Original article

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Results of new-generation intrapericardial continuous flow left ventricular assist devices as a bridge-to-transplant

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Aims **We analysed the outcomes with the use of a new-generation continuous-flow left ventricular assist device (CF-LVAD) as a bridge-to-transplant (BTT).**

Materials and methods **We included all patients implanted with an intrapericardial CF-LVAD as BTT, between January 2012 and December 2016. Primary outcomes were overall survival, survival on waiting list and postheart transplant (HTx) survival. The outcomes after HTx were compared with those of a contemporary cohort of patients transplanted without previous CF-LVAD (No-LVAD group, $n = 73$).**

Results **We included 53 patients with a median age of 52 years (interquartile range: 43–59 years). Seventy-two percent were in INTERMACS profile 1–2 before implant; all entered the HTx waiting list after receiving the CF-LVAD. HTx was performed in 42 (79%) cases (LVAD group). Overall estimated survival (considering both pre-HTx and post-HTx) was 89% [95% confidence interval (CI) 81–98%] at 1 year and 80% (CI 70–92%) at 2 years. The estimated survival on waiting list was 91% (CI 80–100%) at 6 months, whereas the 1-year estimated post-HTx survival was 88% (CI 79–98%). The Kaplan–Meier curves of survival after HTx of LVAD versus No-LVAD group were comparable (log-rank $P = 0.54$), as well as the rates of post-HTx adverse events. A multivariable model of survival after HTx, accounting for the most relevant patient characteristics, identified LVAD use as a significant protective factor [LVAD versus No-LVAD hazard ratio 0.22 (CI 0.06–0.91)].**

Conclusion **The use of new-generation intrapericardial CF-LVADs as a BTT resulted, in our series, in satisfactory pre-HTx and post-HTx outcomes.**

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Keywords: bridge-to-transplant, continuous flow, heart transplant, intrapericardial, left ventricular assist device

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Introduction

Heart failure is a major healthcare issue; its prevalence varies among 1–2% of the adult population in developed countries, and is expected to further increase in the near future.[1–3] Heart transplantation (HTx) is the gold standard therapy for advanced heart failure; however, its application is restricted by the limited number of suitable donor organs available, and the mortality on waiting lists remains high.[4,5] Implantable continuous-flow left ventricular assist devices (CF-LVADs) are, nowadays, established as an alternative treatment for advanced heart failure and their use as a bridge-to-transplant (BTT) is widely increasing.[6–9] However, the impact of currently available CF-LVADs on the survival of patients waiting for HTx and on post-HTx outcomes is still under investigation.[10]

In this study, we sought to assess the outcomes of new-generation intrapericardial CF-LVADs implanted as a BTT, to evaluate whether the strategy of supporting patients with end-stage heart failure is valuable and effective at both pre-HTx and post-HTx times.

Materials and methods

We retrospectively reviewed our institutional experience and included all 53 consecutive patients diagnosed with end-stage heart failure, who underwent the implantation of an intrapericardial CF-LVAD with a BTT device strategy, between January 2012 and December 2016. We referred to the device strategy intended before the implant. We excluded the patients implanted with a bridge to candidacy indication, because of the presence of relative contraindications to HTx.

Primary outcomes were: overall survival (considering both pre-HTx and post-HTx periods), survival on waiting lists and post-HTx survival.

During the same study period, 80 patients underwent HTx without previous LVAD support. Among these, we excluded seven patients ineligible to LVAD because of technical/anatomical contraindications: congenital heart diseases (CHDs) with prohibitive body dimensions ($n = 3$) or prohibitive cardiac anatomy ($n = 4$). This cohort of 73 No-LVAD patients was used as the control group to evaluate the post-HTx outcomes.

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The study was approved by the Institutional Review Board; all patients provided written informed consent to data use for research purposes.

Left ventricular assist device and heart transplantation management

LVAD and HTx eligibility were concordant with the latest International Society for Heart Lung Transplantation (ISHLT) recommendations.[11,12]

Preoperative evaluation of right ventricular (RV) function was based on echocardiographic parameters: tricuspid annular plane systolic excursion (TAPSE), RV dimensions, qualitative assessment of RV systolic function, presence and degree of tricuspid regurgitation, pulmonary artery systolic pressure. These data were integrated with right-heart catheterization measures (pulmonary vascular resistance, pulmonary wedge pressure), with central venous pressure (CVP) and with clinical signs/symptoms of right-heart failure, if any.

