Clinical Challenge
What can we offer a 70-year-old retired schoolteacher hospitalized with congestion for the third time in 6 months? The LVEF is 21%. Shortness of breath interrupts sleeping and dressing, and peak oxygen consumption of 9 mL/kg per minute confirms NYHA Class IV status. He has noninsulin-dependent diabetes and chronic coronary artery disease, with patent grafts to thin-caliber vessels. His systolic blood pressure is 88 mm Hg and jugular venous pressure of 15 cm. Angiotensin-converting enzyme inhibitor (ACEI) and spironolactone were stopped during his last hospitalization because of progressive increase in serum creatinine to 3.8 mg/dL, currently 2.7, estimated clearance of 25 cc/min, and proteinuria. His regimen includes low doses of hydralazine and isosorbide dinitrate and digoxin, and he cannot tolerate beta-blockers. Although he is followed in an advanced heart failure management program, fluid retention has recurred despite torsemide 200 mg twice daily, intermittent metolazone and compliance with 2-L fluid restriction, 2-g sodium diet, and daily weights. Serum sodium is 135 mEq/L, and B-type natriuretic protein (BNP) level is 1822 pg/mL. He expresses a willingness to try anything to feel better.

Beyond Standard Therapy
This patient has recurrent heart failure despite having received the standard therapies known to improve outcome and clinical status. Renal dysfunction would preclude cardiac transplantation, which, in the setting of limited donor availability, would not often be offered to patients in this age group with major comorbidities. In patients with comprehensive home support, chronic inotropic infusion might be considered for palliation of end-stage symptoms, understanding that death is imminent and may be accelerated by inotropic therapy. For most patients with refractory “stage D” heart failure, the focus should shift toward comfort and planning with patient and family (Figure 1).

Data suggest that highly selected patients with refractory heart failure may be candidates for implantable (“wearable”) left ventricular assist devices (LVAD) as a permanent or “destination” therapy (Table). If this patient were seen at 1 of the approximately 65 US heart failure centers approved for this procedure, then would he be a candidate?

Current Outcomes With Implantable Pulsatile LVADs
A key to selection of patients for implantable ventricular assist devices, or for any available therapy, is the expected benefit that is defined as the improvement in predicted outcomes with the device. Benefit can be dominated by either survival or quality of life, as long as the other factor is sufficient to render the improvement meaningful.

Survival
Survival with LVADs is currently about 50% at 1 year. The REMATCH (Randomized Evaluation of Mechanical Assistance Therapy as an alternative in Congestive Heart failure) trial demonstrated 52% overall survival in 68 nontransplantation candidates randomized to destination therapy. Subsequent 1-year survival in registries also centers around 50%. Final 2-year survival for REMATCH device recipients was 29%. Outcomes are improving with device modifications and with strong emphasis on preventing infection.

Function and Quality
The current pulsatile assist devices can pump 8 to 9 L/min in response to increased venous return, which is ade-
quate to support exercise at an NYHA Class II-III level. Patients have returned to golfing, bowling, bicycling, and various employments. Quality of life is measured between Class II and III, which is similar to that achieved by successful biventricular pacing.

Large pulsatile devices placed in the left upper quadrant, with tunneling of the driveline site to exit on the right side of the abdomen, are the approved wearable support for long-term use. Each pulsation is associated with strong torque and accompanied by a distinctive noise. Some patients experience decreased appetite and early satiety from impingement on their abdominal space. When the patient is away from the bedside console, the batteries are worn in a vest. Some patients voice concern about dependence on community power sources and batteries with limited capacity.

Nonpulsatile devices under investigation are smaller and quieter, but issues such as anticoagulation and physiological flow control remain challenging.

Who Is Sick Enough to Benefit From a VAD?

Before considering support devices, patients with advanced heart failure should traverse through the highest level of heart failure management. Patients who are still refractory are considered first for transplantation, which, with 50% survival at 10 years, is the preferred procedure unless contraindicated. Many patients with expected benefit from transplantation would not have sufficient indications yet for VAD, with 50% survival at 1 year. At this time, the only patients indicated for device placement as primary therapy are those with anticipated 1-year mortality of more than 50%.

No single stable descriptor identifies a subpopulation with a 50% 1-year mortality caused by heart failure. Class IV symptoms at presentation is not sufficient because prognosis is best determined after an intensive hospitalization for redesign of therapy. Most patients who have had Class IV heart failure symptoms can be restored to Class III status with an expected 1-year mortality of 10% to 20%, and should be observed in a heart failure clinic with the same intensity as would occur in the VAD clinic (Figure 2). Patients who cannot be weaned from intravenous inotropic therapy have a mortality approaching 50% at 6 months, and they should be considered for VAD before additional deterioration.

