Elective Bridging to Recovery After Repair: The Surgical Approach to Ventricular Reverse Remodeling

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Abstract: We described our “surgical approach to reverse ventricular remodeling” in advanced chronic heart failure, based on the unique idea that “downstaging” class IV heart failure by supporting patients with left ventricular assist devices (LVADs) allows treatments mainly indicated for class III patients. The types of surgeries include mitral valve repair, surgical ventricular remodeling, coronary artery bypass grafting, and cardiac resynchronization. This approach has been applied to two patients with class IV chronic heart failure due to idiopathic dilated cardiomyopathy who were supported with the magnetically levitated Levacor LVAD. These were the first in-human implantations of this device. Sustained short- to medium-term recovery has been achieved in both patients. Key Words: Heart failure operations—Left ventricular assist device—Left ventricular reshaping/restoration—Mitra valve repair—Pacing—Resynchronization/biventricular.

Despite significant progress in the treatment of heart failure, patients with advanced chronic heart failure (ACHF) continue to experience significant morbidity and mortality. As ACHF reaches end-stage, the only viable options currently available are transplantation, long-term mechanical circulatory support (MCS), or terminal care. Strategies that can induce the recovery of ventricular function to avoid such outcomes are attractive, though little explored.

The recovery of ventricular function facilitated by ventricular assist devices (VADs), referred to as “bridging to recovery,” is of increasing interest. Bridging to spontaneous recovery during left ventricular assist device (LVAD) support has been achieved in only a small percentage of patients (1,2). Also, there are no indices that predict which patients are more or less likely to recover and therefore, patient selection criteria for bridging to recovery are not established. Furthermore, neither the required duration nor the preferred method of MCS to achieve sufficient and lasting recovery has been defined (3).

To maximize recovery and achieve lasting results, a strategy that combines MCS and pharmacologic treatment to induce reverse remodeling and prevent atrophy has been employed (4). This strategy is known as “pharmacologically augmented bridging to recovery” (5). Another approach that we are pursuing can be described as “bridging to recovery after surgical repair” (3). Surgical repair to promote recovery in patients with very advanced, end-stage heart failure is being explored, though still in the early stages and with results that have not been widely reproduced. While we have had success with surgical repair alone, it is possible that selected high-risk surgical patients are made better candidates for ventricular recovery by the combination of surgical repair and concurrent bridging to recovery with MCS. Elective support with VADs implemented at the same time as surgical repair could improve outcomes by (i) assuring favorable perioperative hemodynamics reducing early morbidity and mortality and/or by (ii) improving the magnitude and duration of eventual ventricular recovery.

We hypothesized that the combination of (i) surgical reparative procedure(s), including mitral valve repair, surgical ventricular remodeling (SVR), and coronary artery bypass grafting (CABG) with (ii) immediate, elective implementation of VAD support followed by (iii) supplemental heart failure therapy (i.e., optimal medical treatment [OMT] and, when indicated, cardiac resynchronization therapy [CRT]) will lead to better outcomes with ventricular recovery than any one of the three modalities alone in patients with advanced, chronic, end-stage heart failure (Fig. 1).

We applied our strategy by implanting for the first time in a human a “next generation” continuous flow centrifugal pump (Levacor, WorldHeart, Inc., Oakland, CA, USA) employing magnetics to fully levitate the rotor. The design of the LVAD and of the relevant feasibility study, including the patient inclusion and exclusion criteria, as well as the individualized patient selection method, has been published elsewhere (3).

CASE STUDIES

Two men (67 and 78 years old) with New York Heart Association (NYHA) class IV symptoms, chronically decreased cardiac index (CI: 1.7 and 1.4 L/min/m²) and left ventricular ejection fraction.
(LVEF: 24.8 and 22%) due to long-standing idiopathic dilated cardiomyopathy have been treated with the current strategy. Other baseline demographic and hemodynamic data are summarized in Tables 1 and 2. Both patients had severe mitral regurgitation (MR), ventricular dysynchrony, and concomitant single-vessel coronary artery disease. Both patients were nontransplant eligible and, despite optimal medical management, were homebound with a history of deteriorating and debilitating disease and repeated hospitalizations. The patients were referred for heart failure surgery, but due to advanced disease, they were considered poor candidates with high expected morbidity and mortality.