After device implant, usual management included early extubation and, compatibly with clinical conditions, mobilization. Anticoagulation therapy was generally implemented 6–12 h after implant (in absence of significant bleeding) with unfractionated heparin, which was, then, shifted to low molecular weight heparin or fondaparinux, first, and warfarin later. The anticoagulation was monitored through blood parameters and thromboelastometric analysis. Antiplatelet therapy (with acetylsalicylic acid and/or clopidogrel) was administered as needed according to device used, platelet count and aggregometry test.

Generally, post-LVAD right-heart failure (RHF) was suspected in the presence of low-pump output with signs of low cardiac output (low mean arterial pressure, decreased urine output, increasing lactate levels) and of congestive heart failure (increased CVP, worsening hepatic function, peripheral oedema, ascites). Diagnosis was made by transthoracic and/or trans-oesophageal echocardiography. After exclusion of cardiac tamponade, echocardiographic signs of RHF included: dilated right ventricle, qualitatively reduced RV systolic function, shifting of the interventricular septum toward the left ventricle, reduced or virtual left ventricle cavity, new or worsened tricuspid regurgitation, dilated not-collapsing inferior vena cava. Cases of post-LVAD acute RHF were first managed by multiple high-dosage inotropic support. When the low output state persisted, a temporary para-corporeal right ventricular assist device (RVAD) was implanted by connecting the inflow to the femoral vein and the outflow to the pulmonary artery. Chronic RHF was managed by inotropic support, Levosimendan infusion and diuretics.

After discharge, all patients followed a period of cardiac rehabilitation and were then periodically evaluated at our dedicated outpatient clinic. Our general policy, after device implant, is to wait for a complete physical recovery before listing the patient for HTx. Thus, patients usually enter the waiting list 3–5 months after implant. Listed patients undergo a right-heart catheterization every 6 months and a body CT-scan is performed in all before HTx.

All heart transplants were orthotopic, with bicaval anastomosis. Induction immunosuppressive therapy was carried out with antithymocyte globulins and methylprednisolone. Immunosuppression was, then, maintained with cyclosporine or tacrolimus, associated with mycophenolic acid and prednisone (usually discontinued after the first year). Patients intolerant to mycophenolic acid were treated with either azathioprine or everolimus. Monitoring endomyocardial biopsies were performed once a week, starting 15 days after HTx, in the first month, then every 2 weeks untill the fourth month and monthly untill the end of the first year; afterward, we repeated them yearly or in case of suspected rejection. To screen for cardiac allograft vasculopathy (CAV), we performed a coronary angiography with intravascular ultrasound (IVUS) biannually starting at 1 year after HTx.

Definitions

Definitions of adverse events on the device were concordant with those of the INTERMACS registry.[7] Right-heart failure was identified as the need for RVAD or prolonged (>14 days) inotropic support after device implant or subsequent readmission because of RHF requiring inotropic support. 'Previous cerebral event' included ischemic and haemorrhagic stroke. Acute kidney failure was considered as the need for continuous renal replacement therapy (CRRT). 'Effusion' was pleural or pericardial effusion requiring drainage; the same applied to 'pneumothorax'. 'Bowel ischemia' was documented as small or large bowel ischemic damage. 'Hepatic or pancreatic complication' included ischemic damage, documented hepatic or pancreatic failure, pancreatitis.

The HTx waiting list, in our reference (inter-regional) organ procurement organization, is structured as follows:

(1) Status 1:
   (a) mechanical circulatory support (MCS) because of acute hemodynamic deterioration: RVAD or biventricular assist device (BiVAD); LVAD with device-related complications; total artificial heart (TAH); intra-aortic balloon pump (IABP); extracorporeal membrane oxygenation (ECMO);
   (b) mechanical ventilation;
(2) Status 2A: uncomplicated LVAD; continuous inotrope infusion; patients with implantable cardioverter defibrillator (ICD) and malignant relapsing ventricular arrhythmias;
(3) Status 2B: outpatients, not included in the categories listed above;
(4) Status 3: temporarily inactive.

