LVADs Open Window to Myocardial Recovery

Structural and functional changes in the recovering heart may guide future treatments.

BY MARK S. LESNEY

FROM THE JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Left ventricular unloading in patients with end-stage heart failure has been shown to improve with the use of a left-ventricular assist device, according to the results of several recent clinical studies. This improvement includes favorable changes in myocardial structure and function, including beta-adrenergic responsiveness and myocyte contractility.

Several molecular and genetic mechanisms have been correlated with these changes and might provide the basis for improvements in device behavior, as well as indications for potential targets for new therapeutic drugs and altered regimens for existing drugs.

Such new treatments may have the potential to benefit not only patients who have received LVADs, but also heart failure patients as a whole, as reported in a state-of-the-art article (J. Am. Coll. Cardiol. 2011;57:641-52).

The LVAD population presents a unique and valuable opportunity to obtain myocardial tissue of patients with end-stage heart failure (HF) at the time of implantation, and often at the time of heart and/or LVAD explantation, after a period of unloading, according to Jennifer L. Hall, Ph.D., of the University of Minnesota, Minneapolis, and her colleagues in the United States and Europe. These tissue samples allow paired comparisons of before and after changes in molecular, genetic, and cytologic markers indicative of improvements that occur with the reverse remodeling of the human heart seen in response to LVADs.

The researchers supported their conclusions with a review of recent clinical trials and assembled data from a report by the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) covering the years 2006-2009, which included the introduction of continuous-flow technology as well as the original pulsatile flow devices.

Mechanical improvements in failing hearts treated with LVADS have been characterized by partial recovery of the contractile performance of myocytes. This includes improvements of the magnitude of shortening in isolated myocytes in response to beta-adrenergic agonists, of basal relaxation, and in the rise and fall in tension in trabecular muscle preparations.

Relevant markers and pathways found to be improved or normalized by LVAD support included:

► **Beta-adrenergic signalling.** Improvements in developed tension with LVADs have been shown to be associated with an increased beta-adrenergic receptor density. Because a novel combination of LVAD support and pharmacologic therapy – including the selective beta-2 agonist clenbuterol – showed promise in restoring ventricular function in patients with heart failure, investigators analyzed six paired human heart samples isolated at the time of LVAD implantation and at the time of LVAD explantation due to sufficient myocardial recovery. Significant changes to a number of genes in the beta-adrenergic signaling pathway occurred in recovering hearts.

► **Calcium handling.** Although improvements in basal relaxation rates with LVADs have not been definitively linked to changes in calcium handling, the largest improvements in action potential and sarcoplasmic reticulum calcium content occurred in patients who achieved clinical recovery in response to LVADs and pharmacological therapy. However, improvements in calcium handling and contractility appear time dependent, with patients with shorter durations of support (less than 115 days) showing improvement, which reverted back to failing levels in patients with longer durations of support.

► **Metabolism and growth factor–related genes.** Several genes that regulated metabolism were found to change their expression during LVAD-supported recovery. These included arginine:glycine amidinotransferase (AGAT), a rate-limiting enzyme in the creatine synthesis pathway, which was significantly down-regulated after unloading in the recovered hearts, returning to normal levels, in direct contrast to the up-regulation of AGAT seen in patients with heart failure. Insulin growth factor was elevated in patients at the time of LVAD explantation due to recovery. This was thought to aid in limiting atrophy and apoptosis during reverse remodeling and to promote repair and regeneration.

► **Natriuretic peptides and chromogranin A.** Unloading a failing heart with an LVAD was associated with a decrease in natriuretic peptides (which are activated during heart failure) and reestablishment of the local responsiveness of a key enzyme, chromogranin A, to cardiac atrial natriuretic peptide.

But all is not perfect in the LVAD-supported heart. In one study, there was a significant increase in total and cross-linked collagen in the myocardium, compared with nonfailing and medically managed patients with heart failure, which correlated with increased left ventricular stiffness. "Interestingly, the majority of [these] LVAD patients after implantation were not on ACE inhibitors, which have been demonstrated to improve fibrosis and remodeling," the authors wrote.

