Published in final edited form as:

J Heart Lung Transplant. 2015 February ; 34(2): 161–166. doi:10.1016/j.healun.2014.09.033.

Mechanical Circulatory Support as a Bridge to Cardiac Retransplantation: A single center experience

Kevin J. Clerkin, MD^a, Sunu S. Thomas, MD^c, Jennifer Haythe, MD^a, P. Christian Schulze, MD, PhD^a, Maryjane Farr, MD^a, Hiroo Takayama, MD, PhD^b, Ulrich P. Jorde, MD^a, Susan W. Restaino, MD^a, Yoshifumi Naka, MD, PhD^b, and Donna M. Mancini, MD^a

^aDivision of Cardiology, Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York

^bDivision of Cardiothoracic Surgery, Department of Surgery, Columbia University College of Physicians and Surgeons, New York, New York

^cDivision of Cardiology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts

Abstract

BACKGROUND—Cardiac retransplantation is increasing in frequency. Recent data have shown that retransplantation outcomes are now comparable with primary transplantation. The use of mechanical circulatory support (MCS) as a bridge to retransplantation has similar post-retransplant outcomes to those without MCS, but the success of bridging patients to retransplant with MCS has not been well studied.

METHODS—From January 2000 to February 2014 at Columbia University Medical Center, 84 patients were listed for retransplantation. Of this cohort, 48 patients underwent retransplantation, 15 were bridged with MCS, 24 died, and 6 clinically improved. A retrospective analysis was performed examining waiting list time, survival to retransplantation, and survival after retransplant. The effect of the United Network of Organ Sharing (UNOS) allocation policy change in 2006 on waiting list time and MCS use was also investigated.

RESULTS—Of 48 patients who underwent retransplantation, 11 were bridged with MCS. Overall 1-year survival to retransplantation was 81.3%. There was no significant difference in waiting list survival ($p = 0.71$) in those with and without MCS. Death from cardiac arrest or multiorgan failure with infection was more frequent in the medically managed group ($p = 0.002$). After the UNOS 2006 allocation policy change, waiting list time (599 ± 936 days in Era 1 vs 526 ± 498 days in Era 2, $p = 0.65$) and waiting list survival ($p = 0.22$) between eras were comparable, but there was a trend toward greater use of MCS ($p = 0.13$). Survival after retransplant was acceptable.

Reprint requests: Donna M. Mancini, MD, Center for Advanced Cardiac Care, Department of Medicine, Division of Cardiology, 622 W 168th St, PH 1273, New York, NY, 10032. Telephone: 212-305-4629. Fax: 212-305-2591. dmm31@columbia.edu.

Disclosure statement

Dr Jorde has received consulting fees from Thoratec and HeartWare, and Dr. Naka has received consulting fees from Thoratec and HeartWare. None of the other authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

CONCLUSION—The use of MCS as a bridge to cardiac retransplantation is a reasonable strategy.

Keywords

mechanical circulatory support; retransplant; waiting list survival; UNOS allocation policy

Originally described in 1977,¹ cardiac retransplantation can be used for acute (primary graft failure and acute rejection) and chronic (cardiac allograft vasculopathy) rejection.² Cardiac retransplantation remains controversial due to the scarcity of organs and the ever-lengthening candidate waiting list. Overall, retransplantation remains rare but is increasing in prevalence: from 1992 to 2000 it represented 1.9% of transplants worldwide, increasing to 2.5% in 2012.² Poor outcomes for retransplantation were initially reported^{3–7}; however, recent reviews have shown that retransplantation that occurs more than 1 year after primary transplant has a 1-year survival of 75% to 94%,^{2,3,8}

The use of mechanical circulatory support (MCS) as a bridge to retransplantation has been described for acute rejection,^{3,4,7,9} with few reports of its use outside of this setting. A recent study analyzing retransplantation in the United Network of Organ Sharing (UNOS) database from 1987 to 2011 demonstrated that patients with chronic rejection who were bridged with MCS had similar outcomes after retransplant as those who underwent a retransplant without MCS.⁷ During that period, the UNOS cardiac allocation policy was amended to promote greater sharing but has had the unintended consequence of increasing waiting list time.¹⁰ In this study, we examined the survival to retransplant in patients bridged with MCS vs those who were not bridged at our institution. We also examined if the allocation policy change affected waiting list time and use of MCS for retransplant candidates before and after 2006.