Table 1 Baseline (predevice implant) patient characteristics and clinical data

	Overall patients ($n=53$)		Overall patients ($n=53$)
Age (years)	52 (43–59)	Peak-VO_2 (ml/kg/min)	11.5 (9.9–12.6)
Female	11% (6)	CI (l/min/m^2)	1.6 (1.5–1.9)
BSA (m^2)	1.8 (1.7–2)	PAP (mmHg)	43 (37–53)
Cardiac diagnosis		Bilirubin (μmol/l)	18 (11.5–29)
DCM	45% (24)	GFR (ml/min/m^2)	77 (58–90)
ICM	45% (24)	TAPSE (mm)	14 (12–16)
Other	9% (5)	RVFS (%)	30 (21–38)
Dyslipidaemia	36% (19)	TR (>mild)	49% (25)
Hypertension	32% (17)	MR (>mild)	53% (27)
Malignancy	6% (3)	ICU stay	68% (36)
Diabetes	19% (10)	Inotropic infusion	74% (39)
PAD	4% (2)	Mechanical ventilation	0% (0)
COPD	11% (6)	CRRT	2% (1)
ICD/CRTD	74% (39)	IABP	4% (2)
Previous cerebral event	23% (12)	ECMO	21% (11)
INTERMACS profile		Para-corporeal LVAD	19% (10)
1	42% (22)	Waiting list status (at entry)	
2	30% (16)	2B	0% (0)
3	8% (4)	2A	94% (50)
4	21% (11)	1	2% (1)
Waiting list time (months)	5 (2–9)	HU	4% (2)

Data expressed as % (*N*) or median (IQR). BSA, body surface area; CI, cardiac index; COPD, chronic obstructive pulmonary disease; CRRT, continuous renal replacement therapy; DCM, idiopathic dilated cardiomyopathy; ECMO, extracorporeal membrane oxygenation; GFR, glomerular filtration rate; IABP, intraaortic balloon pump; ICD/CRTD, implantable cardiac defibrillator/cardiac resynchronization therapy defibrillator; ICM, ischemic cardiomyopathy cardiac diagnosis 'other' – hypertrophic cardiomyopathy, postmyocarditis cardiomyopathy, chemotherapy-induced cardiomyopathy; LVAD, left ventricular assist device; MR, mitral regurgitation; PAD, peripheral artery disease; PAP, pulmonary artery pressure; RVFS, right ventricle fractional shortening; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

Patients in Status 1 may enter the national high-urgency program, where they are prioritized at a national level.[13]

Acute cellular rejection (ACR) and antibody-mediated rejection (AMR) were classified according to the ISHLT criteria.[14,15] A modified cellular-mediated rejection score (CRS) was calculated as follows: number of rejections, labelled as ACR 0–1 = 0, ACR 2 = 2, ACR 3 = 3, divided by the total number of biopsies performed during the study period. Cardiac allograft vasculopathy was defined according to the ISHLT grading.[16]

Statistical analysis

Continuous variables are expressed as median and interquartile range (IQR). Categorical variables are presented as count and percentage. Overall survival was calculated from the device implant to the latest follow-up. Survival on waiting list was calculated starting from the date of entry in the waiting list until the date of HTx. Post-HTx survival was calculated from the date of HTx to the latest follow-up. Survival estimates were provided with the Kaplan–Meier method. The multivariable survival analysis (of post-HTx survival) was performed with the Cox hazard model.[17]

