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In this issue of *Circulation*, Birks et al report their recent experience using the combination of continuous-flow (CF) circulatory support and pharmacological therapy to treat advanced heart failure in patients requiring left ventricular assist device (LVAD) support. Thirty-three patients underwent HeartMate II (HMII) LVAD implantation at Harefield hospital during the 3-year study period. Twenty-three patients (70%) with nonischemic cardiomyopathy were considered appropriate for the recovery protocol at the time of HMII LVAD implantation, and 20 patients (61%) who survived LVAD implantation formed the study cohort. With their strategy of aggressive neurohormonal blockade (phase I) followed by high-dose clenbuterol (phase II), 12 (60%) of the study cohort met criteria for LVAD explantation, and all 10 (50%) who survived the perioperative period demonstrated sustained recovery over 56 to 1112 days of follow-up. Therefore, 30% of all patients and 43% of all nonischemic patients undergoing HMII implantation could be managed to long-lasting recovery. In an era in which transplant waiting times have blurred the distinction between bridge-to-transplant and destination therapy for some patients, this single-center experience is intriguing and offers hope for a new strategy for select patients supported with CF LVADs.

Reports in the literature regarding rates of cardiac recovery during pulsatile LVAD support are quite varied (Table 1). The Columbia University group reported a 1% rate of sustained cardiac recovery in 111 patients with both ischemic and nonischemic etiology of heart failure. In contrast, the German Heart Institute reported that 13% of patients with nonischemic heart failure demonstrated sustained recovery (minimum follow-up of 36 months) after LVAD explantation. The LVAD Working Group was the first multicenter, prospective initiative to study recovery. Sixty-seven LVAD patients (only 1 CF LVAD) with both ischemic and nonischemic causes underwent serial echocardiograms at reduced flow to seek recovery. Six percent of the whole cohort and 7% of all nonischemic patients could undergo LVAD explantation. None of these reports described the consistent use of pharmacological therapy during LVAD support, and it was not until the first Harefield recovery study that data regarding combined pharmacological and mechanical support were available.

In the first Harefield study, 15 LVAD patients (1 CF LVAD) received maximal doses of heart failure medications, followed by high-dose clenbuterol. All patients had a nonischemic etiology, and most (80%) had heart failure for >6 months. The authors reported that 75% of patients receiving clenbuterol could undergo LVAD explantation and 46% of all patients with nonischemic heart failure presenting for LVAD could be managed successfully to recovery in this way. These data from Harefield represented the most successful reported recovery strategy to date, and prompted a multicenter study in the United States (to replicate the Harefield recovery protocol) called the Harefield Recovery Protocol Study (HARPS). HARPS has now completed enrollment of 17 patients with the HMI pulsatile LVAD, 13 of whom received both maximal neurohormonal blockade and high-dose clenbuterol. Results from the US HARPS study will be presented in the near future.

With the approval of the HMII LVAD for both bridge-to-transplant and destination therapy, implantable pulsatile LVADs are now used rarely. As the authors note, differences in left ventricular unloading with CF devices suggest that our experience with bridge to recovery with pulsatile devices might not apply in the CF era. Pulsatile devices offer more profound pressure and volume unloading than CF LVADs. Furthermore, cardiac-LVAD synchrony plays a role in pulsatile LVAD support not seen in CF physiology. One small retrospective study has compared echocardiographic and cellular changes in patients supported with pulsatile and CF LVADs. There was a significantly larger reduction in ventricular volumes during pulsatile support, but no difference in pulmonary pressures. Only patients supported with a pulsatile device had reduction in left ventricular mass and improvement in right ventricular function during LVAD support. Interestingly, the type of LVAD support did not influence the effect on reductions in myocyte size, collagen content, and cytokine expression.

Limited clinical data are available about rates of cardiac recovery during CF LVAD support. A recent analysis of 1108 patients enrolled in the HMII bridge-to-transplant and destination therapy trials showed a 1.8% overall recovery rate. Of the 20 patients who underwent LVAD explantation, most (65%) had heart failure for <1 year, and most (67%) were aged <40 years. Patients in these trials were not systemati-
cally treated with heart failure medications after LVAD implantation.

The patients enrolled in the current study utilizing CF support were relatively young (16 to 58 years), but had advanced nonischemic cardiomyopathy (all but 1 requiring at least 1 inotrope). Preoperative echocardiography showed significant ventricular dilation (left ventricular end-diastolic diameter 57 to 91 mm) and severe left ventricular dysfunction (left ventricular ejection fraction 7% to 34%), and histological analysis of the left ventricular core demonstrated stigmata of advanced cardiomyopathy. Despite the severity of disease at the time of CF LVAD implantation, 60% of the study cohort demonstrated complete normalization of left ventricular size and function. Although it is recognized that most of the patients who recovered (66%) had short durations (<6 months) of heart failure before LVAD, these data give credence to the notion that advanced heart failure is reversible. Furthermore, when heart failure is reversed in this manner, it appears to be durable.