Patients in whom ACEI have to be discontinued permanently because of symptomatic hypotension or progressive renal dysfunction, as is the case for the present patient, have a 1-year mortality exceeding 50%. For other patients, previous risk scores from eras without widespread implantable cardioverter-defibrillators (ICDs) and biventricular pacing implantation have limited relevance. Although beta-blocker therapy has diminished the importance of peak oxygen consumption of less than 14 mL/kg per minute, peak oxygen consumption of less than 10 mL/kg per minute continues to predict poor survival. The ESCAPE (Evaluation Study of Congestive heart failure and Pulmonary Artery catheterization Effectiveness) risk score for early mortality is being constructed based on high blood urea nitrogen, creatinine, BNP levels, and loop diuretic doses, low blood pressure, low serum sodium, and limitation to neurohormonal antagonist therapy.

The patient in our case study has persistent Class IV symptoms, intolerance to ACEI because of circulatory-renal limitations, renal dysfunction, low sodium, and a high BNP level, all of which converge to predict a mortality greater than 50% at 1 year and probably at 6 months. His expected 1-year survival would be doubled by placement of an LVAD, and thus he meets indications for benefit.
Patient Selection for LVAD as Destination Therapy

**Indications:** All of the following conditions should be met.

- NYHA Class IV symptoms for at least 60 of 90 days
- Optimal medical therapy as tolerated with ACEI, beta-blockers, spironolactone, digoxin, and titration of high-dose combination diuretics to relieve congestion; compliance with salt and fluid restriction and weight monitoring; supervised in advanced heart failure management program
- Left ventricular ejection fraction ≤25% and
t- dependence on IV inotropic infusions despite multiple weaning attempts, limited by symptomatic hypotension, progressively declining renal function, or worsening symptoms (usually dyspnea) OR peak oxygen consumption ≤10–12 mL/kg/min during exercise testing with demonstrated achievement of cardiac limitation (usually anaerobic metabolism indicated by respiratory quotient ≥1.1) OR imminent risk profile, undergoing definition

**Contraindications**

- Heart failure with obstructive hypertrophic cardiomyopathy or potentially reversible cause of cardiomyopathy
- Technical obstacles that pose high surgical risk for successful LVAD implantation and maintenance
- Coexisting terminal condition (for example, advanced metastatic cancer or clinically significant comorbidities that may limit functional survival [severe lung, liver, peripheral vascular disease or intrinsic kidney disease])
- Active systemic infection or major chronic risk for infection
- Fixed pulmonary hypertension (generally ≥8 Wood units)
- Severe RV dysfunction out of proportion to LV failure, deemed unlikely to resolve after LVAD implantation
- Presence of mechanical valve that will not be converted to bioprosthetic valve at time of LVAD implantation
- Abdominal aortic aneurysm ≥5 cm
- Body surface area <1.5 m², inadequate transverse abdominal dimension, or other physical restriction to device placement
- Body mass index >40 kg/m²
- Patient unable to understand and provide informed consent
- Inability of patient and companions to maintain VAD in operating condition (change batteries, recognize alarms, use hand pump)

≤ indicates less than or equal to; ≥, more than or equal to; RV, right ventricular; LV, left ventricular; other abbreviations as in text.

Many derived from design of randomized trial of LVAD as destination therapy, and may evolve with subsequent clinical experience. Adapted from *N Engl J Med.* 2001;345:1435.

VAD (Figure 1). A relative exception is renal dysfunction, which, when related to poor cardiac output, often improves after VAD placement but worsens on the calcineurin inhibitors for transplant immunosuppression. Renal dysfunction in the patient in our case study would rule out transplantation but not VAD.

**Age**

The target population for VAD for permanent support is anticipated to be composed largely of people in their 60s and 70s. Additional data will be required on VAD outcomes beyond 1 year because the current limited data suggest that the best outcome with support devices has been for patients under 65 years old. Nevertheless, the patient under discussion is in the age range most often considered for durable VAD support.

**Size**

The present implantable VADs require a body surface area of at least 1.5 m². Approximately half of all women patients are too small for these, and they can be supported only by the external Thoratec pumps that are attached next to (paracorporeal) rather than within the body, and only if they are candidates for transplantation. The investigational nonpulsatile pumps, having the advantage of being a smaller size, should soon provide implantable support for patients with a smaller body surface area.

**Right Ventricular Failure**

Implantable VADs are available only for the left ventricle. Unloading the left-sided pressure, consequently the pulmonary artery pressure and right ventricular afterload, often leads to marked improvement of right ventricular function. This improvement may take days, during which time right ventricular failure can compromise LVAD inflow. Right heart failure can be improved acutely by inotropic therapy and pulmonary vasodilators, such as inhaled nitric oxide, nitroglycerin, or nesiritide. Right ventricular support devices, usually the Thoratec VAD, have been combined with the LVAD for approximately 20% of the LVADs placed. Long-term outcomes have not been favorable with current combinations of right and left ventricular devices; 6-month survival in the Mechanical Cardiac Support Database is only 40% as compared with 74% with LVAD alone.

