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ORIGINAL ARTICLE

Impact of bridging with left ventricular assist device on right ventricular function following heart transplantation

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Abstract

Aims Patients awaiting orthotopic heart transplantation (OHT) can be bridged utilizing a left ventricular assist device (LVAD) that reduces left ventricular filling pressures, decreases pulmonary artery wedge pressure, and maintains adequate cardiac output. This study set out to examine the poorly investigated area of if and how pre-treatment with LVAD impacts right ventricular (RV) function following OHT.

Methods and results We prospectively evaluated 59 (LVAD n = 20) consecutive OHT patients. Transthoracic echocardiography (TTE) was performed in conjunction with right heart catheterization (RHC) at 1, 6, and 12 months after OHT. RV function TTE-parameters included tricuspid annular plane systolic excursion (TAPSE), systolic tissue velocity (S′), fractional area change, two-dimensional RV global longitudinal strain and longitudinal strain from the RV lateral wall (RVfree). At 1 month after OHT, the LVAD group had significantly better longitudinal RV function than the non-LVAD group: TAPSE (15 ± 3 mm vs. 12 ± 2 mm, $P < 0.001$), RV global longitudinal strain (−19.8 ± 2.1% vs. −14.3 ± 2.8%, $P < 0.001$), and RVfree (−19.8 ± 2.3% vs. −14.1 ± 2.9%, $P < 0.001$). At this time point, pulmonary vascular resistance (PVR) was also lower [1.2 ± 0.4 Wood Units (WU) vs. 1.6 ± 0.6 WU, $P < 0.05$] in the LVAD group compared with the non-LVAD group. At 6 and 12 months, no difference was detected in any of the TTE and RHC measured parameters between the two groups. Between 1 and 12 months, all parameters of RV function improved significantly in the non-LVAD group but remained unaltered in the LVAD group.

Conclusions Our results indicate that pre-treatment with LVAD decreases PVR and is associated with significantly better RV function early following OHT. During the first year following transplantation, RV function progressively improved in the non-LVAD group such that at 6 and 12 months, no difference in RV function was detected between the groups.

Keywords Two-dimensional echocardiography; Early follow up; Strain; Heart transplantation; Right heart catheterization; Left ventricular assist device

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Introduction

In selected severe cases of heart failure, refractory to medical therapy, orthotopic heart transplantation (OHT) is considered the end-stage treatment option. In patients suffering from heart failure due to left heart disease, left ventricular (LV) dysfunction usually includes both 'forward' and 'backward' failure with reduced cardiac output (CO) and elevated LV filling pressure, respectively. Eventually, as the disease progresses, vasoconstriction and remodelling of the pulmonary

vasculature may lead to increased pulmonary vascular resistance (PVR) and pulmonary hypertension (PH).[1] If pressures are sufficiently high over time, this may cause right ventricle (RV) dysfunction. Fixed PH in combination with high PVR can cause RV failure following OHT as the allograft is not conditioned to function during such conditions.[2–5] Moreover, RV failure in the early period following OHT results in prolonged clinical recovery and is a well-described complication in OHT patients.

Following OHT, extensive monitoring of cardiac allograft function is conducted during the first year. Patients are scheduled for routine controls including right heart catheterization (RHC), to characterize intra-cardiac pressures and blood flow, along with endomyocardial biopsies to rule out cellular or antibody-mediated rejection, as well as transthoracic echocardiography (TTE) to assess LV and RV function. TTE has gained increased importance since the introduction of strain imaging, utilizing speckle tracking echocardiography (STE), which allows detection of subtle changes in myocardial contractility.

To reduce mortality while on the OHT waiting list, an increasing number of patients receive 'bridging' support with a left ventricular assist device (LVAD). Besides increasing CO, this treatment results in reduced pulmonary arterial wedge pressure (PAWP) and PVR.[6] It has even been demonstrated that LVAD can reduce PVR in patients with established PH and thereby make them suitable for transplantation.[7–9] The fact that LVAD support may reduce RV afterload (i.e. PVR) at time of transplantation might be beneficial for post-operative allograft RV function.

Whether LVAD as bridge-to-transplantation impacts RV adaptation post-OHT and whether this possible impact correlates to invasively measured pulmonary pressures has to the best of our knowledge not been described. Therefore, we aimed to assess RV function with TTE in conjunction to invasive haemodynamic parameters obtained by RHC at 1, 6, and 12 months post-OHT, to evaluate if pre-treatment with LVAD affect initial RV function after OHT. Furthermore, we sought to assess whether the putative effect was sustained during 1 year follow up.