These patients were considered good candidates for our combined approach and they were offered mitral valve repair, CABG for incidental coronary artery disease, and, in one case, SVR. Both patients were concurrently and electively implanted with the Levacor device (3). The patients subsequently received OMT and CRT. Both patients received MCS for approximately 3 months (87 and 84 days) without any major adverse events.

Our aim during the period of mechanical support was to ensure adequate left ventricular (LV) off-loading (left ventricular end-diastolic diameter [LVEDD] <55–60 mm) and good tissue perfusion, providing initially full LV replacement and then progressively weaning to partial support.

According to the pump output and flow pattern, which was closely related to the patients’ clinical status, the support period can be roughly subdivided into two periods. The first was the “resting period,” during which the pump was operated at a speed sufficient to ensure LV off-loading. The second period was a “retraining period” with full LV loading and reconditioning.

The “resting period” was further subdivided into two phases: early and late. The “early resting phase,” during which mean LVAD flows were approximately 5–5.5 L/min, lasted for 15 and 6 days in the first and second patient, respectively. During the early resting phase, the pump rotational speed and output was at the highest level of the period of support. Under these conditions, the LVAD almost fully replaced the left ventricle. During the first postoperative day, mean CI increased by 72 and 130% in the first and second patient, respectively. During the first three postoperative days, the range of increase in CI encountered were 72–101% and 92.5–152% in the first and second patient, respectively. Concomitantly, left atrial filling pressures decreased substantially, and systolic arterial pressures were maintained.

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![Diagram](image.png)

**FIG. 1.** The surgical approach to recovery induced by VADs. MV, mitral valve.

**TABLE 1.** Hemodynamic and 6-min walk test data

<table>
<thead>
<tr>
<th></th>
<th>Preoperatively</th>
<th>Mean values on POD 1</th>
<th>Postdevice explantation</th>
<th>At discharge</th>
<th>At 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P1</td>
<td>P2</td>
<td>P1</td>
<td>P2</td>
<td>P1</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>3.5</td>
<td>2.47</td>
<td>6</td>
<td>5.66</td>
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<tr>
<td>CI (L/min/m²)</td>
<td>1.78</td>
<td>1.43</td>
<td>3.06</td>
<td>3.29</td>
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<tr>
<td>BP (S/D) (mm Hg)</td>
<td>100/70</td>
<td>100/60</td>
<td>92/85</td>
<td>116/69</td>
<td>—</td>
</tr>
<tr>
<td>PAP (S/D) (mm Hg)</td>
<td>61/34</td>
<td>50/22</td>
<td>39.5/24.6</td>
<td>32.5/20</td>
<td>—</td>
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<tr>
<td>PCWP (mm Hg)</td>
<td>35</td>
<td>31</td>
<td>21.5</td>
<td>18</td>
<td>—</td>
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<tr>
<td>RAP mean (mm Hg)</td>
<td>15</td>
<td>8</td>
<td>16.4</td>
<td>13.5</td>
<td>380</td>
</tr>
<tr>
<td>6-min walk (m/6 min)</td>
<td>140*</td>
<td>300</td>
<td>—</td>
<td>—</td>
<td>—</td>
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</tbody>
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*One hundred forty: 140 m in 2.5 min (the patient did not complete the test due to severe dyspnea and fatigue).

POD 1, postoperative day 1; P1, patient 1; P2, patient 2; at discharge, at hospital discharge, 22 and 17 days postdevice explantation for the first and second patient, respectively; at 1 year, at 1 year postdevice explantation; CO, cardiac output; BP, systemic blood pressure; S/D, systolic over diastolic; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; 6-min walk, 6-min walk test.
The aortic valve (AV) remained mainly closed, and the pump flow pattern as well as the arterial pressure waveform showed absent or blunt pulsatility. During this phase, the LVAD ensured good vital organ perfusion, reversal of organ dysfunction, relief of tissue edema, and in theory, by providing postcardiotomy support, established a milieu to allow recovery of the myocardium from the surgical insult. The heart was allowed to rest and decompress until recovery appeared sufficient to allow partial LV filling and ejection, without inducing LV distension, tachycardia, or arrhythmias.

