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ORIGINAL ARTICLE

Cardiac Transplantation After Bridged Therapy with Continuous Flow Left Ventricular Assist Devices

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Introduction Cardiac transplantation is an effective surgical therapy for end-stage heart failure. Patients (pts) may need to be bridged with a continuous flow left ventricular assist device (CF-LVAD) while on the transplant list as logistic factors like organ availability are unknown. Cardiac transplantation post-LVAD can be a surgically challenging procedure and outcome in these pts is perceived to be poorer based on experience with earlier generation pulsatile flow pumps. Data from a single institution comparing these pts with those undergoing direct transplantation in the present era of continuous flow device therapy are limited.

Aim Evaluate results of cardiac transplantation in pts bridged with a CF-LVAD (BTx) and compare outcomes with pts undergoing direct transplantation (Tx) in a single institution.

Results From June 2007 till January 2012, 106 pts underwent cardiac transplantation. Among these, 37 (35%) pts (51 ± 11 years; 85% male) were bridged with a CF-LVAD (BTx), while 70 (65%) comprised the Tx group (53 ± 12 years; 72% males). The median duration of LVAD support was 227 (153,327) days. During the period of LVAD support, 10/37 (27%) pts were upgraded to status 1A and all were successfully transplanted. Median hospital stay in the BTx (14 days) was slightly longer than the Tx group (12 days) but not statistically significant ($p = 0.21$). In-hospital mortality in the BTx (5%) and Tx (1%) were comparable ($p = 0.25$). Estimated late survival in the BTx cohort was 94 ± 7, 90 ± 10 and 83 ± 16% at the end of one, two and three years, respectively which was comparable to 97 ± 4%, 93 ± 6% and 89 ± 9% for the Tx group ($p = 0.50$).

Conclusion Cardiac transplantation after LVAD implant can be performed with excellent results. Patients can be supported on the left ventricular assist device even for periods close to a year with good outcome after cardiac transplantation.

Keywords Cardiomyopathy • Circulatory assist devices • Transplantation (heart) • Heart failure • Surgical therapy

Introduction

The proportion of patients with end-stage congestive heart failure is increasing exponentially. Even after listing the candidate as status IA, organ availability, patient's blood group and many such factors dictate the wait times for an eventual transplant. Bridging patients with a ventricular assist device is now an accepted therapy for patients on the transplant waiting list. The current generation of continuous flow devices (CF-LVAD) needs reduced surgical

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dissection for implantation, reduced post-operative blood loss and less complications in the post-operative support period.

We present our results with cardiac transplantation in the era of CF-LVAD bridge therapy and retrospectively compare outcomes between patients who underwent direct cardiac transplantation (Tx) and those bridged with a CF-LVAD (BTx) at our institution.

Patient and methods

After Institutional Board Review approval, a retrospective data analysis was conducted of 106 consecutive adult patients who underwent cardiac transplantation at our institution from June 2007 till January 2011. The UNOS® (United Network for Organ Sharing) activation date, duration of wait time till transplant, initial UNOS® status and subsequent changes were obtained and analysed for all patients. Data regarding pre-transplant clinical condition, laboratory variables and haemodynamic parameters were collected and analysed for all patients. For the Btx cohort, surgical details of LVAD implant, duration of LVAD support, and the presence of any complications during the support period were collected from our prospectively maintained LVAD registry. Early adverse outcomes including post-operative bleeding needing re-exploration, respiratory failure, renal failure and neurological events were compared between Tx and BTx pts. Follow-up was obtained from regular post-operative clinic visits, and correspondence received from treating physicians at other centres.

The CMS criteria for device therapy were implemented to make the decision to bridge pts with an LVAD. All pts underwent LVAD implant at our institution via a median sternotomy in the routine manner. Rigorous follow-up was conducted by our LVAD coordinators to ensure adherence of appropriate anticoagulation and driveline site care protocols. Re-admissions for LVAD related complications were done at our institution or communicated to us from the admitting centre. Pre-transplant evaluation was conducted at regular intervals for all pts on the wait list.

Orthotropic heart transplantation was performed via median sternotomy under moderate hypothermia for all pts. A bi-caval or a bi-atrial anastomotic technique was performed as per patient factors and surgeon's discretion. Selection of donors was conducted as per institutional protocol. Marginal donors were not considered as candidates for organ donation. Our immunosuppressive therapy regime did not differ depending upon the presence/absence of an LVAD.