Methods

This was a retrospective study of patients who were listed for cardiac retransplantation from January 2000 to February 2014 at Columbia University Medical Center. The analysis excluded patients with primary graft failure or intractable acute rejection occurring less than 6 months after transplantation.

Study outcomes

The primary study end point was survival to retransplantation. Patients listed for retransplantation who required MCS were identified. All MCS used to bridge to retransplantation was biventricular. The consensus of our transplant committee was that biventricular support was required to maximize support and limit immunosuppression. All patients who received MCS were critically ill (all on multiple inotropes, 4 were intubated, and 1 was on venoarterial extracorporeal membrane oxygenation) and were Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) Profile 1 at the time of device implantation.

Immunosuppression in patients with MCS was reduced to prednisone at a daily dose that ranged from 10 to 30 mg. Medically managed retransplant candidates remained on their

standard immunosuppressive regimens, which included prednisone, tacrolimus, or cyclosporine, and mycophenolate mofetil or sirolimus.

Devices used included Centrimag BiVAD (Thoratec Corporation; Pleasanton, CA),⁸ Thoratec IVAD (Thoratec Corporation),⁵ Heartware BiVAD (HeartWare International, Framingham, MA),¹ and total artificial heart (TAH; SynCardia Systems, Tucson, AZ).¹ Other data collected and analyzed included waiting list time, indication for retransplantation, time since initial orthotopic heart transplantation (OHT), indication for initial OHT, gender, and age.

Statistical analysis

The Student's *t*-test and chi-square test were used to compare continuous and categorical variables, respectively. Kaplan-Meier survival curves were derived and compared using a log-rank test. A *p*-value < 0.05 was considered statistically significant. Statistical analyses were performed using XLStat (Addinsoft, New York, NY) and GB Stat (Dynamic Microsystems Inc, Silver Springs, MD).

Results

From 2000 to February 2014, 1,030 adults underwent OHT at Columbia University Medical Center. During this period, 84 patients were listed for retransplantation, with 48 patients (4.7% of all OHT) retransplanted. The patients (81% male) were an average age of 49 years. The mean time to relisting was 8.2 ± 5.1 years, and the indication for relisting was cardiac allograft vasculopathy (CAV) in 76.2%, followed by acute rejection in 9.5% and chronic rejection in 9.5%.

Of the 48 patients who underwent retransplantation, 11 (22.9%) were bridged with MCS. The MCS group was younger (35.5 ± 10.6 vs 51.6 ± 12.6 years, $p = 0.0001$) and tended to have a shorter time from initial transplant to relisting (6.0 ± 4.4 years for MCS vs 8.7 ± 5.2 years, $p = 0.07$). Significantly more of these patients had acute rejection (33.3% in the MCS group), whereas CAV predominated (82.6%) in the non-MCS group ($p = 0.001$, Table 1). Device placement and relisting was concurrent in 53% of the MCS patients; in the remaining patients, the median time to device implantation after relisting was 89 days (range, 2–1,778 days). The mean duration of device support to outcome was 95 days (range, 1–318 days).

One-year waiting list survival for the entire cohort was 81.3%. Overall waiting list survival did not statistically differ between those who were and were not bridged with MCS ($p = 0.71$, Figure 1). Intergroup comparison demonstrated that the MCS group had a higher incidence of mortality due to cardiac arrest and multiorgan failure from infection, whereas the MCS group had more refractory cardiogenic shock ($p = 0.002$, Table 2). The 2 groups did not differ significantly in the rate of transplantation (73.3% for MCS vs 53.6%, $p = 0.16$) or death on the waiting list (20% for MCS vs 30.4%, $p = 0.42$; Table 2).

Of the 15 patients who received MCS, 14 had at least moderate right ventricular dysfunction based on trans-thoracic echocardiography at time of device implantation. With immunosuppression reduced to single-agent prednisone, there were no clinically significant

episodes of rejection. However, a review of the explanted hearts showed evidence of rejection in 7: 6 with pathologic antibody-mediated rejection (pAMR 1i) and 3 (2 with pAMR 1i) with areas of cellular rejection ranging from International Society for Heart and Lung Transplantation Grade 1R/1A to 2R/3A. Each patient who received MCS had acute kidney injury at the time of implantation, with an average serum creatinine of 2.7 mg/dl, but with improved hemodynamics, there was a 44% decrease at the time of retransplantation or decannulation ($p = 0.014$). One patient became dialysis dependent, and 1 patient received a dual heart-kidney transplant. When analyzed by device category, the patients who received paracorporeal MCS had a shorter waiting list time after MCS implantation to outcome (35 days vs 146 days, $p = 0.02$), had equivalent survival to retransplantation (75% vs 86%, $p = 0.6$), and no appreciable difference in complications was noted on a medical record review between device type.