Most heart failure patients with good right ventricular function can maintain fluid balance and modest daily activity. Decompensation is usually characterized by a profile of biventricular failure, as in the schoolteacher presented here. Information from right heart catheterization and the echocardiogram are used to help assess the degree to which the right ventricular dysfunction would reverse after an LVAD. Patients with right ventricular dysfunction of severity equal to or greater than left ventricular dysfunction usually do not receive implantable LVADs as permanent therapy.

**Surgical Approach**

Pulsatile devices are placed through a median sternotomy during cardiopulmonary bypass. Intracorporeal VADs require a laparotomy as well to place the device either in the pre- or intra-
Postoperative Management

Early postoperative issues include hemodynamic instability, bleeding, and the consequences of preoperative organ dysfunction. Patients who receive an LVAD often require inotropic therapy and pulmonary vasodilation because the native unassisted right ventricle receives increased cardiac output. Control of hypertension, both with drugs and adjustment of device flow characteristics, becomes important during long-term support to improve the longevity of the current-generation pulsatile pumps. The optimal fluid regimen for LVAD function requires frequent titration.

Cerebrovascular events remain one of the most dreaded complications of assist devices, within which thrombi form. The HeartMate (Thoratec), for which documented thromboembolic rates have been the lowest, requires only aspirin therapy. The other pulsatile devices and newer nonpulsatile devices require more intensive anticoagulation. Overall, approximately 10% to 30% of patients receiving mechanical circulatory assistance will experience a thromboembolic or cerebral hemorrhagic event.15,16

Infection is the other common complication that limits the success of these devices. In the REMATCH trial, 17 of 41 deaths in the VAD group were related to sepsis,17 and other series also report an infection rate of around 30% to 40%. Beyond general principles of infection control, infection has been reduced with the use of longer tunnels and modified cannula to promote tissue ingrowth and exit-site sealing. An abdominal binder helps to limit erosive motion of the driveline at the abdominal skin incision site.17

In addition to complications that reflect the host–device interface, device durability has been inconsistent for long-term use. In the REMATCH trial, 35% of devices had some component malfunction at 2 years.3 The most common malfunction in the HeartMate LVAD has been the development of inflow valve regurgitation and/or breakdown of pusher plate mechanics, requiring replacement of the valve or the entire device. Various modifications have been made since the REMATCH trial, with anticipated improved durability.6 Long-term data are most extensive for the HeartMate, from both destination trial and bridging experience. The patient-years of follow-up are accruing rapidly for all devices approved or under investigation.

Progress With VADs for Durable Support

The Thoratec HeartMate VAD is the only device approved by the Food and Drug Administration for chronic support in non-transplantation candidates. The Novacor N1000PC is a similar implantable pulsatile device that is approved only as a bridge to transplantation, but it is providing durable support for increasing lengths of time. The pulsatile Thoratec VAD is paracorporeal rather than intracorporeal. Although external, this device is the only one approved that can provide right (and left, if 2 devices are used) ventricular support outside of the hospital with a portable rolling driver. Although the implantable total artificial heart is not approved for outpatient use, the CardioWest is an implanted biventricular system with a large external console that has been approved for inpatient support before transplantation.18

These devices provide pulsatile flow with normal range blood pressures. Implantable devices that instead provide continuous flow are classified as nonpulsatile, although some degree of pulsatility is conferred when venous return increases. The device flow in these investigational devices can be axial (for example, Jarvik 2000, Thoratec HeartMate II, DeBakey Micromed...
VAD) or centrifugal (for example, Terumo, HeartMate III). These devices are smaller, quieter, fully internal, and more convenient than the pulsatile devices. Thromboembolic events and hemorrhage with anticoagulation regimens have been a major focus of concern for nonpulsatile devices and are of concern for all VADs.

With more than 35 devices under development, this field is likely to progress quickly. Any of these devices, with minor modifications, could be found in the near future to offer prolonged support without major complications, as a “breakthrough.”

These devices continue to be evaluated in the laboratory provided by patients awaiting transplantation; however, many patients are supported with assist devices for durations beyond 1 year, and some never receive hearts. Other patients initially ineligible for transplantation may improve sufficiently to be listed later. The interface between those devices for bridge and those for destination is disappearing in the outpatient VAD clinic. Advances in this field should be tracked not in terms of bridge versus destination therapy but rather on the length and quality of life provided by durable support.

As outcomes improve, devices will be used in patients earlier in the course of their disease, with perhaps greater success for postponing rather than reversing decompensation. At the same time, the advances of medical management provide less dramatic but broader impact on disease progression. As both the disease and therapeutic options evolve, the challenge for clinicians is to translate reported outcomes into selection of the therapy most likely to provide benefit for an individual patient.

References

Ventricular Assist Devices for Durable Support
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Circulation. 2005;112:e111-e115
doi: 10.1161/CIRCULATIONAHA.104.506451
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
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