A subsequent retrospective cohort study of the same group, comparing LVAD patients who did and did not receive ACE inhibitor therapy after implantation, showed a significant decrease in collagen content and myocardial stiffness in the cohort with LVADs and ACE inhibitors. "These findings support the hypothesis that maximizing optimal medical management after ventricular unloading with LVADs may promote myocardial recovery."

The study was sponsored by the National Institutes of Health, the American Heart Association, and the National Institutes for Health Research Cardiovascular Biomedical Research Unit at the Royal Brompton and Harefield National Health Service Foundation Trust, and Imperial College London. Several of the authors reported receiving research support and/or honoraria or speakers fees from Thoratec, Heartware Inc., and Medtronic, all manufacturers of LVADs. ■

High-Altitude Simulator Improves Heart Failure Measures

BY BRUCE JANCIN

FROM THE ANNUAL SCIENTIFIC SESSIONS OF THE AMERICAN HEART ASSOCIATION

CHICAGO – Exposing patients with heart failure to altitude training using a portable simulated altitude device appears to provide clinical benefits.

The 10 patients with systolic heart failure enrolled to date in a pilot study responded to a maximum simulated altitude of 2,700 m with significant improvements in left ventricular ejection fraction, quality of life, and three different measures of exercise performance, Dr. Philip Formica reported at the meeting.

Importantly, these benefits were sustained for at least 4 weeks after completion of the simulated altitude treatment sessions using the Hypoxico Inc. altitude tent, added Dr. Formica of Albert Einstein College of Medicine and Montefiore Medical Center, New York.

Commercially available high-altitude simulators such as this are popular with elite bicycle racers, distance runners, and other endurance athletes because adaptation to altitude results in physiologic changes that enhance oxygen delivery to the periphery. Athletes use the devices at home in order to, as their coaches preach, "sleep high and train low."

The hypothesis tested in this study was that patients with heart failure would also benefit from acclimatization to altitude. The physiologic changes accompanying this acclimatization include an erythropoietin-induced increase in RBC mass, a rightward shift of the oxyhemoglobulin dissociation curve, improved oxygen transport stemming from increased tidal volume and hypoxic ventilatory response, improved left ventricular end-systolic diameter and stroke volume, and greater skeletal muscle capillary density.

The treatment protocol consisted of 10 sessions with the patient sitting in the normobaric hypoxic enclosure; the sessions, each lasting 3-4 hours, were spread over the course of 22 days and were done on an alternate-day schedule. Forty-eight hours prior to the first session, patients went on twice-daily 125-mg oral acetazolamide, a drug long used to prevent headache and other altitude sickness symptoms. Patients started at a simulated altitude of 1,500 m, increasing by 300 m per session to a maximum elevation of 2,700 m.

The altitude simulation device draws in ambient air, separates the oxygen from the nitrogen, and then pumps high-flow hypoxic air into a semisealed enclosure. Altitudes of up to 6,500 m can be simulated.

The patients had a mean 83-month duration of heart failure. All of them tolerated the treatment sessions without any adverse effects. A mean 91% oxygen saturation was maintained at maximum simulated altitude. Nine of 10 patients showed significant improvement in all three measures of exercise performance (see table).

These results are promising, but need to be confirmed in a larger number of heart failure patients, said Dr. Formica, who had no relevant financial disclosures. ■

Significant Improvements Seen With Altitude Therapy

End point	Baseline	48 hours after session 1	4 weeks after final session
Left ventricular ejection fraction	32%	35.3%	37.7%
Quality of life*	33.7	24.1	18.4
Peak O_2 consumption (mL/kg per min)	13.4	14.1	15.1
6-minute walk distance (m)	385.4	408.4	431.2
Exercise time (sec)	589.8	670.4	668.1

*Based on the Minnesota Living With Heart Failure Questionnaire score.
Note: Based on data from 10 patients.
Source: Dr. Formica