

Left ventricular assist devices decrease fixed pulmonary hypertension in cardiac transplant candidates

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Objective: Fixed pulmonary hypertension is a contraindication for cardiac transplantation because of the increased risk of donor heart failure. We sought to determine whether left ventricular assist devices improve fixed pulmonary hypertension in cardiac transplant candidates to enable safe cardiac transplantation.

Methods: Thirty-five consecutive cardiac transplant candidates (age 56 ± 6 years, 88.5% were men) with fixed pulmonary hypertension (5.1 ± 2.6 Wood units) resistant to medical treatment received a left ventricular assist device as a bridge to transplantation. Three left ventricular assist device systems were used (pulsatile blood flow: Novacor [World Heart Inc, Oakland, Calif] $n = 8$; continuous blood flow: MicroMed DeBakey [MicroMed Technology Inc, Houston, Tex] $n = 24$, DuraHeart [Terumo Heart Inc, Ann Arbor, Mich] $n = 3$). Right-sided heart catheter data were obtained before left ventricular assist device implantation at 3-day and 6-week follow-ups. Clinical data and complications were recorded.

Results: Before left ventricular assist device implantation, the pulmonary vascular resistance was 5.1 ± 2.8 Wood units. Values were comparable in patients receiving pulsatile (5.1 ± 3.4 Wood units) or continuous blood flow left ventricular assist devices (5.1 ± 2.7 Wood units, $P = .976$). Left ventricular assist device implantation decreased pulmonary vascular resistance at 3-day (2.9 ± 1.3 Wood units, $P < .0001$) and 6-week (2.0 ± 0.8 Wood units, $P < .0001$) follow-ups compared with before implantation. This effect was independent of the type of left ventricular assist device system used (3-day follow-up: pulsatile flow: 3.2 ± 1.3 Wood units vs continuous flow: 2.7 ± 1.2 Wood units; $P = .310$ and 6-week follow-up: pulsatile flow: 1.9 ± 0.9 Wood units vs continuous flow: 2.1 ± 0.8 Wood units; $P = .905$). Twenty-four patients had successful bridges to transplantation (69%, mean time on left ventricular assist device 210 ± 83 days), and 11 patients died before transplantation (31%, mean time on left ventricular assist device 67 ± 30 days). The 1-year survival after transplantation was 95%.

Conclusion: Left ventricular assist devices decrease fixed pulmonary hypertension in cardiac transplant candidates and allow patients to overcome a contraindication for cardiac transplantation. Therefore, left ventricular assist devices should be considered in all cardiac transplant candidates with fixed pulmonary hypertension.

The prevalence of congestive heart failure is continuously increasing in the Western world.¹ Despite continuous advances of medical therapy for congestive heart failure, cardiac transplantation is the most effective treatment for patients with end-stage heart failure.²

Pulmonary hypertension (PH) is a risk factor for early and late death after cardiac transplantation. The reason for this is the unacceptably high risk of acute donor right-sided heart failure immediately after implantation.³⁻⁷ There is consensus that the risk of death after cardiac transplantation is increased in patients with pulmonary

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Abbreviations and Acronyms

LVAD	= left ventricular assist device
PG	= prostaglandin
PH	= pulmonary hypertension
PVR	= pulmonary vascular resistance
WU	= Wood units

vascular resistance (PVR) greater than 2.5 Wood units (WU), if PVR cannot be decreased by pharmacologic interventions (fixed PH).^{8,9} Various pharmacologic agents have been evaluated for their ability to decrease PVR in these patients.¹⁰ Pharmacologic agents tested include sodium nitroprusside, inhaled nitric oxide, phosphodiesterase inhibitors, urapidil, prostaglandins (PGE1 and PGI1), and levosimendan.¹⁰⁻¹⁴ However, even by combining these pharmacologic agents, PH cannot be significantly decreased in many of these patients. No safe and efficient treatment can be offered to those patients with end-stage heart failure and fixed severe PH today. Left ventricular assist devices (LVADs) have been reported to reduce PH in patients with terminal heart failure. We are the first to study this topic in a prospective fashion and to compare pulsatile and continuous flow LVADs.¹⁵⁻¹⁷

In this prospective study we report on our experience with the treatment strategy of improving fixed PH in cardiac transplant candidates by means of LVAD implantation and subsequent orthotopic cardiac transplantation.