The “late resting phase,” during which mean LVAD flows were about 4 L/min, lasted until the 57th and the 69th day of support in the first and second patient, respectively. Despite decreased LVAD flow, serial echocardiography demonstrated maintenance of decreased LV dimensions, no MR, and restoration of LV–right ventricular (RV) synchrony. During the late resting phase, dampened pulsatility was noted with intermittent partial opening of the AV. This phase can be characterized as a period of resting during which, in theory, LV remodeling may continue while the left ventricle is subjected to minimal volume load, in order to allow reversal of dilatation and also not to induce significant atrophy. The patients were progressively mobilized, and normal end-organ function was established during this phase.

We characterized the second period of support as the “training period” during which the pump speed was decreased to flows of approximately 3.5 L/min. This loaded the LV and allowed ventricular ejection as evidenced by regular, partial AV opening. During this period, the heart was given the physiologic stimulus of regular loading to an extent that would not cause LV distension or MR or arrhythmias. During this period of support, the patients were fully mobilized and became anabolic.

Cardiac function and recovery were assessed by the general functional status of the patients, by repeated echocardiography at nominal pump flows during all phases of support, at a low pump flow (1 L/min for 2–3 min) during the training period and by the “recovery trials.”

The clinical functional status was a constant and reliable index of adequate support and treatment in general. Normal (or improving at the early stage) appearance, good skin color and temperature, normal neurologic and psychologic status, normal breathing and urine output, increasing physical activity, and improving appetite and nutrition were some clinical indices of adequate treatment. Apart from the continuous monitoring of the clinical indices, normalization of the routine biochemistry

| TABLE 2. Echocardiographic values preoperatively, during support, and 12 months post-VAD explantation |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Pre-op  | VAD flow 1 L/min  | VAD flow 3.5 L/min  | Resting period  | Peak stress  | Stress echo  |
| P1      | P2              | P1               | P2              | P1          | P2          |
| LVEDD (mm) | 71   | 78   | 55   | 56   | 55   | 56   | 52   | 56   | 55   | 56   | 55   | 56   | 55   | 56   | 55   | 56   | 55   | 56   | 55   | 56   |
| LVESD (mm) | 71   | 78   | 55   | 56   | 55   | 56   | 52   | 56   | 55   | 56   | 55   | 56   | 55   | 56   | 55   | 56   | 55   | 56   | 55   | 56   |
| FS (FS %) | 5.6  | 6.5  | 6.5  | 6.5  | 6.5  | 6.5  | 4.5  | 4.5  | 4.5  | 4.5  | 4.5  | 4.5  | 4.5  | 4.5  | 4.5  | 4.5  | 4.5  | 4.5  | 4.5  | 4.5  |
| LVESVI (mL/m^2) | 141  | 185  | 83  | 150  | 83  | 102  | 70  | 179  | 83  | 99  | 87  | 112  | 87  | 85  | 114  | 87  | 85  | 114  | 87  | 85  | 114  |
| EF (EF %) | 24.8 | 19.2 | 24.8 | 19.2 | 24.8 | 19.2 | 19.2 | 19.2 | 19.2 | 19.2 | 19.2 | 19.2 | 19.2 | 19.2 | 19.2 | 19.2 | 19.2 | 19.2 | 19.2 | 19.2 |
| MR grade | 0.1  | 0.1  | 0.1  | 0.1  | 0.1  | 0.1  | 0.1  | 0.1  | 0.1  | 0.1  | 0.1  | 0.1  | 0.1  | 0.1  | 0.1  | 0.1  | 0.1  | 0.1  | 0.1  | 0.1  |
| ORS width (ms) | 80  | 80  | 80  | 80  | 80  | 80  | 80  | 80  | 80  | 80  | 80  | 80  | 80  | 80  | 80  | 80  | 80  | 80  | 80  | 80  |
| SDI (%) | 15.8 | 15.8 | 15.8 | 15.8 | 15.8 | 15.8 | 15.8 | 15.8 | 15.8 | 15.8 | 15.8 | 15.8 | 15.8 | 15.8 | 15.8 | 15.8 | 15.8 | 15.8 | 15.8 | 15.8 |
and hematology, the cardiothoracic ratio, the LV shape and end-diastolic diameter, and absence of MR and lung congestion, on the regular running pump without any intravenous inotropic medication were indices of adequate support and prerequisites for consideration of entering the next phase during which pump flow would be reduced and “recovery trials” could be performed.

