Myocardial Recovery Using Ventricular Assist Devices
Prevalence, Clinical Characteristics, and Outcomes

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Background—Ventricular assist devices (VADs) are important bridges to cardiac transplantation. VAD support may also function as a bridge to ventricular recovery (BTR); however, clinical predictors of recovery and long-term outcomes remain uncertain. We examined the prevalence, characteristics, and outcomes of BTR subjects in a large single center series.

Methods and Results—We implanted VADs in 154 adults at the University of Pittsburgh from 1996 through 2003. Of these implants, 10 were BTR. This included 2/80 (2.5%) ischemic patients (supported 42 and 61 days, respectively). Both subjects had surgical revascularization, required perioperative left VAD support, and were alive and transplant-free at follow up (232 and 1319 days, respectively). A larger percentage of nonischemic patients underwent BTR (8/74, 11%; age 30+14; 88% female; left ventricular ejection fraction 18+6%; supported 112+76 days). Three had myocarditis, 4 had post-partum cardiomyopathy (PPCM), and 1 had idiopathic cardiomyopathy. Five received biventricular support. After explantation, ventricular function declined in 2 PPCM patients who then required transplantation. Ventricular recovery in the 6 nonischemic patients surviving transplant-free was maintained (left ventricular ejection fraction 54+5%; follow-up 1.5+0.9 years). Overall, 8 of 10 BTR patients are alive and free of transplant (follow-up 1.6+1.1 years).

Conclusions—In a large single center series, BTR was evident in 11% of nonischemic patients, and the need for biventricular support did not preclude recovery. For most BTR subjects presenting with acute inflammatory cardiomyopathy, ventricular recovery was maintained long-term. VAD support as BTR should be considered in the care of acute myocarditis and PPCM. (Circulation. 2005;112[suppl I]:I-32–I-36.)

Key Words: heart-assist device ■ heart failure ■ transplantation ■ cardiomyopathy ■ myocarditis

Ventricular assist devices (VADs) have a long history as essential bridges to transplant (BTT) for patients with end-stage congestive heart failure, and more recently as long-term destination therapy for nontransplant candidates.1,2 For transplant candidates, VAD therapy can improve survival post-transplantation.3,4 Hemodynamic unloading and myocardial rest after VAD placement may lead to recovery of native cardiac function, allowing for removal of the device without cardiac transplantation.5–11 VAD support is also associated with decreases in neurohormonal activation, alterations in myocyte calcium handling, and improvement in the proinflammatory cytokine milieu.12–20 Histological analysis of the explanted heart at the time of transplantation demonstrates decreased fibrosis and myocyte size after VAD placement.16,21,22

Despite these salutatory changes as a result of VAD support, the frequency of bridge to recovery (BTR) in subjects supported long term remains low. Additional data are needed to predict long-term outcomes of BTR patients and the extent to which observed ventricular recovery is sustained. The subjects most likely to benefit from a BTR strategy remain poorly defined. We sought to further define the characteristics of successful BTR patients and their long-term outcomes in a large single center series.

Methods

Study Design and Data Collection
This study was approved by the institutional review board of the University of Pittsburgh Medical Center. All subjects who underwent VAD support as intended BTT from 1996 to 2003 were retrospectively reviewed. Pediatric patients and those receiving only devices designed for transient support were excluded. Subjects received 1 of 3 VAD systems: Thoratec VAD (Thoratec Corp), Novacor LVAS (World Heart Corporation), or Heartmate LVAS XVE (Thoratec Corp).

Statistical Analysis
The clinical characteristics of subjects who underwent BTR were compared with the remaining (BTT) subjects. For BTR subjects,
clinical outcomes and left ventricular ejection fraction (LVEF) by transthoracic echocardiography were reviewed. Data are expressed as mean±SD. Continuous variables were analyzed using Student’s t test. Categorical variables were analyzed using ANOVA. All tests were 2-tailed. A probability value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS, version 12 (SPSS, Inc).

Recovery Assessment
All 10 BTR patients and a subset of 36 BTT patients underwent specific echocardiographic weaning studies using automated border detection from mid-ventricular short-axis images and noninvasive arterial pressure, as previously described.5 These echocardiographic data were used as a principal identifier of LV recovery. Subjects were selected for screening if they were on support >30 days and if the clinician felt the patient had a reasonable chance for LV recovery, but no other criteria were prespecified. Initial echocardiographic weaning studies were performed approximately 1 month after transplant and repeated as necessary every 2 to 3 weeks until the time of explantation. Briefly, on-line beat-to-beat responses were recorded during 2- to 5-minute trials of decreased device flow to half. With transient low assist device flow, device removal patients had increases in echo stroke area and fractional area change that did not occur in VAD-dependent BTT patients. Estimates of preload-adjusted maximal power, a relatively load-independent index, were significantly higher in BTR patients compared with BTT patients. An increase in stroke area, >40% increase in fractional area change, or a preload adjusted maximal power >4.0 mW/cm² with low device flow were associated with successful device removal.5