Results

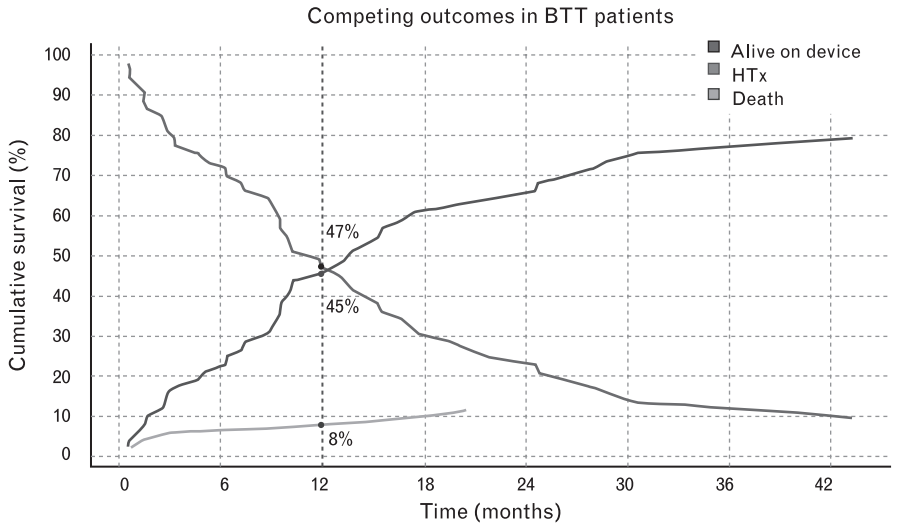
We included 53 patients with a median age of 52 years (IQR: 43–59 years). Table 1 summarizes overall baseline (predevice implant) patient characteristics and clinical data. Before the LVAD implant, 72% of patients were in INTERMACS profile 1 and 2 and 40% of cases were supported with a temporary mechanical device [ECMO 21% and para-corporeal LVAD 19%; median time of temporary support was 3 days (IQR 2–4 days)]. Thirty-one (58%) cases were implanted with HVAD (HeartWare International Inc., Framingham, Massachusetts, USA): 21 (40%) with Jarvik 2000 FlowMaker (Jarvik Heart Inc., New York, New York, USA) and 1 (2%) with HeartMate 3 (Abbott Laboratories Inc., Chicago, Illinois, USA). The LVAD was implanted through a minimally invasive approach in 43 (81%) patients: 25 (47%) received double mini-thoracotomy and 18 (34%) had mini-sternotomy and mini-thoracotomy. Remaining patients were managed with a full sternotomy in seven cases (13%) and a left thoracotomy in three (6%). Off-pump implantation was performed in 11 (21%) patients. All patients entered the HTx waiting list after implant. Totally, 54 device-related adverse events occurred in 28 (53%) patients, requiring prioritization in 12 (23%) cases and leading to death in 6 (11%) patients (Table 2). Thirty-day post implant mortality was 4% ($n=2$). Right-heart failure was the most common adverse event (36% of patients) and required RVAD implant in nine (17%) cases. Major bleeding

Table 2 Postdevice implant adverse events

	Overall patients ($n=53$)		
	Total number	Requiring prioritization	Leading to death
Right-heart failure	36% (19)	9% (5)	0% (0)
Major bleeding	23% (12)	0% (0)	0% (0)
Drive-line infection	21% (11)	4% (2)	0% (0)
Device thrombosis	11% (6)	8% (4)	2% (1)
Sepsis	4% (2)	0% (0)	4% (2)
Major arrhythmias	2% (1)	2% (1)	0% (0)
Haemorrhagic stroke	4% (2)	0% (0)	4% (2)
Ischemic stroke	2% (1)	0% (0)	2% (1)

Data expressed as % (*N*).

Fig. 1



Competing risk analysis.

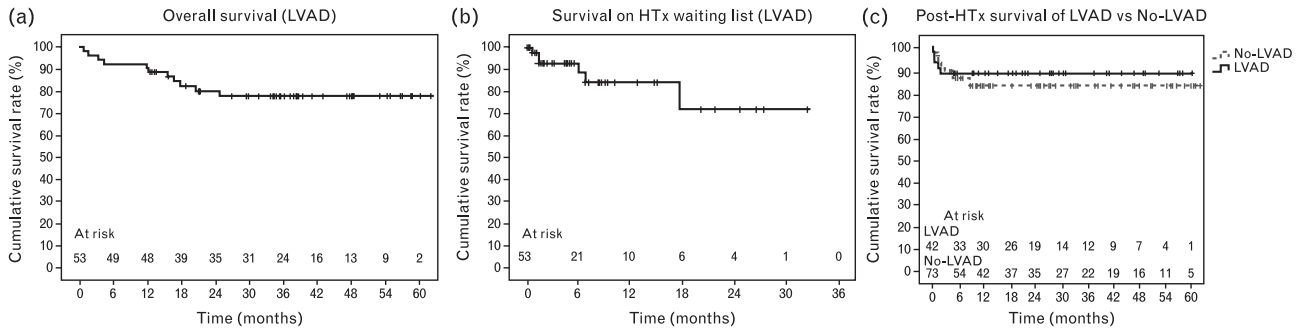
occurred in 12 (23%) patients: 9 perioperative mediastinal bleeding managed by surgical revision; 2 femoral bleeding with pseudoaneurysm formation at the cannulation site, one managed surgically, the other by endovascular repair; 2 enteric bleeding, both managed by endovascular intervention and temporary reduction of the anticoagulation level. In no cases, major bleeding caused prioritization or death.

Figure 1 shows the competing risk analysis: at 12 months almost half of our population (45%) was transplanted, whereas mortality was 8%. Overall estimated survival (considering both pre and post-HTx periods) in LVAD patients was 89% [95% confidence interval (CI) 81–98%] at 1 year and 80% (CI 70–92%) at 2 years (Fig. 2). Estimated survival on waiting list, was 91% (CI 80–100%) at 6 months and 82% (CI 67–97%) at 12 months (Fig. 2).