Decisive for pump explantation were the trials to evaluate cardiac function without mechanical support, defined as “recovery trials.” These trials were performed during the “late resting” and the “training period” with the pump running at a low speed (net forward flow 0–1 L/min) for about 10–15 min. To prevent thrombus formation inside the pump, in addition to the regularly administered anticoagulation (acenocoumarol, aiming for an international normalized ratio of 3–3.5, plus aspirin and clopidogrel or dipyridamole), heparin was administrated intravenously (aiming for an activated clotting time of 220–250 s) before each low flow recovery trial.

Cardiac recovery at low pump flow (0–1 L/min) was evaluated at baseline with no inotropic stimulation, and then reserve capacity was assessed by dobutamine stress echocardiography. A LVEF of 40% without dobutamine, and a LVEF ≥ 45% and LVEDD ≤ 55 mm on dobutamine stress echocardiography were considered as good prognostic indices of recovery (6,7).

When recovery was considered sufficient, as judged by the clinical well-being of the fully mobilized patients, normal end-organ function, improved LV geometry, and achievement of good prognostic indices on the “recovery trials” (Table 2), the patients underwent LVAD explantation (following 87 and 84 days of support). The design and anatomic positioning of the Levacor LVAD allowed removal without sternotomy or cardiopulmonary bypass. Through an upper midline abdominal incision, the pump and the inflow conduit were explanted, while the outflow conduit was ligated and divided below the diaphragm (Fig. 2). A specially designed plug was secured inside the LV apical cuff.

Both patients survived and remain alive with good life quality 16 and 14 months after explantation. They remained in NYHA class II, free of cardiac-related hospitalization with dramatically improved 6-min walk tests (to 550 m in both patients vs. their respective baseline values of 140 and 300 m; Table 1). In addition, LVEF has almost doubled compared to baseline, and the LV end-diastolic volume indexes are dramatically reduced (to 87 and 85 vs. their respective baseline values of 141 and 185 mL/m²; Table 2).

**DISCUSSION**

This experience offers encouragement that the combination of (i) surgical repair plus (ii) VAD support followed by (iii) optimal medical therapy may be superior to any of these three modalities alone in selected patients with advanced, end-stage heart failure. Improved outcomes may include reduced perioperative mortality and morbidity and/or improved ventricular recovery and reverse remodeling.

Patient selection plays a key role in successful outcomes and was individualized (among patients fulfilling the study inclusion and exclusion criteria). Concerning the clinical status, severely ill nontransplant eligible patients, with continuous deterioration despite OMT but not in preterminal condition (i.e., not inotrope dependent, without severely compromised RV and end-organ function), were selected. Concerning the underlying pathology, patients with a significant expected benefit from repair of surgically correctable causes of heart failure and also a high anticipated operative mortality with reparative heart failure surgery alone, and at the same time, a low expected recovery from MCS alone (due to advanced age, long-standing pathology, concomitant left anterior descending coronary artery disease), were considered as good candidates for the application of the combined protocol.

Ventricular recovery is probably a continuous process, and although there is some overlap between the described support periods, we can schematically differentiate between the immediate postoperative course when the pump fully replaced the left ventricle, providing an initial period of unloading with...
ventricular reconfiguration, and the remaining period when the pump provided LV assistance rather than replacement, acting synergistically with the left ventricle, allowing progressive loading and retraining (Fig. 3).

Surgical repair is expected to improve the likelihood of achieving adequate and sustained ventricular recovery of the mechanically supported decompensated ventricles. With the addition of immediate elective implementation of MCS, the surgeon can address as many structural abnormalities as possible during an otherwise high-risk operation, with the knowledge that the patient will be well supported during the postprocedure period (8). Competence of the mitral valve and LV surgical geometrical remodeling probably allow earlier initiation of partial support without pulmonary congestion or increased LV wall stress. Early systemic recovery and rehabilitation of the patient should likewise be facilitated by MCS.

The addition of optimal medical therapy should further facilitate recovery. MCS support may allow earlier and more aggressive medical therapy. The addition of RV–LV resynchronization therapy when indicated may help at this stage, whereas its use prior to these interventions would not likely have been beneficial in class IV critically ill patients.