When analyzed by era, centering on the July 2006 UNOS allocation policy change, for the era after the change (Era 2), there was more MCS use overall (23.4% vs 10.8%, $p = 0.13$), and acute rejection became a more common indication (Table 3). Between eras, for all candidates, there was no difference in waiting list time (599 ± 936 days in Era 1 vs 525 ± 498 days, $p = 0.65$), nor was there a difference in survival to retransplantation ($p = 0.22$, Figure 2). However, when additional analysis was performed with device implantation and mortality both included as adverse outcomes in an effort to demonstrate the importance of MCS on survival to retransplantation in patients with critical cardiogenic shock, waiting list event-free survival decreased in Era 2, with the p -value decreasing to 0.037 (Figure 3).

Within Era 2, the waiting list time to retransplantation for the MCS group (143 ± 94 days vs 565 ± 427 days, $p = 0.01$) was significantly shorter than for those without MCS support. However, the shorter waiting list time did not translate to a significant difference in waiting list mortality (18.2% for MCS vs 41.7% non-MCS, $p = 0.16$). Survival analysis showed no significant difference between those with MCS support and the medically treated patients ($p = 0.6$, Figure 4).

Survival after retransplant was acceptable for both strategies. At 1 year and 3 years after retransplantation, 100% of MCS patients were alive, and survival for medically treated patients was 81% at 1 year and 68% at 3 years (Figure 5).

Discussion

Retransplantation is increasing in prevalence, with our rate of retransplantation, 4.6%, higher than what is generally reported in the literature.² A recent analysis of the UNOS database⁷ demonstrated that patients bridged to retransplantation with MCS have outcomes after retransplant that are similar to those managed medically. Our study focused on outcomes before retransplant and addressed the safety and utility of MCS bridging to retransplantation. This observational study suggests use of MCS is a valid strategy. Our patients supported with MCS required earlier support after the first transplant, with acute allograft rejection being the most common indication. Despite this more frequent indication, survival before and after retransplantation was acceptable.

Our series from a single high-volume center demonstrated that a strategy of bridging with MCS was non-inferior in waiting list survival. Furthermore, the importance and benefit of MCS bridging was demonstrated when MCS implantation was considered with death as an adverse event, and Era 2 event-free waiting list survival was significantly less than in Era 1. The cause of death between the MCS and medically managed patients differed, with cardiac arrest and infection predominating amongst the medically treated group compared with refractory cardiogenic shock in the MCS group. Interestingly, fatal infection was not more common in the MCS group. The initial hesitation to proceed with mechanical support in retransplant patients was concern for implantation of devices in immunosuppressed patients. However, by reducing immunosuppression to a single agent (steroids), the infectious complications were manageable.

The non-inferiority of MCS bridging to transplantation coupled with the recent findings of Khan et al⁷ would suggest that patients bridged with MCS have equivalent outcomes before and after retransplantation than those who do not require MCS. This has the potential to have a broad clinical effect. As reported, the use of MCS has increased nationwide, and at the same time, waiting list times have increased markedly in certain regions since the 2006 allocation policy change.¹⁰ Patients in these regions waiting for primary OHT have increased MCS use compared with other regions, and so the ability to use MCS to bridge to retransplantation is valuable in these regions.

Our experience has not identified an ideal device for bridging patients to retransplantation. During this 13-year period, our initial options for biventricular support were short-term devices or the Thoratec IVAD. After our initial experience supporting transplant patients with the Centrimag BiVAD, we then considered using a long-term option (i.e., the IVAD). This device was not ideal due to infections, frequent inadequate right ventricular support, and the cumbersome portable driver. When the TAH became available at our institution in 2011, we tried this option for retransplant candidates, and again, our experience with this device was not optimal due to renal failure, infections, and bleeding complications. We then tried the Heartware HVAD as a BiVAD in 2013, while still using the Centrimag BiVAD in other patients. The use of the Heartware HVAD as a BiVAD was technically successful, but has been hampered by lack of insurance reimbursement for this approach. Currently, the Centrimag BiVAD remains the principal device used at our center.