Additional evaluation of recovery involved exercise physiology with gas exchange analysis and invasive hemodynamics by right heart catheterization, both with the VAD rate lowered. Right heart catheterization was performed using the same VAD flow reduction protocol as for echocardiography. VAD flow was decreased by half; if this was tolerated for 3 minutes, heparin 5000 U was given intravenously, the VAD rate decreased to single strokes every 10 min if this was tolerated for 3 minutes, heparin 5000 U was given intravenously, the VAD rate decreased to single strokes every 10 min if this was tolerated for 3 minutes, heparin 5000 U was given intravenously, the VAD rate decreased to single strokes every 10 min if this was tolerated for 3 minutes, heparin 5000 U was given intravenously, the VAD rate decreased to single strokes every 10 min if this was tolerated for 3 minutes, heparin 5000 U was given intravenously, the VAD rate decreased to single strokes every 10 min if this was tolerated for 3 minutes, heparin 5000 U was given intravenously, the VAD rate decreased to single strokes every 10 min. Briefly, on-line beat-to-beat responses were recorded during 2- to 5-minute trials of decreased device flow to half. With transient low assist device flow, device removal patients had increases in echo stroke area and fractional area change that did not occur in VAD-dependent BTT patients. Estimates of preload-adjusted maximal power, a relatively load-independent index, were significantly higher in BTR patients compared with BTT patients. An increase in stroke area, >40% increase in fractional area change, or a preload adjusted maximal power >4.0 mW/cm² with low device flow were associated with successful device removal.5

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Values are mean±SD.
NYHA indicates New York Heart Association; MR, mitral regurgitation; IABP, intraaortic balloon pump; PCWP, pulmonary capillary wedge pressure.

Baseline Characteristics

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<tr>
<td>Age</td>
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<td>34±15</td>
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<td>Male gender, n (%)</td>
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<td>Duration of heart failure, mo</td>
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<td>NYHA class</td>
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<td>PCWP, mm Hg</td>
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<td>Aspartate aminotransferase, Units/L</td>
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<td>Blood urea nitrogen, mg/dL</td>
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Recovery Assessment
For BTR subjects overall, recovery of function was generally seen by 1 to 2 months of support. Mean peak oxygen consumption with the VAD rate lowered to 40 bpm was 17±3 mL O₂·kg⁻¹·min⁻¹. All underwent hemodynamic assessment before

Results
Prevalence of BTR and Comparison With BTT
Between 1996 and 2003, a total of 161 VAD implants were performed at the University of Pittsburgh for planned long-term support. Of these, 7 were pediatric patients that were excluded from further analysis. Of the remaining 154 adult VAD implants, 10 (6.5%) were BTR, as recovery of ventricular function allowed successful removal of the device without transplantation (Figure 1). BTR patients were younger, more often female, and less likely to have ischemic cardiomyopathy when compared with the BTT patients; other
expansion. The mean pulmonary capillary wedge pressure was 12±5 mm Hg; mean cardiac output was 4.15±1.71 L/min on minimal support (hand pump once every 10 seconds).

**BTR Cohort: Ischemic**
Overall, 10 subjects were identified as BTR. This included 2 of 80 ischemic patients (2.5%). Both ischemic BTR subjects had new-onset HF after surgical revascularization for an acute myocardial infarction and required perioperative Left ventricular assist device (LVAD) support, and were felt to be candidates for BTR because of their recent-onset of HF. Patient 1 was a 48-year-old man with an LVEF of 10% after experiencing an acute myocardial infarction and undergoing bypass surgery. Postoperatively, he was transferred to our institution on pressor support and an intra-aortic balloon pump. He was supported for 42 days with a Thoratec VAD. Patient 2 was a 52-year-old man with papillary muscle rupture and severe mitral regurgitation after acute myocardial infarction with an LVEF of 20%. He underwent mitral valve and revascularization surgery and postoperatively required extracorporeal membrane oxygenation. He was supported for 61 days with a Thoratec extracorporeal LVAD.

**BTR Cohort: Nonischemic**
A larger percentage of nonischemic patients underwent successful BTR (8 of 74, 11%). The 8 nonischemic patients in the BTR group were age 30±14 years and 88% were female, with a mean LVEF 18±6%. Etiology was acute myocarditis in 3 (38% of nonischemic BTR cohort, 33% of myocarditis cases requiring VAD), peripartum cardiomyopathy (PPCM) in 4 (50% of nonischemic BTR cohort, 44% of PPCM cases requiring VAD), and 1 had recent onset idiopathic dilated cardiomyopathy (IDCM, 12% of nonischemic BTR cohort, 3% of IDCM cases requiring VAD). Of note, histology at the time on VAD implantation revealed evidence of myocarditis in only 1 subject and nonspecific inflammation in 1 and was negative in the remaining 6. The subject with recent-onset IDCM was diagnosed with active pulmonary tuberculosis while on VAD support. This was successfully treated, and his ventricle improved and he was subsequently weaned from the device.