Postheart transplantation outcomes

HTx was performed in 42 (79%) cases. Median time of support for transplanted patients was 10 months (IQR 5-17). The post-HTx results of these patients (LVAD group) were compared with a control group of 73 No-LVAD cases (No-LVAD group). Pre-HTx patient characteristics, clinical data and donor data are presented in Table 3. Female sex was more frequent in the No-LVAD group. Cardiac risk factors were similarly distributed amongst the two groups. No-LVAD patients showed a higher bilirubin level, with a lower glomerular filtration rate, and a higher proportion of patients hospitalized in ICU, on inotropic support and on temporary MCS. Donor characteristics were similar in the two groups.

Fig. 2



Kaplan–Meier survival curves. (a) Overall survival in LVAD patients. (b) Survival on waiting list in LVAD patients. (c) Survival after heart transplant of LVAD versus No-LVAD patients (log-rank $P = 0.54$). LVAD, left ventricular assist device.

Table 3 Preheart transplant baseline patient characteristics, clinical data and donor data

	All patients ($n=115$)	No-LVAD ($n=73$)	LVAD ($n=42$)	*P* value
Age at HTx (years)	55 (44–62)	58 (44–63)	52 (43–59)	0.05
Female	23% (27)	30% (22)	12% (5)	0.03
BSA (m^2)	1.8 (1.7–1.9)	1.8 (1.7–1.9)	1.8 (1.7–2)	0.33
Cardiac diagnosis				0.05
DCM	38% (44)	34% (25)	45% (19)	
ICM	40% (46)	37% (27)	45% (19)	
Other	22% (25)	29% (21)	10% (4)	
Dyslipidemia	35% (40)	34% (25)	36% (15)	0.87
Hypertension	35% (40)	34% (25)	36% (15)	0.87
Malignancy	3% (4)	1% (1)	7% (3)	0.10
Diabetes	13% (15)	12% (9)	14% (6)	0.76
PAD	5% (6)	5% (4)	5% (2)	0.87
COPD	8% (9)	7% (5)	10% (4)	0.61
ICD/CRTD	74% (85)	75% (55)	71% (30)	0.65
Previous cerebral event	22% (25)	21% (15)	24% (10)	0.68
Waiting list status (before HT)				0.02
2B	32% (37)	51% (37)	0% (0)	
2A	36% (41)	14% (10)	74% (31)	
1	4% (5)	3% (2)	7% (3)	
HU	28% (32)	33% (24)	19% (8)	
Peak-VO_2 (ml/kg/min)	11.3 (9.5–13.6)	11 (10–13.2)	11.8 (8.5–13.7)	0.95
PVR (WU)	2 (1.3–2.6)	2 (1.3–2.6)	2.5 (2.3–2.6)	0.33
CI (l/min/m^2)	2.1 (1.8–2.3)	2 (1.8–2.3)	2.2 (2.1–2.5)	0.19
PAP (mmHg)	38 (27–45)	40 (28–47)	30 (24–40)	0.05
Bilirubin (μmol/l)	14.6 (7.8–21.8)	16 (11–25)	11 (7.2–18.9)	0.02
GFR (ml/min/m^2)	67 (49–90)	55 (42–78)	80 (64–104)	<0.01
TAPSE (mm)	13 (10–16)	14 (11–17)	12 (10–14)	0.10
RVFS (%)	27 (21–34)	27 (20–32)	29 (24–37)	0.32
TR (>mild)	43% (43)	49% (33)	29% (10)	0.05
MR (>mild)	54% (55)	67% (45)	29% (10)	<0.01
ICU stay	37% (43)	47% (34)	21% (9)	<0.01
Inotropic infusion	34% (39)	45% (33)	14% (6)	<0.01
Mechanical ventilation	3% (3)	3% (2)	2% (1)	0.91
CRRT	3% (4)	5% (4)	0% (0)	0.12
ECMO	12% (14)	19% (14)	0% (0)	<0.01
Paracorporeal LVAD/RVAD	8% (9)	11% (8)	2% (1)	0.15
Donor age	46 (27–58)	47 (30–59)	42 (21–55)	0.12
D/R age	−5 (−19/3)	−4 (−19/4)	−5 (−17/3)	0.94
Donor female	44% (51)	52% (38)	31% (13)	0.03
D/R sex mismatch	31% (36)	33% (24)	29% (12)	0.63
Donor BSA	1.9 (1.7–2)	1.9 (1.7–2)	1.9 (1.7–2)	0.87
D/R BSA	0 (−0.1/0.2)	0 (−0.1/0.2)	0 (−0.1/0.1)	0.27
Donor inotropic infusion	67% (77)	63% (46)	74% (31)	0.24
Donor hypertension	16% (18)	15% (11)	17% (7)	0.82
Donor smoking habit	22% (25)	25% (18)	17% (7)	0.32
Donor dyslipidemia	4% (5)	4% (3)	5% (2)	0.87
Donor diabetes	3% (3)	1% (1)	5% (2)	0.27
Donor cold ischemia time	218 (160–241)	210 (150–240)	221 (180–258)	0.20