Statistical analysis

Statistical analysis has been conducted with JMP9.0® for Windows OS (SAS Inc., Cary, NC, USA). Nominal data have been presented as number (percentages). Continuous data have been appropriately presented as mean ± SD or median (interquartile range). Categorical variables are compared using the Fisher's exact test while continuous data are analysed with the *T*-test or the Wilcoxon test as per normality. The two-tailed p-value <0.05 is considered significant for all statistical analyses and 95% confidence intervals are mentioned where appropriate.

Kaplan–Meier curves have been generated to estimate survival. The log-rank method has been used to compare the Tx and BTx cohorts.

Results

During the study period, 106 pts (mean age 52.8 ± 11.5 years, male 76%) underwent orthotropic cardiac transplantation. The detailed pre-operative variables in both groups are outlined in Table 1. 37/106 (35%) pts were bridged with a left ventricular assist device (Btx) while the remaining 69/106 (65%) underwent transplant directly (Tx). More patients in the Btx category were initially listed as UNOS IA (22% vs 6%; $p = 0.02$). Patients with blood group O experienced the longest median wait-time (303 days) while in the AB group pts received a heart with the shortest wait time (31 days). A larger proportion of pts (83%) who underwent LVAD bridging were from either blood group O or A ($p = 0.08$).

In the entire cohort, 6/106 (14%) pts had a PRA > 10% pre-transplant; in these six pts, two (3%) were from the Tx cohort and the remaining (11%) from the BTx group ($p = 0.18$).

BTx cohort

During the study period, 37 pts (mean age 50.9 ± 11 years; male 86%) who were bridged with a CF-LVAD underwent transplantation. The HeartMate II (Thoratec Corp., Pleasanton, CA) was present in 24 pts, while the rest underwent implantation with the Jarvik device (5), Ventrassist (6) or the DuraHeart LVAD (2). The median wait time from UNOS listing to transplant was 278 (147,537) days. These pts were supported on the LAVD for a median duration of 227 (153,328) days. Among these pts, 22% were listed as UNOS status IA before LVAD implantation. Among these 37 pts, 14 (37%) were upgraded to UNOS status IA due to issues with the left ventricular assist device. In eight pts, the reason was LVAD related intravascular haemolysis; in five it was mechanical problems and power surges, while one had persistent driveline infection. All pts with LVAD complications were upgraded to status IA and successfully underwent cardiac transplantation. Only one pt needed a pump exchange due to severe intravascular haemolysis while waiting for transplantation.

Our 30-day and one-year survival for LVAD implant as BTT during the same study period is 93% and 87 ± 10%, respectively.

Early post-operative period (X) (Table 2)

Operative duration for cardiac transplantation was longer for the Btx cohort (398 ± 103 min) as compared to the Tx group (316 ± 188 min) of pts ($p = 0.005$). PRBC (packed red blood cell) transfusion was more in the BTX cohort (median 7 units)

Table 1 **Pre-operative variables in the two cohorts prior to heart transplantation.**

Variable	Bridged to Tx (*N* = 37)	Direct Tx (*N* = 69)	*p*-Value
Age (years)	51.3 ± 11	53.4 ± 11.8	0.43
Male	72%	68%	0.14
Ischaemic cardiomyopathy	33%	16%	0.98
Duration from UNOS listing to Tx (days)	370 ± 52	314 ± 39	0.39
Duration from LVAD implant to Tx (days)	227 (153,328)	NA	
UNOS status IA at the time of listing	22%	6%	0.02*
NYHA class IV at the time of UNOS listing	48%	30%	0.10
Need for upgrade in UNOS status while on wait list	51%	53%	0.83
Six Minute Walk test (feet)	1110 ± 425	1255 ± 352	0.10
VO_2 (ml/kg/min)	12 ± 5	16 ± 8	0.0028*
Pre-operative inotropes	5%	25%	0.02*
Haemodynamic parameters			
RA mean	11 ± 5	14.4 ± 6	0.01*
PA mean	32 ± 9	31 ± 10	0.69
PCWP	20 ± 7	20 ± 8	0.84
Trans-pulmonary gradient	11 ± 5	12 ± 5	0.51
PVR	3.4 ± 2	3.7 ± 1.7	0.51
PVRI	6 ± 3.7	7 ± 3.1	0.52
Laboratory parameters			
Haemoglobin	12.1 ± 1.9	12.5 ± 1.7	0.29
Creatinine	1.2 ± 0.4	1.2 ± 0.7	0.67
Bilirubin	0.9 ± 0.6	1.1 ± 0.7	0.22
Albumin	4.1 ± 0.4	4 ± 0.5	0.49

*Statistically significant.