Materials and Methods**Patients**

During the study period, 242 cardiac transplant candidates were admitted to our hospital. Of those, 72 patients received an LVAD. Indication for LVAD implantation was terminal heart failure without fixed PH in 36 patients (50%), destination therapy in 1 patient (1%), and terminal heart failure with fixed PH (>3.5 WU) in 35 patients (49%). The 35 consecutive patients with terminal heart failure and fixed PH entered this prospective study. To qualify, all patients had to fulfill institutional inclusion criteria for terminal heart failure and had to have fixed PH unresponsive to maximum medical treatment. With the exception of fixed PH, patients had to be suitable for cardiac transplantation. The study was approved by the institutional review board, and all patients gave their written and informed consent before LVAD implantation and subsequent cardiac transplantation.

The duration of support, survival, incidence of neurologic complications, device malfunctions, and infections were monitored. Infections were defined as the presence of a positive blood culture along with a leukocytosis.

Devices, Implant Procedure, and Anticoagulation

Three different systems of LVADs were used in the present study. The technical details and implantation procedures of the

MicroMed DeBakey (MicroMed Technology Inc, Houston, Tex), DuraHeart (Terumo Heart Inc, Ann Arbor, Mich) (continuous blood flow), and Novacor LVADs (World Heart Inc, Oakland, Calif) (pulsatile blood flow) have been described.¹⁸⁻²⁰

Anticoagulation protocol was identical in all patients. During extracorporeal circulation and implantation of the pump, patients received intravenous heparin (300 U/kg body weight), and the heart–lung machine was primed with 1,000,000 IU aprotinin. After discontinuation of extracorporeal circulation, heparin was reversed with an appropriate dose of protamine. Intravenous heparin was instituted 6 hours after surgery to achieve activated partial thromboplastin target times of 50 to 60 seconds. Platelet anti-aggregation therapy with 150 mg per day of aspirin and 225 mg per day of dipyridamole was started after removal of all chest drains. Administration of heparin was stopped when anticoagulation with coumarin reached target levels of 2.5 to 3.5 international normalized ratio.

Measurement of Pulmonary Hypertension

Right-sided heart catheterization was performed according to the guidelines published by the American College of Cardiology/American Heart Association using a Swan–Ganz thermodilution catheter. Right-sided heart catheterization was performed before LVAD implantation and 3 days and 6 weeks after LVAD implantation.²¹ The PH variables assessed included PVR (Wood units), systolic pulmonary artery pressure (millimeters of mercury), mean pulmonary artery pressure (millimeters of mercury), pulmonary capillary wedge pressure (millimeters of mercury), and cardiac output (liters per minute). Cardiac output was measured with the Fick method.

Testing for Reversibility of Pulmonary Hypertension

PH was defined as PVR greater than 3.5 WU. Reversibility of PH was assessed by nitroglycerin, prostaglandin (PGI2), nitric oxide, and levosimendan (only available in the last 10 patients). Nitroglycerin was applied intravenously at increasing doses of 2 to 6 mg per hour with dose increments every 10 minutes. PGI2 was given intravenously at increasing doses of 10 to 200 ng/kg/min with dose increments every 5 minutes. Nitric oxide was administered in doses of 40, 60, and 80 ppm through a tight-fitting facemask. In the last 10 patients, levosimendan was additionally used for testing for reversibility of PH. If PH was not reversible with this treatment, it was considered as fixed. All of the mentioned substances were tested in all patients (Figure 1).

Statistical Analysis

Data are presented as frequency distributions and percentages. Values of continuous variables are expressed as mean \pm standard deviation. Continuous variables were compared using analysis of variance (Bonferroni). Categorical variables were compared by means of the chi-square or Fisher exact test as appropriate. Kaplan–Meier analysis was used to calculate long-term survival along with a log–rank *P* value when comparing groups. The study was analyzed with the Statistical Package for the Social Sciences 11.5 (SPSS Inc, Chicago, Ill).