% (*N*) or median (IQR); CI, cardiac index; CRRT, continuous renal replacement therapy; D/R, donor/recipient; DCM, idiopathic dilated cardiomyopathy; ICD/CRTD, implantable cardiac defibrillator/cardiac resynchronization therapy defibrillator; ICM, ischemic cardiomyopathy, cardiac diagnosis other – congenital heart disease, arrhythmogenic right ventricular dysplasia, hypertrophic cardiomyopathy, postmyocarditis cardiomyopathy, chemotherapy-induced cardiomyopathy, valvular heart disease; LVAD, left ventricular assist device; MR, mitral regurgitation; PAD, peripheral artery disease; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; RVFS, right ventricle fractional shortening; TR, tricuspid regurgitation.

Early and late post-HTx adverse events are summarized in Table 4. Median cardiopulmonary bypass (CPB) and procedural times were higher in LVAD patients. Rates of postoperative complications were comparable, except for effusion and tracheostomy, which both occurred more frequently in No-LVAD patients. Rates of ACR, AMR and CAV were similar, as well as median CRS.

With a median time of follow-up of 21 months (IQR 6-41 months), post-HTx mortality was 16% in No-LVAD group versus 12% in LVAD ($P=0.51$). One-year estimated post-HTx survival was 83% (CI 74–92%) in the No-LVAD group and 88% (CI 79–98%) in LVAD; survival curves (Fig. 2) were comparable (log-rank $P=0.54$).

To account for the most relevant baseline factors, a multivariable analysis of post-HTx survival was performed, which included: pre-HTx LVAD support, age and BSA at HTx, sex, waiting list status before HTx, time spent on waiting list, donor cold ischemia time and donor age. LVAD support resulted in a significant protective factor [LVAD versus No-LVAD hazard ratio 0.22 (CI: 0.06-0.91)]; waiting list status 2B resulted in protective versus status 2A (Table 5).

Table 4 Postheart transplantation outcomes

	All patients ($n=115$)	No-LVAD ($n=73$)	LVAD ($n=42$)	*P* value
CPB time (min)	180 (170–240)	180 (163–208)	192 (180–246)	0.04
HTx time (min)	420 (360–498)	360 (330–445)	480 (400–540)	<0.01
NO administration	77% (89)	77% (56)	79% (33)	0.82
ECMO	18% (21)	16% (12)	21% (9)	0.51
RBC transfusion	95% (109)	93% (68)	98% (41)	0.30
FFP transfusion	70% (81)	67% (49)	76% (32)	0.31
PLTs transfusion	34% (39)	27% (20)	45% (19)	0.05
Mechanical ventilation (hours)	26 (11–62)	27 (11–70)	24 (13–48)	0.42
CRRT	33% (38)	37% (27)	27% (11)	0.27
Documented infection	28% (32)	30% (22)	24% (10)	0.51
Revision because of bleeding	11% (13)	14% (10)	7% (3)	0.30
Cerebral event	11% (13)	11% (8)	12% (5)	0.88
Ischemic stroke	10% (12)	10% (7)	12% (5)	0.70
Haemorrhagic stroke	1% (1)	1% (1)	0% (0)	0.45
Bowel ischemia	7% (8)	5% (4)	10% (4)	0.39
Abdominal bleeding	1% (1)	1% (1)	0% (0)	0.45
Major arrhythmia	3% (3)	3% (2)	2% (1)	0.92
Wound complication	3% (3)	4% (3)	0% (0)	0.20
Pneumothorax	1% (1)	1% (1)	0% (0)	0.45
Effusion	23% (26)	30% (22)	10% (4)	0.01
Reintubation	13% (15)	17% (12)	7% (3)	0.16
Tracheostomy	10% (12)	15% (11)	2% (1)	0.03
Hepatic or pancreatic complication	4% (5)	5% (4)	2% (1)	0.43
ICU stay (days)	5 (3–8)	5 (3–9)	5 (3–8)	0.88
Hospital-stay (days)	35 (29–51)	35 (30–53)	34 (28–46)	0.37
Follow-up time (months)	21 (6–41)	18 (6–44)	21 (10–40)	0.99
ACR	58% (63)	51% (36)	69% (27)	0.07
ACR (>2R)	39% (42)	39% (27)	39% (15)	0.99
CRS	0.13 (0–0.38)	0.13 (0–0.37)	0.18 (0–0.38)	0.46
AMR	2% (2)	3% (2)	0% (0)	0.29
CAV	20% (14)	18% (7)	23% (7)	0.58
CAV (>2)	3% (2)	3% (1)	3% (1)	0.85
30-day death	4% (5)	3% (2)	7% (3)	0.27
In-hospital death	11% (13)	11% (8)	12% (5)	0.88
Late death	4% (4)	6% (4)	0% (0)	0.29
Overall post-HTx death	15% (17)	16% (12)	12% (5)	0.51