Any time retransplantation is discussed, the associated ethical dilemma needs to be acknowledged. With a limited supply of donor hearts, the question remains: is it fair for a patient to receive a second transplant when others await their first? Now, with the use of MCS as a bridge to retransplantation, other dilemmas arise: There is concern that patients placed on MCS might derive an unfair advantage in terms of waiting list time and/or priority, the fact that MCS is a more expensive approach, and what to do if a patient acquires a comorbidity while on device support that precludes transplantation. In our series, patients with MCS in the current era did have a significantly shorter waiting list time, but this did not result in any difference in waiting list mortality compared with patients treated medically. This shorter waiting list time is likely a manifestation of these patients having critical cardiogenic shock (i.e., INTERMACS Profile 1). Furthermore, the patients bridged with

MCS did not have an untoward advantage with regards to prevalence of retransplantation when compared with the medically treated group.

Our study is not without limitations. First among them is the retrospective nature of this analysis. Other limitations are that this study reports the experience of a single center and the small numbers. Accompanying the small numbers is that the 2 groups are not matched, with those requiring MCS likely having higher clinical acuity than those not requiring MCS.

The body of evidence for cardiac retransplantation remains small but continues to grow. Prior studies have demonstrated comparable post-retransplant outcomes to primary OHT, poor outcomes when used for primary graft failure, improved outcomes when performed at least 1 year after primary OHT, and successful outcomes for retransplantation when bridged with MCS. Our study adds to these data and demonstrates that bridging to retransplantation with MCS is a viable strategy.

References

1. Copeland G, Griep RB, Bieber CP, et al. Successful retransplantation of the human heart. *J Thorac Cardiovasc Surg.* 1977; 73:242–7. [PubMed: 319302]
2. Stehlik J, Edwards LB, Kucheryavaya AY, et al. The registry of the International Society for Heart and Lung Transplantation: 29th official adult heart transplant report—2012. *J Heart Lung Transplant.* 2012; 31:1052–64. [PubMed: 22975095]
3. John R, Chen JM, Weinberg A, et al. Long-term survival after cardiac retransplantation: a twenty-year single-center experience. *J Thorac Cardiovasc Surg.* 1999; 117:543–55. [PubMed: 10047659]
4. Radovancevic B, McGiffin DC, Kobashigawa JA, et al. Retransplantation in 7,290 primary transplant patients: a 10-year multi-institutional study. *J Heart Lung Transplant.* 2003; 22:862–8. [PubMed: 12909465]
5. Goerler H, Simon A, Gohrbandt B, et al. Cardiac retransplantation: is it justified in times of critical donor organ shortage? Long-term single-center experience. *Eur J Cardiothorac Surg.* 2008; 34:1185–90. [PubMed: 18693029]
6. Shuhaiber JH, Kim JB, Hur K, et al. Comparison of survival in primary and repeat heart transplantation from 1987 through 2004 in the United States. *Ann Thorac Surg.* 2007; 83:2135–41. [PubMed: 17532412]
7. Khan MS, Mery CM, Zafar F, et al. Is mechanically bridging patients with a failing cardiac graft to retransplantation an effective therapy? Analysis of the United Network of Organ Sharing database. *J Heart Lung Transplant.* 2012; 31:1192–8. [PubMed: 22906499]
8. Tsao L, Uriel N, Leitz K, Naka Y, Mancini D. Higher rate of comorbidities after cardiac retransplantation contributes to decreased survival. *J Heart Lung Transplant.* 2009; 28:1072–4. [PubMed: 19782289]
9. Noirhomme P, d'Udekem Y, Jacquet L, et al. Is mechanical circulatory support helpful before cardiac retransplantation? *Cardiovasc Surg.* 1997; 5:584–7. [PubMed: 9423943]
10. Schulze PC, Kitada S, Clerkin KJ, Jin Z, Mancini DM. Regional differences in recipient waitlist time and pre- and post-transplant mortality following the 2006 UNOS policy changes in the donor heart allocation algorithm. *JACC Heart Fail.* 2014; 2:166–177. [PubMed: 24720925]

Figure 1. Waiting list survival to retransplant according to device usage compared with medical management.

