’ with other centres and performing multicentre trials.

Real progress, however, is critically dependent on integrating clinical and basic science studies, bringing the benefit of laboratory research to the clinic as soon as possible (the essence of translational research) (Figure 1). Following different forms of myocardial injury, progressive heart failure is accompanied by profound changes in the myocardium, involving the cardiomyocytes, the endothelial cells, the fibroblasts, as well as the extracellular matrix, which is collectively referred to as ‘remodelling’.6 These are associated with neurohumoral changes which play an important additional role in progression.

Together with improving perfusion, LVAD treatment can produce important functional and structural changes in the LV as well as other tissues and organs, including the aortic valve and arterial wall. These changes can be device-specific7 and need to be studied in detail.

Unloading is sensed by mechanoreceptors on the cell membrane of different types of cells in the myocardium as well as in the sarcomeres,8 and are transmitted to the nucleus by a variety of pathways involving cytoskeletal proteins. These result in a change in gene expression with profound alterations in the structure and function of the myocardium in a time-related fashion.9–11

The opinions expressed in this article are not necessarily those of the Editors of the European Heart Journal or of the European Society of Cardiology.

* Corresponding author. Tel: +44 1 895 828893, Fax: +44 1 895 828893, Email: m.yacoub@imperial.ac.uk

† doi:10.1093/eurheartj/ehq353

Published on behalf of the European Society of Cardiology. All Rights Reserved. © The Author 2011. For permissions please email: journals.permissions@oup.com.
Some of these changes are beneficial while others are harmful and constitute a process of progressive ‘atrophy’.11,12 Thorough understanding of these processes is essential to evolve new strategies to maximize the beneficial effects while minimizing or eliminating the harmful effects. An example of devising supplemental strategies is the use of pharmacological therapy to enhance reverse remodelling, and to counteract atrophy with the use of drugs such as clenbuterol.13 Clenbuterol, classified as a β2-adrenoceptor agonist, has a unique and still unclear signalling pathway. It has been shown to induce cardiac ‘physiological’ hypertrophy, and improvement in cardiac contractility and metabolic profiles in normal and failing hearts, with or without mechanical unloading in animal models.12,14 Other strategies could include the use of an exercise programme to enhance physiological cardiac hypertrophy. Analysis of myocardial tissue in patients who recovered compared with those who did not showed that increased sarcoplasmic reticulum calcium content is associated with clinical recovery.15 This finding supports the use of gene therapy to optimize sarcoplasmic reticulum calcium regulation, e.g. by manipulating the expression of SERCA2A. Other strategies could be the combined use of LVAD and cell therapy in order to obtain myocardial recovery or regeneration, through stimulation of the myocardial cell cycle, recruitment of circulating stem cells, or transplantation of stem cells directly into the unloaded myocardium.

To date, recovery programmes have been limited to patients with ischaemic cardiomyopathy who develop progressive ‘remodelling’ of the remaining myocardium, following a single myocardial infarct, could also be candidates for this form of therapy. Another important area to explore is appropriate timing of this form of therapy before the onset of irreversible damage of the myocardium, while realizing that even fibrosis can be reversible!16 We believe that concerted efforts in this field could be a fruitful way to maximize the ability to reverse heart failure in increasing subsets of patients and possibly to identify new targets for therapy.

**Conflict of interest:** none declared.

**References**


Corrigendum
doi:10.1093/eurheartj/ehr115


The above article was originally published with standard subscription-based access, however, the authors have since decided to take up the Oxford Open model of publication. The article is now freely available online under the Oxford Open model and the copyright line now reads:

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2011. For permissions please email: journals.permissions@oup.com. The online version of this article has been published under an open access model. Users are entitled to use, reproduce, disseminate, or display the open access version of this article for non-commercial purposes provided that the original authorship is properly and fully attributed: the Journal, Learned Society and Oxford University Press are attributed as the original place of publication with correct citation details given; if an article is subsequently reproduced or disseminated not in its entirety but only in part or as a derivative work this must be clearly indicated. For commercial re-use, please contact journals.permissions@oup.com.

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2011. For permissions please email: journals.permissions@oup.com.