Methods

Study cohort

The current study recruited 66 consecutive patients that had undergone OHT with bicaval surgical technique. Seven patients were excluded or lost during follow up due to: biopsy proven rejection requiring treatment at time of examination (n = 1), insufficient image quality (n = 3), death during follow up (n = 2), and biopsy-induced flail tricuspid valve (n = 1). Finally, 59 patients remained available for analysis (n = 43 male, mean age 49 ± 12 years). All participants had LV ejection fraction $\geq$ 45% and no haemodynamically important regurgitation of any cardiac valve. None of the patients had any previous detected ischaemia–reperfusion events. Three patients had severe primary graft dysfunction within 24 h from the OHT according to ISHLTs' consensus document.[10]

Patients were prospectively enrolled in the study between 2014 and 2020. The LVAD group consisted of 20 patients (n = 18 male) and the non-LVAD group of 39 patients (n = 25 male), which represent the normal distribution among OHT recipients receiving LVAD support at our centre. At time of the examinations all patients were in sinus rhythm. Patient characteristics at 1 month post-OHT are depicted in *Table 1*.

Median time between initial RHC and OHT was 146 days. Patients on LVAD support had significantly longer time on waiting list than non-LVAD patients. When evaluated for OHT, 44 patients (LVAD n = 16 and non-LVAD n = 28) had PH according to criteria[11] with mean pulmonary artery pressure (mPAP) $>$ 25 mmHg at rest. In 46 patients (LVAD n = 18 and non-LVAD n = 28), elevated PAWP defined as $>$15 mmHg was present. Moreover, 14 patients had systolic pulmonary artery pressure (sPAP) $>$ 50 mmHg (non-LVAD n = 7 and LVAD n = 7). Among these, two patients had TPG $>$ 15 mmHg (non-LVAD n = 1 and LVAD n = 1), and one patient (non-LVAD) had PVR $>$ 5 Wood Units (WU). None of the patients exhibited all three of these features, and the patient with PVR $>$ 5 WU exhibited a positive nitroprusside test indicating reversibility of PH.

A subgroup of the LVAD patients (n = 8) were re-examined with RHC on clinical indication (e.g. deterioration) while on LVAD support. Comparisons of RHC data for this subgroup are depicted in the Result section. After OHT patients were examined with TTE according to an extended protocol and examination was conducted in conjunction to RHC in line with clinical practice at 1, 6, and 12 months. Pre-transplant patient characteristics and haemodynamic parameters are shown in *Table 2*. The study was approved by the local scientific ethical committee in Lund (Dnr: 2010/114, 2010/442, 2011/777) with informed consent from all participants.

Echocardiographic evaluation

Patients were examined with two-dimensional echocardiography using an iE33 platform equipped with a S5-1 transducer (Philips Healthcare, Eindhoven, NL). Measurements and calculation of echocardiographic standard parameters were performed according to guidelines from the American Society of Echocardiography.[12] RV function was assessed with two-dimensional echocardiography including tricuspid annular plane systolic excursion (TAPSE), systolic tissue velocity (S$'$), and fractional area change (FAC). All measurements were conducted by an experienced sonographer (AI). Assessment of intra-observer variability, based on blinded repeated