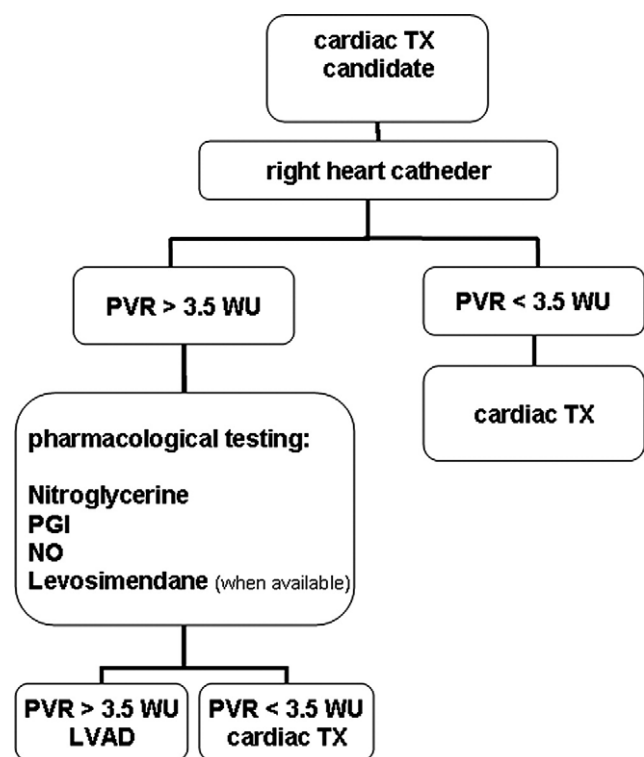


Figure 1. Pharmacologic testing: decision-making tree. TX, Transplant; PVR, pulmonary vascular resistance; WU, Wood units; PG, prostaglandin; NO, nitric oxide; LVAD, left ventricular assist device.

Results

Demographics

The characteristics of LVAD recipients are shown in Table 1. The mean overall age was 56.6 years (88.5% were male). All patients were in New York Heart Association class IV and had fixed PH (PVR 5.1 ± 2.8 WU) before LVAD implantation. Idiopathic cardiomyopathy was the most common cause of heart failure present in 23 patients (65.5%), and ischemic cardiomyopathy was present in 12 patients (34.5%). Recipients of pulsatile and continuous flow LVAD were comparable with regard to patient characteristics (Table 1). Overall mechanical support time was 202 ± 169 days (range, 35-700 days).

Survival

Twenty-four patients (69%) had successful bridges to transplantation (bridge to transplant time 210 ± 83 days), and 11 patients (31%) died during LVAD support (survival time 67 ± 30 days). One patient (5%) died after cardiac transplantation. We found no difference in bridge to transplant success between patients treated with pulsatile (62.5%) or continuous flow (71.1%) LVAD ($P = .147$). One-year survival after cardiac transplantation was

95%. The mean follow-up after cardiac transplantation was 25 ± 17 months. Overall survival is displayed in Figure 2.

Right-sided Heart Catheterization

Before LVAD implantation, PVR was 5.1 ± 2.8 WU. Values were comparable in patients receiving pulsatile (5.1 ± 3.4 WU) and continuous blood flow LVADs (5.1 ± 2.7 WU, $P = .976$). LVAD implantation decreased PVR at 3-day (2.9 ± 1.3 WU, $P < .0001$) and 6-week follow-ups (2.0 ± 0.8 WU, $P < .0001$) compared with before implantation. This effect was independent of the type of LVAD system used (3-day follow-up: pulsatile flow 3.2 ± 1.3 WU vs continuous flow 2.7 ± 1.2 WU, $P = .310$; 6-week follow-up: pulsatile flow 1.9 ± 0.9 WU vs continuous flow 2.1 ± 0.8 WU, $P = .905$). Detailed hemodynamic data are shown in Table 2.