Five patients were supported with Thoratec biventricular assist devices and 3 with Thoratec LVAD. Mean duration of support was 112±76 days (median 91 days). The mean duration of heart failure before device implant was significantly shorter in the BTR patients compared with the nonischemic BTT patients (0.9±1.1 months, median 0.4, versus 55.5±40.4 months, median 46.0, P<0.0005; Figure 2). Similar results were seen in comparison with ischemic BTT patients (duration of heart failure 30.2±36.9 months, median 16.5) or all BTT patients (duration of heart failure 44.0±47.2 months, median 31.0). BTR patients also had a smaller left ventricular end-diastolic diameter (56±11 versus 69±12 mm, P=0.04), likely reflective of the shorter duration of heart failure.

**BTR Follow-Up**
Overall, 8 of 10 BTR patients are alive and free of transplant, with a mean length of follow-up 1.6±1.1 years (median 1.5 years, range 3 months to 3.6 years). Both ischemic patients remain alive and transplant-free with follow-up of 8 months and 3.6 years (most recent LVEF 30% and 36%, respectively). Of the 8 nonischemic patients, LV function declined in 2 PPCM patients who required transplantation or repeat VAD support within 1 year. The most recent LVEF was 54±5% in the 6 nonischemic patients surviving transplant-free with follow-up of 1.5±0.9 years (median 1.5 years, range 3 months to 3.0 years).

Complete recovery of LVEF was evident before explantation in the 6 nonischemic patients surviving transplant-free, but not in the 2 patients who subsequently declined (LVEF before explantation 56±3% versus 39±2%, P=0.002). The 6 nonischemic patients surviving transplant-free maintained normal LVEF up to 3 years after explantation. The 2 ischemic patients recovered to LVEFs of 35% and 45%, respectively, before explantation. For these subjects, LVEF subsequently declined in the first month after device removal but then stabilized (Figure 3).

**Discussion**
In this study, 6.5% of all adult patients implanted with a VAD for planned long-term support recovered ventricular function sufficient for device removal. The majority of these patients were nonischemic (80% of the cohort, representing 11% of the nonischemic patients), with the etiology in most cases being acute myocarditis or PPCM. This is consistent with the multicenter experience previously reported, which suggests BTR is predominantly seen in myocarditis and acute inflammatory cardiomyopathies such as PPCM. The high degree of biventricular failure in this recovery cohort, as evidenced by the large percentage requiring biventricular support, is not apparent in previous series. The present study demonstrates that the need for biventricular support should not preclude consideration of recovery.

The current report also suggests that clinical measures of acute illness, in particular duration of symptoms and LV diameter, are potentially important predictors of recovery. This article also demonstrates the limitations of histology for predicting outcomes. The majority of BTR subjects had no evidence of inflammation on myocardial histology at the time of implant, despite a clinical history suggesting acute inflam-
matory cardiomyopathy. Though histological evidence of myocarditis may suggest a potentially reversible process, a negative biopsy seems to have little predictive value.

The current report differs from the Berlin experience, which reported successful BTR in subjects with long-standing chronic dilated cardiomyopathy. No chronic subject (ie, history of heart failure greater than six months) was successfully weaned in our series. This may reflect a screening bias, as acute patients are may have been examined more closely for BTR than chronic subjects. Many chronic subjects, however, underwent echocardiographic weaning studies but failed to meet recovery criteria, and this cohort of “screened” BTT subjects had a duration of HF similar to that of the remaining BTT patients who were not studied (37±3, median 35, versus 45±48 months, median 30, respectively; P<NS). The finding that BTR subjects all had short durations of symptoms is consistent with the finding in nonischemic cardiomyopathy that dynamic recovery is common in recent-onset disease but extremely rare in more chronic disease. In addition to optimal medical therapy for heart failure, future adjunctive treatments, such as stem cells or tissue engineering with gene therapy, will be necessary to assist myocardial recovery in long-standing chronic cardiomyopathy and allow VAD as BTR to become an option for this subset of patients.

For subjects with acute onset of inflammatory myocarditis or PPCM, VAD support allows long-term restoration of cardiac function and avoidance of transplantation. Whether VAD support is therapeutic and facilitates recovery in this subset or functions as a bridge to spontaneous innate recovery remains to be determined. As knowledge of the mechanisms of VAD-induced ventricular recovery progresses, the therapeutic role of VAD support in acute inflammatory cardiomyopathy and the appropriate timing of support needs to be more clearly defined.

The results of this retrospective study must be interpreted with caution and considered primarily hypothesis-generating. The predictive value of LV size and the limited value of histology should be revaluated prospectively in a multicenter format. In particular, the absence of BTR in more chronic subjects may reflect screening bias and needs to be better delineated prospectively in a larger series.

Conclusions

In a large single center series, VAD as BTR was seen in 6.5% overall and in 11% of nonischemic patients and was most successful with acute inflammatory cardiomyopathy or PPCM. When used in acute inflammatory cardiomyopathy or PPCM, VAD support appears to allow long-term restoration of cardiac function and the avoidance of transplantation. VAD support as BTR should be an important component of the care of acute inflammatory myocarditis.

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Disclosure

Dr Kormos is on the medical advisory boards of Thoratec Corporation and World Heart Corporation.
References


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