Early recovery and rehabilitation of the patient should likewise be facilitated by MCS.

The use of MCS as a means of “downstaging” advanced heart failure with associated risks and consequences could allow more high-risk end-stage heart failure patients to benefit from reparative surgical procedures. Such a safety margin may broaden the acceptance and utilization of high-risk surgical reparative procedures. Conversely, it is likely that patients who have undergone reparative surgical procedures may be more likely to exhibit ventricular recovery during MCS and be eligible for weaning of support. Thus, simultaneous MCS and reparative heart failure surgery is a logical recovery strategy. This approach could enlarge significantly the subgroup of patients offered treatments other than transplantation or MCS as permanent, destination therapy. The application of this technique is expensive but the cost of care postdevice explantation is significantly reduced in comparison to the cost of care preimplantation or the cost of care in destination therapy.

This report summarized the outcomes in two patients. Furthermore, as the combined approach (including MCS, heart failure reparative surgery, pharmacologic treatment, and CRT) has been followed without appropriate control groups, it is impossible to determine the impact and the degree of contribution of each therapeutic approach applied. We speculate, though, that the outcome is not just a summation of the possible benefit of each treatment alone, but rather the synergistic effect of these treatments. Further investigation is required to evaluate our hypothesis that the multidisciplinary approach leads to improved results in selected patients with the malignant syndrome of ACHF, but the recovery achieved and sustained for more than 1 year after device explantation in both our patients is encouraging.

CONCLUSION

The surgical approach of bridging to recovery with MCS after surgical repair should be investigated further as an alternative treatment of ACHF.

REFERENCES


and ligaments, possess high tensile strength values—Musculoskeletal tissue engineering.

umbilical vein—Mesenchymal stem cells—Mechanical ligament or tendon regeneration. The sections were inverted such that the luminal side possessed longitudinal stiffness comparable to 10-fold greater than human tendons and ligaments (13–125 MPa) (11,12).

Musculoskeletal soft tissues, which include tendons and ligaments, possess high tensile strength values compared with other tissues, but have poor intrinsic healing capabilities (1). Current remedies to musculoskeletal pathologies and injuries include autografts, allografts, xenografts, and prosthetic implants (2,3). Donor site morbidity and inflicted pain are the two major problems in autografts, whereas patients with allografts and xenografts often develop an immune response to the implanted tissue. Prosthetic devices are a short-term solution as their performance declines with time (2). Lacking a satisfactory clinical treatment for tendon and ligament pathologies, research has been directed toward alternative approaches such as tissue engineering (4). The first component of functional tissue engineering is the scaffold. Previous studies proposed using decellularized allogenic tissue as scaffolds for tissue-engineered constructs (5–7). When decellularized adequately, biological tissues have several advantages over polymeric scaffolds, because they usually retain their biocompatibility, may evade the immune response, and, once seeded with viable cells, have the ability to self-repair and grow (7).

The human umbilical cord is a widely available tissue, easily procured directly after delivery. Even though cord blood cells and cord matrix (Wharton’s jelly) cells were classified as stem cells with regenerative potential (13), the majority of umbilical cords are still discarded. The Wharton’s jelly that surrounds the human umbilical vein (HUV) is rich with growth factors, glycosaminoglycans, and proteoglycans (14,15). With such a composition, the HUV provides a biocompatible environment that potentially supports cell proliferation and tissue regeneration.

Recent studies were targeted toward the use of the HUV as a vascular graft (16,17). Hoenicka et al. (17) suggested cryopreserving the HUV for possible future vascular autograft. Daniel et al. (16) decellularized the HUV suggesting its use as an allograft or as a tissue-engineered blood vessel. In this study, the concept of using the HUV as a biological scaffold is expanded to include other tissues by taking advantage of the HUV’s axial mechanical properties. The HUV possesses longitudinal stiffness comparable with human tendons and ligaments (>10 MPa) (18), and a tensile strength (1.56 ± 1.04 MPa) (18) 10-fold higher than seeded collagen gels (11,12). The main goal of this study was to investigate the HUV seeded with bone marrow mesenchymal stem cells (MSCs)