Complications and Causes of Death

The incidence and nature of complications and the causes of death are shown in Table 3. None of the patients required mechanical right-sided heart support after LVAD implantation. A total of 51.3% of patients experienced a complication while on LVAD support. Cerebrovascular events occurred in 31% of patients, and infections occurred in 25.7% of patients. We found no difference in the incidence and nature of complications between patients treated with pulsatile and continuous blood flow devices (Table 3). Cerebrovascular events were the most common cause of death present in 45.4% of patients, followed by multiorgan failure (36.3%) and infections (18.3%). We found no difference in the incidence and nature of complications between patients treated with pulsatile and continuous blood flow devices (Table 3).

Discussion

Severe fixed PH is a contraindication for cardiac transplantation because of an increased risk of postoperative donor heart failure. LVADs decrease fixed PH in cardiac transplant candidates and enable them to undergo orthotopic cardiac transplantation.

Pulmonary vascular hypertension is a common complication of severe long-standing heart failure. Approximately 72% of patients with terminal heart failure who are eligible for cardiac transplantation have PH.²² The pathophysiology behind PH in patients with terminal heart failure is the result of a multifactorial process mainly relating to left ventricular failure.²³ Left atrial hypertension resulting from left ventricular failure translates into increased postcapillary pressure in the pulmonary circulation.²³ This enhances pulmonary endothelial dysfunction with decreased availability of nitric oxide and prostacyclin and increased production of thromboxane A₂ and endothelin-1.²³ The activity of serine

TABLE 1. Patient characteristics and heart failure therapy

Variable	All patients	Continuous flow*	Pulsatile flow†	P value‡
n	35	27	8	
Age (y)	56.6 ± 7	54.2 ± 5	58.2 ± 8	.853
Male (%)	88.5	92.5	87.5	.345
Disease (CAD/ICM, %)	34.5/65.5	37.3/62.7	36.6/63.4	.679
Weight (kg)	80.4 ± 12.2	78.6 ± 13.5	82.3 ± 14.1	.872
Height (cm)	170 ± 12	172 ± 9	171 ± 6	.941
Ejection fraction (%)	18.2 ± 6.3	17.9 ± 7.3	18.3 ± 8.2	.762
COPD (%)	12.5	11.1	12.5	.928
Renal failure (%)	28.1	22.2	37.5	.675
Diabetes (%)	22.8	22.2	25.5	.314
Heart rate (beats/min)	95 ± 7	93 ± 8	96 ± 6	.345
AOP (mm Hg)	90/60	93/58	88/62	.476
Heart failure (y)	5.3	5.5	5.1	.674
Diuretics (%)	100	100	100	1.000
Beta-blockers (%)	94.5	92.3	87.5	.429
ACE inhibitor (%)	100	100	100	1.000
Inotropic support (%)	0	0	0	1.000

CAD, Coronary artery disease; ICM, idiopathic cardiomyopathy; COPD, chronic obstructive pulmonary disease; AOP, aortic pressure (only mean values given); ACE, angiotensin-converting enzyme. Renal failure: defined as creatinine > 2.0 mg/dL (177 μmol/L). Heart failure (y): duration of heart failure. *Patients treated with continuous flow LVADs. †Patients treated with pulsatile flow LVADs. ‡P value: continuous flow LVADs versus pulsatile flow LVADs.

elastase is up-regulated in the subendothelium causing glycoprotein deposition and smooth muscle cell hypertrophy and hyperplasia.²⁴ Intermittent hypoxia stimulates vasoconstriction in the pulmonary vascular tree. Changes in the expression of von Willebrand factor result in the development of platelet fibrin microthrombi.²⁵ In addition, this process is associated with smooth muscle cell hypertrophy and hyperplasia.²³ Depending on the duration of these processes, remodeling of the pulmonary vascular tree takes place.

Fixed PH is considered to be present when elevated PVR cannot be significantly decreased (>20%) by pharmacologic interventions.^{6,26} Although there is no international consensus, most transplant centers will not offer cardiac transplantation in patients with PVR greater than 3 to 4 WU for the following reasons. In the case of cardiac transplantation, the relatively thin-walled right ventricle of the organ donor does not function adequately in the presence of abnormally elevated PVR. This carries the high risk of distension of the donor right ventricle, resulting in right ventricular failure. In this case, neither high doses of inotropes nor mechanical support of the right ventricle results in a satisfying outcome.²⁶⁻²⁹ Posttransplant survival in patients with fixed PH is significantly worse compared with patients with normal PVR in both short and long-term follow-ups.^{3-7,29}