Figure 2. Waiting list survival to retransplant before (Era 1) and after (Era 2) the United Network of Organ Sharing policy change in 2006.

Figure 3. Death or mechanical circulatory support (MCS) placement as adverse outcomes before (Era 1) and after (Era 2) the policy change in 2006.

Figure 4. Survival to retransplant according to device use after the United Network of Organ Sharing policy change in 2006

Figure 5.
Survival after retransplant according to device use compared with medical management.

Table 1

Baseline Characteristics

Variables	Overall (N = 84)	With MCS (n = 15)	Without MCS (n = 69)	p-value
Age, mean $\pm$ SD years	48.7 $\pm$ 13.7	35.5 $\pm$ 10.6	51.6 $\pm$ 12.6	0.00001
Female, No. (%)	15 (17.9)	3 (20)	12 (17.4)	0.81
Primary Tx to relisting time, years				
Mean $\pm$ SD	8.2 $\pm$ 5.1	6.0 $\pm$ 4.4	8.7 $\pm$ 5.2	0.07
Range	0.5–21.7	0.5–16.7	0.85–21.7	
Re-Tx listing indication, No. (%)				0.001
Cardiac allograft vasculopathy	64 (76.2)	7 (46.7)	57 (82.6)	
Acute rejection	8 (9.5)	5 (33.3)	3 (4.3)	
Chronic rejection	8 (9.5)	1 (6.7)	7 (10.1)	
Restrictive	3 (3.6)	1 (6.7)	2 (2.9)	
Eosinophilic	1 (1.2)	1 (6.7)	0 (0)	

MCS, mechanical circulatory support; SD, standard deviation; Tx, transplantation.

Table 2

Waiting List Survival

Variables	With MCS (<i>n</i> = 15)	Without MCS (<i>n</i> = 69)	<i>p</i> -value
Retransplantation, No. (%)	11 (73.3)	37 (53.6)	0.16
Time to event, days			0.3
Mean ± SD	308.1 ± 528.0	536.2 ± 655.0	
Range	29–1,865	4–2,996	
Death on waiting list, No. (%)	3 (20)	21 (30.4)	0.42
Time to event, days			0.11
Mean ± SD	36.0 ± 37.8	512.8 ± 482.7	
Range	1–76	0–1,418	
Cause of death, No. (%)			0.002
Refractory cardiogenic shock and MOF	2 (67)	2 (9.5)	
MOF with infection	0 (0)	6 (28.6)	
Cardiac arrest	0 (0)	12 (57.1)	
Support withdrawn	1 (33)	...	
Unknown	0 (0)	1 (4.7)	
Clinically improved	1 (6.7)	5 (6.9)	
Still waiting	0 (0)	6 (8.7)	

MCS, mechanical circulatory support; MOF, multiorgan failure; SD, standard deviation.

Table 3

Comparison Between Eras

Variables	<u>Era 1</u>	<u>Era 2</u>	<i>p</i> -value
	2000–June 2006 (<i>n</i> = 37)	July 2006–Feb 2014 (<i>n</i> = 47)	
Age, mean ± SD years	50.8 ± 13.6	47.4 ± 13.8	0.26
Female, No. (%)	5 (13.5)	10 (21.2)	0.36
Primary Tx to relisting, mean ± SD years	7.8 ± 5.2	8.5 ± 5.1	0.52
MCS use, No. (%)	4 (10.8)	11 (23.4)	0.13
Re-Tx listing indication, No. (%)			0.16
Cardiac allograft vasculopathy	33 (89.2)	31 (66.0)	
Acute rejection	1 (2.7)	6 (12.8)	
Chronic rejection	2 (5.4)	7 (14.9)	
Restrictive	1 (2.7)	2 (4.3)	
Eosinophilic	0 (0)	1 (2.0)	
Waiting list time to outcome, mean ± SD days			
Overall	598.8 ± 935.5	525.9 ± 498.1	0.65
Retransplantation	547.4 ± 736.8	387.2 ± 388.4	0.39
Death	260.9 ± 309.8	492.7 ± 505.4	0.27

MCS, mechanical circulatory support; SD, standard deviation; Tx, transplantation.