% (*N*) or median (IQR); ACR, acute cellular rejection; AMR, antibody-mediated rejection; CAV, cardiac allograft vasculopathy; rates of ACR and AMR are considered among patients who underwent at least one biopsy; rate of CAV is considered among patients who underwent at least one control coronary angiography; late deaths are considered among hospital survivors.; CPB, cardiopulmonary bypass; CRRT, continuous renal replacement therapy; CRS, cellular-mediated rejection score; FFP, fresh frozen plasma; LVAD, left ventricular assist device; NO, nitric oxide; PLTs, platelets; RBC, red blood cell.

Discussion

In the current era, the growing number of patients with advanced heart failure needing transplant faces a progressive shortening of donor organs available. In this scenario, implantable LVADs could represent an option to increase their survival.

In this study, we reviewed our institutional experience with the use of new-generation intrapericardial CF-LVADs as a BTT and analysed the outcomes at both pre-HTx and post-HTx times. Most of the patients in our series had critical conditions at baseline; many of them presented impaired renal and/or hepatic function and many required a temporary MCS. When these factors are present, the risk of mortality before or after direct HTx is expected to be high.[9,18,19] Whenever feasible, supporting those patients with a long-term LVAD could allow clinical improvement and end-organ recovery,

Table 5 Multivariable analysis of survival after heart transplant

	Difference	Hazard ratio	Lower 95% CL	Upper 95% CL
LVAD	LVAD/No-LVAD	0.22	0.06	0.91
Age at HTx (years)	18.6	0.86	0.30	2.04
BSA (m^2)	0.2	0.88	0.50	1.53
Sex	Female/male	0.12	0.01	1.05
Waiting list status (before HTx)	HU:2A	0.43	0.11	1.77
	1:2A	0.30	0.03	2.80
	2B:2A	0.12	0.03	0.57
Waiting list time (months)	5.5	1.22	0.77	1.93
Donor cold ischemia time (min)	81	1.04	0.49	2.22
Donor age (years)	0.1	3.15	1.02	9.69

BSA, body surface area; CL, confidence limit; LVAD, left ventricular assist device.

enhancing the chances to achieve a successful transplantation at a second time.[20,21] Though it cannot be generalized to all the INTERMACS 1–2 patients and to all the different device strategies, the results of our experience were considerably favourable, with an estimated survival on waiting lists of more than 90% at 6 months. Although frequent, device-related adverse events were successfully managed without patient prioritization in the majority of cases. Post-HTx outcomes were satisfactory, as well, confirming previous findings with older devices.[22–25] A contemporary cohort of No-LVAD patients was used to compare these outcomes and the results obtained were similar. Of note, in the control group, the rate of patients on ECMO or temporary para-corporeal support was 30%. These were cases of refused LVAD implant or abrupt worsening of clinical conditions while on waiting lists. Moreover, No-LVAD patients showed worse renal and hepatic function, with a considerable rate of patients needing inotropic support. These findings lead us to two considerations. First, although the potential drawback of postimplant adverse events, LVAD patients tend to reach HTx in better clinical condition. Second, the results of our comparison between patients transplanted with or without LVAD need to be viewed under the light of the baseline differences of these two groups. Nevertheless, we also provided a multivariable model accounting for the most relevant patient characteristics, which identified LVAD use as a significant protective factor for mortality after HTx. This result is perfectly in line with the latest report on adult HTx from the ISHLT registry, which showed the same effect in the multivariable analysis of 1-year survival.[9]