Table 2 **Post-operative events in pts stratified by Tx and BTx cohorts..**

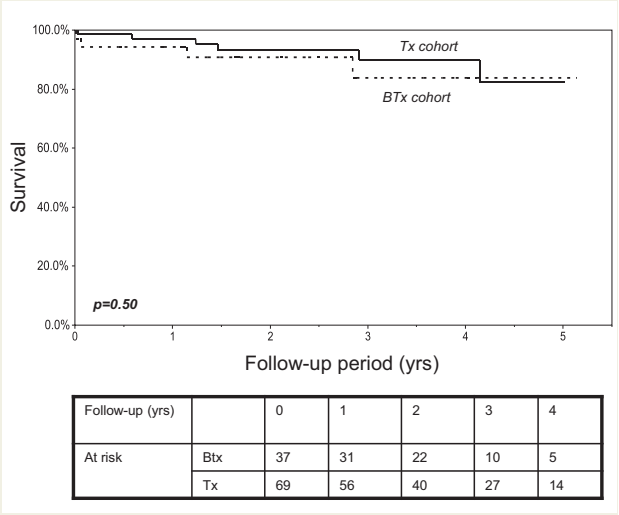
Post-operative adverse event	Bridged to Tx (*N* = 37)	Direct Tx (*N* = 69)	*p*-Value
Transferred to ICU with temporary chest closure	10%	5%	0.44
Re-exploration for bleeding	0%	4%	0.29
Median pRBC transfused during hospital stay (units)	7 (3.10)	2 (0.3)	<0.0001*
Infection during hospital stay	21%	10%	0.14
Need for renal replacement therapy	8%	3%	0.41
Need for a permanent pacemaker	13%	7%	0.31
Median ICU stay (days)	7	5	0.07#
Median hospital stay (days)	14	12	0.21
Surgical/30 day mortality	5%	4%	0.27

*Statistically significant.
#Trend towards statistical significance.

as compared to the patients undergoing direct transplant (median 2 units) ($p < 0.0001$). Surgical or 30 day mortality was 5% and 4% for the Btx and Tx cohorts, respectively ($p = 0.27$). Although the BTx pts were in the intensive care unit for a longer period as compared to the Tx group (7 vs 5 days; $p = 0.07$), overall hospital stay was comparable (14 vs 12 days; $p = 0.21$). Two patients had transient graft dysfunction early after transplantation and needed ECMO support in the initial days. However, both patients survived and were dismissed successfully from the hospital.

Late results

The median follow-up for the entire cohort was 29 (14,41) months. During the study period, all-cause mortality was 9/106 (8.5%). Both Btx (10.8%) and Tx (7%) cohorts had comparable mortality rates during the period of follow-up



Follow-up (yrs)		0	1	2	3	4
At risk	Btx	37	31	22	10	5
	Tx	69	56	40	27	14

Fig. 1 The Kaplan–Meier curves demonstrate comparable long-term survival in both cohorts.

($p = 0.71$). Estimated survival was 94.6 ± 7.4%, 91.6 ± 9.6% (BTx) and 96.9 ± 4.2%, 92.9 ± 6.8% (Tx) at the end of one and two years, respectively ($p = 0.43$) as demonstrated in Fig. 1.

During the period of follow-up, 14 (13%) developed 2R or more rejection on right ventricular biopsy (ISHLT grading taskforce 2010). This was not related to the presence of a prior LVAD ($p = 0.20$). A PRA > 10% pre-transplant did not affect long-term outcome (log-rank test, $p = 0.44$).

Comment

End-stage congestive heart failure is increasing in the United States at a rapid rate. The heart transplant volumes have remained relatively constant over the past decade [1]. Bridging sick patients with a left ventricular assist device has helped to reduce the mortality on the transplant waiting list and more than half of the patients undergoing LVAD implant are being considered for eventual transplantation [2]. Earlier reports, including a large systematic meta-analysis have reported conflicting outcomes for transplantation after bridging with an LVAD [3,4]. All these studies were conducted with pulsatile devices and available data regarding post-transplant outcome after bridging with a continuous flow device is limited. The present CF-LVD devices are smaller, require less mediastinal dissection and have smaller drivelines. Hence we present our experience with heart transplantation in the contemporary era of CF-LVAD therapy and compare outcomes between patients undergoing direct transplant vs those bridged with CF-LVAD therapy. One-third of our patients during this study period were initially supported with a continuous flow device. The 2012 ISHLT annual report quotes this figure as being 19% in the last decade [1]. This difference could be simply due to the multi-centric nature of their report with variable indications for bridging in each participating center. Our cohort is quite similar with regard to that reported by John et al. as pre-operative profile [5].