Although this strategy of combined mechanical and pharmacological support appears promising, a number of important issues are raised. Specifically, differing strategies of CF pump management and the challenges of reinitiating heart failure medications after CF LVAD implantation should be considered. Furthermore, the differential effects of the 2 stages of pharmacological management in this protocol (phase I, conventional neurohormonal blockade; phase II, clenbuterol) should be addressed.

We have limited guidelines about optimal management of pump flow during CF support. It has been suggested that pump speed should be adjusted (guided by echocardiography) to maximally unload the left ventricle while preventing leftward shift of the septum. Reducing pump speed to maintain some degree of pulsatility prevents collapse of the left ventricle and inflow obstruction. Recent reports have suggested that maintaining intermittent aortic valve opening might diminish the development of aortic valve commissural fusion and insufficiency. Some centers manage CF pump speed in a biphasic fashion to promote recovery (in select patients). Initially, pump speed is set high enough for maximal ventricular unloading. After a number of weeks (and the initiation of heart failure medications), pump speed is reduced to partially reload the ventricle and allow intermittent opening of the aortic valve. Future studies should focus on optimal pump management strategies to maximize the potential for cardiac recovery.

The target doses of the medications used in the first stage of pharmacological management in this study were ambitious for a patient supported with a CF LVAD. Guidelines for management of blood pressure during CF support suggest that mean arterial pressure should be maintained between 70 and 80 mm Hg, and some patients may not tolerate higher doses of neurohormonal blockade. In this study, most patients appeared to tolerate high doses of losartan, but few reached study target doses of carvedilol or losartan. In our experience, most CF patients will tolerate standard doses of an angiotensin-converting enzyme inhibitor and β-blocker when gradually uptitrated in the outpatient clinic over the course of 6 to 8 weeks.

The role of clenbuterol (a selective β-agonist not approved for any human use in the United States) remains unclear. The authors suggest that clenbuterol is given to induce “physiological hypertrophy” after a period of maximal mechanical and pharmacological unloading. The dose of clenbuterol used in this and the prior Harefield study is 25 times greater than the therapeutic dose used in asthma, but appeared to be well tolerated in those who received it. However, the authors conclude that the relative contribution of clenbuterol to recovery of ventricular function cannot be ascertained from this study. Indeed, ventricular function had already improved significantly by the end of phase I therapy without evidence for further significant improvement after phase II (clenbuterol). This same limitation was true of the first Harefield recovery study because all recovered patients received both phase I and II therapy. Preliminary data from the US HAREPS trial also suggest that pulsatile LVAD support combined with phase I therapy leads to significant reverse remodeling (written communication, 2010). Future studies will need to elucidate whether CF LVAD combined with conventional heart failure therapy alone is sufficient to promote sustained cardiac recovery.

Recent estimates suggest that there are ~200 000 patients with advanced heart failure who might benefit from cardiac

### Table 1. Rates of Sustained Cardiac Recovery After LVAD Explantation

<table>
<thead>
<tr>
<th>Study Population, n</th>
<th>Etiology of Heart Failure</th>
<th>Sustained Cardiac Recovery, n (%)</th>
<th>Minimum Duration of Follow-Up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mancini et al (1998)</td>
<td>111</td>
<td>60 ICM; 51 DCM</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Dandel et al (2005)</td>
<td>131</td>
<td>DCM</td>
<td>17 (13)</td>
</tr>
<tr>
<td>Birks et al (2006)</td>
<td>24</td>
<td>DCM</td>
<td>8 (33)</td>
</tr>
</tbody>
</table>


### Table 2. Cardiac Recovery: Areas for Further Investigation

- Selection of patients for recovery protocols
- Optimal unloading strategies during CF support
- Adjuvant medical therapy to promote recovery
  - Conventional neurohormonal blockade
  - Investigational agents
- Time course of reverse remodeling
- Strategies for the assessment of native cardiac function
- Surgical techniques for explantation
- Postexplant management and prevention of sudden cardiac death
replacement, yet heart transplantation is available for only \( \approx 2000 \) patients each year. Current investigation in advanced heart failure is focusing on improving outcomes with long-term mechanical support. The report of Birk et al in this issue of *Circulation* should prompt further investigation into the combined use of mechanical and pharmacological support to promote cardiac recovery (Table 2). This research might address the selection of patients most likely to recover, optimal pump management, and the role of both conventional and investigational pharmacological therapy during LVAD support. This study adds further support to the premise that advanced heart failure might be reversible in certain patients and is some good news from our colleagues across the Atlantic.

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**References**


**Key Words:** Editorials ■ cardiac transplant ■ cardiomyopathy ■ heart failure ■ recovery ■ ventricular assist device
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