These favourable outcomes are undoubtedly related to the improved features of the currently available LVADs: smaller dimensions, allowing intrapericardial placement; developed technology and design; enhanced performance and reliability.[7] Nevertheless, to maximize the pre-HTx and post-HTx results, also a strict outpatient follow-up and an accurate procedural planning have paramount importance. In our Institution, after the acute phase, LVAD carriers are followed at a dedicated outpatient clinic with periodical visits (generally twice a month) and frequent phone contacts; major complications are always managed at our Unit. Moreover, we extensively adopt minimally invasive techniques for device implant,[26–33] to reduce the incidence of re-entry complications at the time of HTx. Finally, we sight to transplant LVAD patients within 1 year of support, to reduce the impact of device-related adverse events.

Recently, concerns have been raised regarding the immunological sequelae of durable mechanical support.[34,35] In our population, the incidence of significant acute or chronic allograft rejection was comparable with that of not-supported patients. This could be related to the peculiar design of current CF-LVADs, which reduces blood product activation and immunogenicity. Assist devices could also allow a more selective approach to donor–recipient matching, such that clinicians may decide to wait for the immunologically most favourable donor as long as the transplant candidate remains clinically stable.[35] This is particularly relevant in the case of allosensitized patients.

Even though current guidelines discourage LVAD implant in INTERMACS 1,[1] the outcomes of our study, performed in a population in which more than two-thirds of patients were in INTERMACS profile 1–2, could be considered satisfactory. However, we still report a postimplant mortality rate of 11%. Moreover, we focused on a BTT strategy only; if data from BTC e DT strategies are included, also in our experience, the results are much worse, as it occurs in the literature.[7] Current reports from the international registries clearly show that CF-LVAD implantation in INTERMACS profiles 4–7 results in increased survival and reduced adverse events rate, compared with lower profiles.[6,7] Consequently, better outcomes should be expected in such populations. A BTT strategy with durable devices may be pursued not only in patients who failed the inotropic medical therapy, often too sick to benefit from a mechanical support, but also in clinically stable and ambulatory patients with INTERMACS profiles 4–5. The MEDAMACS registry is as an example that shows how, in ambulatory patients, the mortality rate can be high without considering advanced heart failure therapies (including LVAD).[36,37] The ROADMAP was a prospective nonrandomized multicentre trial of INTERMACS 4–7 patients, comparing optimal medical management (OMM) with HeartMate II implantation.[38] Despite the study limitations (high withdrawal rate, nonrandomized design, limited number of patients), the as-treated analysis showed a higher 2-year event-free survival in the LVAD group. Functional status and quality-of-life improvements were higher, as well. On the other hand, the rate of adverse events was significantly lower in the OMM group and the intention-to-treat (ITT) analysis, which included the results of 22 'delayed' implants, showed similar survival. However, as the authors themselves highlighted, the median INTERMACS profile of the 'delayed' LVAD patients minimally changed from 5 to 4. Thus, the results from the ITT cohort should not be generalized to those patients who undergo a delayed LVAD implant with a profile of 1–3. We believe that an early referral of patients for evaluation, together with an early CF-LVAD implantation, when indicated, can improve survival of patients before and after HTx. A multicentre randomized clinical trial could definitely address this issue. The REVIVE-IT was a multicentre, randomized clinical trial designed to analyse the results of CF-LVAD versus OMM in non-inotrope-dependent patients; however, it faced numerous challenges and was discontinued.[39] The need for such trials remains.

Limitations

Our study was limited by the retrospective design and the limited number of patients included. The post-HTx outcomes of LVAD patients were compared with a contemporary cohort of not-supported cases. However, the baseline clinical status of patients was different between the two groups and a matched analysis was prevented by the restricted sample size. Despite these limitations, we still believe that our results provide significant insights for optimizing the management of LVAD patients.

Conclusions

The use of new-generation intrapericardial CF-LVADs as a BTT, in our series, resulted in satisfactory pre-HTx and post-HTx outcomes. A larger patient population is needed to further expand the analysis and validate our results.

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Conflicts of interest

There are no conflicts of interest.

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