We successfully supported pts on an LVAD for a median period of 227 days prior to transplant. Our wait time was comparable to that reported by John et al. in their multi-centre study [5]. Pal et al. had a wait time of only 59 ± 32 days prior to transplantation. This could be as their study included only UNOS status I pts who were likely to get priority for organ allocation [6]. The pts undergoing LVAD implant were naturally much sicker as 22% were listed as status IA. We were also able to demonstrate a modest improvement in haemodynamic parameters in the Btx cohort prior to transplant (Table 3). This was also demonstrated by Pal et al. who reported a fall in the right atrial and pulmonary capillary wedge pressure with a concomitant increase in the cardiac index [6]. An earlier article by Banks et al. using the pulsatile device has also demonstrated an improvement in laboratory and haemodynamic parameters in the LVAD cohort as opposed to the inotropes cohort of patients [7]. However, a major limitation with earlier devices was limited durability

Table 3 Haemodynamic and laboratory values prior to LVAD implant and subsequent cardiac transplantation in the bridged cohort of patients.

Variable	Pre-transplant value	Pre-LVAD value	Mean difference	*p*-Value
Haemodynamic data				
Mean RA pressure (mmHg)	11 ± 5	15 ± 6	2.5 (1.5, 5.7)	0.12
Mean PA pressure (mmHg)	31 ± 10	36 ± 11	3.6 (−0.9, 8.3)	0.11
Trans-pulmonary gradient (mmHg)	12 ± 5	20 ± 11	10 (5, 16)	0.0009*
Mean PCWP (mmHg)	20 ± 8	24 ± 6	3 (−1, 7.1)	0.13
Laboratory data				
Haemoglobin (gm/dl)	12.1 ± 2	12 ± 2	0.09 (−0.5, 0.7)	0.77
Bilirubin (mg/dl)	0.9 ± 0.6	1.3 ± 0.9	0.3 (0.05, 0.7)	0.02*
S. creatinine (mg/dl)	1.2 ± 0.4	1.4 ± 0.8	0.2 (0.01, 0.4)	0.03*
S. albumin (gm/dl)	4.1 ± 0.4	3.8 ± 0.6	0.2 (−0.5, 0.01)	0.05*

*Statistically significant.

with the need for subsequent exchange during the support period [8]. We needed pump exchange in only one patient during the support period. More importantly their study demonstrated that 28% pts from the bridge group died prior to receiving transplant [8], while all our pts were successfully transplanted.

Another important aspect to consider is the patients who either die before transplant or become too sick to undergo surgery while waiting for an appropriate donor. A recent study has demonstrated that this has reduced by 17%, corresponding to an increase in use of LVAD's and cardiovertor-defibrillators [9].

The Btx cohort had a longer operative duration which is understandable as LVAD explant was needed prior to transplantation with all of them being a redo-surgery. In spite of this, post-operative adverse events in both groups were comparable. Thus in spite of these patients being surgically complex, survival has improved due to advances in critical care. Interestingly Pal et al. encountered a trend towards poorer post-operative renal function in their Inotrope cohort ($p = 0.09$) [6]. We wonder if this could be a result of poorer renal reserve at the time of transplant in the cohort treated with inotropes. In our experience, the need for renal replacement therapy did not differ among cohorts, but we have pts in UNOS categories IB and II at the time of transplant.

The median follow-up period in our study is slightly more than two years. We experienced comparable survival in both cohorts. A large study from the UNOS database has reported a slight increase in mortality during the first six months with intra-corporeal LVAD pts [3]. They have surmised that infection is a causative factor for the observed result. While we have encountered infection in 14% during the post-operative period, none has led to mortality. They have further quoted a 10% excess risk of mortality at six to eight years after cardiac transplantation. An important driving factor in their study is the fact that all intra-corporeal devices used were the first generation pulsatile pumps. Although they conclude that stable UNOS IA pts should not be bridged with an LVAD, we have demonstrated that there is a distinct improvement in haemodynamic parameters after LVAD support. This will clearly lead to superior transplant outcomes.

Some authors have discussed the importance of allosensitisation during LVAD implant as a risk factor for allosensitisation and rejection post-transplantation [10,11]. We have not found a higher rate of significant rejection in patients bridged with a prior LVAD, and as discussed earlier long-term survival is similar. Given our small BTx cohort, we appreciate that our study is underpowered to determine a significant increase in the PRA panel due to LVAD implant. Nevertheless, we did not find that a high PRA contributed to a difference in long-term outcome.

Conclusion

Cardiac transplantation in patients bridged with a left ventricular assist device can be performed with excellent results. Patients can be supported on the left ventricular assist device even for periods close to a year with good outcome after cardiac transplantation.

Disclosure

None.

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