In the present study, LVADs decreased fixed PH during a 6-week period of support. PH in terminal heart failure, at least in part, is the consequence of elevated left atrial filling pressures resulting from impaired left ventricular systolic

function. Therefore, it might be speculated that LVADs reverse this process by continuously unloading the left ventricle. It remains to be studied whether LVAD support results in a reverse-remodeling of the pulmonary vascular tree. Pulsatile and continuous blood flow LVADs equally decreased PH during a 6-week period of support. It was previously emphasized that left ventricular unloading is more efficiently done by continuous blood flow devices.³⁰ This was based on the theoretic consideration that continuous blood flow devices unload the left ventricle during the

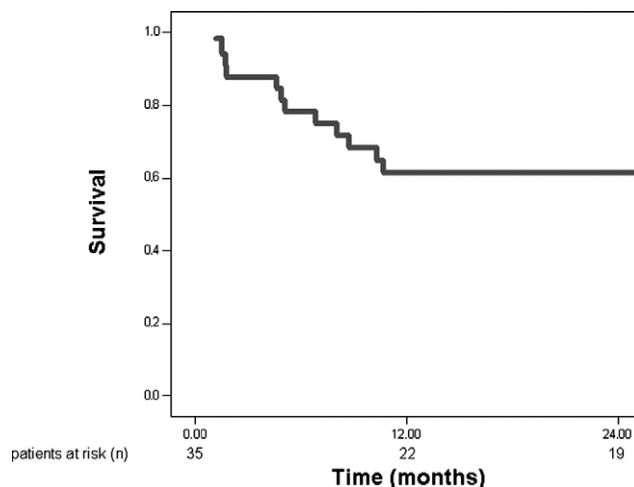


Figure 2. Kaplan-Meier curve displaying overall survival after LVAD implantation.

TABLE 2. Data from right-sided heart catheterization

Variable	All patients	<i>P</i> value*	Continuous flow†	Pulsatile flow‡	<i>P</i> value§
n	35		27	8	
PVR					
Baseline	5.1 ± 2.6	—	5.3 ± 2.7	5.1 ± 3.5	.976
3-d FUP	2.9 ± 1.3	<.0001	2.7 ± 1.2	3.2 ± 1.3	.310
6-wk FUP	2.0 ± 0.8	<.0001	2.1 ± 0.8	1.9 ± 0.9	.905
After testing	4.5 ± 2.1	—	—	—	—
PA _{syst}					
Baseline	63.2 ± 9.3	—	65.2 ± 13.0	65.3 ± 10	.976
3-d FUP	39.6 ± 10.6	<.0001	37.6 ± 9.4	43.4 ± 12.5	.175
6-wk FUP	26.7 ± 3.6	<.0001	29.6 ± 6.5	28.1 ± 7.5	.236
After testing	36 ± 10.2	—	—	—	—
PA _{mean}					
Baseline	44.0 ± 6.2	—	45.5 ± 6.8	43.0 ± 8.4	.397
3-d FUP	28.6 ± 7.3	<.0001	28.1 ± 7.5	29.6 ± 6.5	.604
6-wk FUP	18.4 ± 4.3	<.0001	19.0 ± 4.2	17.8 ± 5.1	.571
After testing	30.2 ± 6.8	—	—	—	—
PCWP					
Baseline	28.1 ± 6.0	—	29.0 ± 5.7	27.1 ± 7.0	.439
3-d FUP	12.0 ± 5.7	<.0001	11.9 ± 4.4	13.0 ± 8.3	.641
6-wk FUP	10.0 ± 3.6	<.0001	10.1 ± 13.7	9.1 ± 3.7	.572
After testing	15.8 ± 1.9	—	—	—	—
CO					
Baseline	3.1 ± 0.8	—	3.0 ± 0.6	2.6 ± 0.7	.601
3-y FUP	5.7 ± 0.7	<.0001	6.2 ± 1.1	5.1 ± 0.8	.375
6-wk FUP	4.0 ± 0.9	.002	4.2 ± 0.8	4.6 ± 0.4	.453
After testing	3.2 ± 7	—	—	—	—

PVR, Pulmonary vascular resistance (WU); FUP, follow-up; PA_{syst}, systolic pulmonary artery pressure (mm Hg); PA_{mean}, mean pulmonary artery pressure (mm Hg); PCWP, pulmonary capillary wedge pressure (mm Hg); CO, cardiac output (l·min⁻¹). **P* value: compared with before LVAD implantation. †Patients treated with continuous flow LVADs. ‡Patients treated with pulsatile flow LVADs. §*P* value: continuous flow LVADs versus pulsatile flow LVADs. Baseline: hemodynamic data immediately before LVAD implantation. After testing: hemodynamic data after pharmacologic testing.

whole cardiac circle. On the basis of this finding, the decision for the type of LVAD in cardiac transplant candidates with fixed PH should depend only on the patient's demands. Especially in large patients, the flow provided by continuous flow LVADs may be too low to increase exercise tolerance and enable recovery of the patient.³¹

Compared with the high risk of donor heart failure in patients with fixed PH and orthotopic cardiac transplantation, the combined approach of LVAD support and subsequent cardiac transplantation seems promising. Successful bridging rates ranging from 65% to 70% have been reported in patients without PH.³² We successfully bridged 69% of patients to safe cardiac transplantation. Posttransplant survivals at 30-day (95%) and 12-month (95%) follow-ups were comparable to those reported in patients without PH at the time of cardiac transplantation.³³ Because of these results, all cardiac transplant candidates with a PVR greater than 3.5 WU (after testing for reversibility) receive an LVAD before cardiac transplantation at our center. Alternative approaches to orthotopic cardiac transplantation, such as heterotopic cardiac transplanta-

tion and right ventricle-sparing transplant techniques, have been recommended in the past in patients with severe PH.^{34,35} In these select cases, the donor heart acts as a biological assist device to the native left ventricle or both ventricles. Survivals reported at 12-month follow-ups range between 83% and 59%.^{34,35} The major limitations of heterotopic transplantation are the availability of a suitable donor, technical difficulties during implantation, and, in particular, late interactions of donor and recipient heart.³⁶ Survivals with these alternative approaches are significantly lower compared with LVAD implantation and subsequent orthotopic cardiac transplantation. The presented algorithm significantly reduces the incidence of right-sided heart failure after cardiac transplantation to less than 1% and is associated with good posttransplant survival.

Nevertheless, patient morbidity while on LVAD support still remains a major concern, because 51% of all patients exhibited a severe adverse event. Most common were neurologic events, which also significantly contributed to patient mortality on LVAD support. Other complications included infections and bleeding. No device-related complications were

TABLE 3. Complications and causes of death

Variable	All patients	Continuous flow*	Pulsatile flow†	P value‡
Incidence of complications	51.3	51.8	50.0	.370
Reoperation for bleeding	17.1	18.1	12.5	.261
CVA	31.4	33.4	25.0	.297
Infection	25.7	25.9	25.0	.284
Causes of death				
No. died while on LVAD	11	8	3	.147
Multiorgan failure (n, %)	36.3	37.5	33.3	.672
CVA	45.4	50.0	33.3	.542
Infection	18.3	12.5	33.3	.082

CVA, Cerebrovascular accident; LVAD, left ventricular assist device. *Patients treated with continuous flow LVADs. †Patients treated with pulsatile flow LVADs. ‡P value: continuous flow LVADs versus pulsatile flow LVADs.

observed. In our series the incidence of adverse events compares with that reported by others.^{37,38} There was no difference in adverse events between pulsatile and continuous flow LVADs. Continuous research, improvement of devices, and careful patient selection are crucial to reduce LVAD-associated complications.

Conclusions

The primary limitation of the present study is the nonrandomized design. The reason for this design is because fixed PH is a contraindication for cardiac orthotopic transplantation. Therefore, comparing cardiac transplantation with and without prior LVAD implantation would be ethically questionable.

LVADs decrease fixed PH in cardiac transplant candidates and allow them to overcome fixed PH as a contraindication for cardiac transplantation. Therefore, LVADs should be considered in all cardiac transplant candidates with fixed PH.

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