Table 1 Early post-OHT characteristics of study cohort and donor characteristics

	All patients (n = 59)		LVAD (n = 20)	Non-LVAD (n = 39)	
	Mean ± SD	Range	Mean ± SD	Mean ± SD	P value
Recipient age at OHT (years)	49	21–70	48 ± 12	49 ± 12	n.s
Time between RHC and OHT (days)	259 ± 235	6–1020	396 ± 318	182 ± 121	<0.01
Male recipient gender (n)	43	—	18	25	N/A
BSA (m^2)	2.0 ± .0.2	1.5–2.5	2.0 ± 0.2	1.9 ± 0.2	n.s.
Pre-existing PH (n)	44	—	16	28	n.s.
Pre-existing diabetes (n)	1	—	1	0	N/A
Severe primary graft dysfunction (n)	3	—	1	2	N/A
Inotropic support post-OHT (days)	4.8 ± 2.4	1–12	5.2 ± 2.6	4.6 ± 2.3	n.s.
Time in intensive care (days)	9.7 ± 9.0	3–36	11.1 ± 9.6	9.0 ± 8.8	n.s.
Intraoperative bleeding (mL)	618 ± 396	250–2100	760 ± 388	553 ± 388	n.s.
Blood transfusion intraoperative (n SAG)	3.2 ± 2.3	0–11	3.9 ± 2.2	2.8 ± 2.2	n.s.
Blood transfusion during intensive care (n SAG)	2.0 ± 2.0	0–8	2.7 ± 2.1	1.6 ± 1.9	n.s.
Recurrent hospitalization <1 year from discharge (n)	7	—	2	5	n.s.
Diabetes post-OHT (n)	24	—	6	18	N/A
Insulin (n)	24	—	7	17	N/A
Beta-blocker (n)	17	—	5	12	N/A
ACE/ARB inhibitor (n)	17	—	7	10	N/A
Diuretics (n)	11	—	4	7	N/A
Prednisolone (n)	59	—	20	39	N/A
Tacrolimus (n)	53	—	17	36	N/A
Mycophenolate (n)	53	—	18	35	N/A
Evrolimus (n)	7	—	3	4	N/A
Ciklosporin (n)	4	—	1	3	N/A
Diltiazem (n)	35	—	10	25	N/A
Acetylsalicylic acid (n)	30	—	8	22	N/A
Donor parameters					
Age (years)	45 ± 13	17–69	44 ± 14	46 ± 13	n.s.
Ischaemic time (min)	182 ± 57	54–293	187 ± 62	180 ± 56	n.s.
Cause of death[a]					
Brain death (n)	45	—	13	32	N/A
Cardiac arrest (n)	3	—	0	3	N/A
Trauma (n)	8	—	4	4	N/A
Suicide (n)	3	—	1	2	N/A

BSA, body surface area; OHT, orthotopic heart transplant.
P values derived from independent sample t-test represent the difference between the LVAD and the non-LVAD group when applicable.
[a]Brain death includes all primary brain insults such as subarachnoid haemorrhage. Cardiac arrest refers to cases where brain damage results from cardiac arrest from transient phenomena.

offline measurement for RV strain by one observer, was performed in 20 randomly chosen patients. Absolute agreement was evaluated using intra-class correlation with two-way mixed-effect models. Low inter-observer variability within our group has previously been performed, validated, and published.[13] The intra-observer variability was 0.99 (95% confidence interval; 0.98–0.99) for right ventricular GLS (RVGLS) and 0.99 (95% confidence interval; 0.97–0.98) for RV lateral free wall strain (RVfree).

Cardiac mechanics

Three-beat cine-loop clips were recorded with patient in free breathing end-respiratory apnoea. Grayscale views were recorded for STE. Offline assessment of images was done using commercial software (CMQ, Q-lab 10.3, Philips iE33, Philips Healthcare, Eindhoven, NL). Frame rate was optimized to a minimum of 50 Hz.

Right ventricular GLS was measured using the LV four-chamber algorithm. Mean peak systolic strain from seven segments was derived by the software. RVfree was obtained by manually averaging the three regional peak systolic strain measures from the RV lateral wall (basal-, mid-, and apical). Shortening of the myocardial fibres will generate negative values because strain represents percentage change in length from the original length.

Right heart catheterization and comparison with echocardiographic measures

Echocardiographic parameters of RV function at 1, 6, and 12 months were compared with haemodynamic measures obtained from RHC, conducted within 2 h of the echocardiographic evaluation. RHC was performed in supine position at rest. Pulsatile and mean right atrial pressures (mRAP), pulmonary arterial pressures (systolic PAP, mean PAP, and diastolic

Table 2 Haemodynamic parameters obtained from RHC when evaluated for OHT prior to LVAD support

	All patients (n = 59)		LVAD (n = 20)	Non-LVAD (n = 39)	P value
	(mean ± SD)	Range	(mean ± SD)	(mean ± SD)	
RHC data					
sAP (mmHg)	101 ± 13	81–137	95 ± 9	104 ± 14	<0.05
dAP (mmHg)	71 ± 9	47–94	67 ± 9	73 ± 9	<0.05
mAP (mmHg)	80 ± 14	60–105	82 ± 19	83 ± 10	<0.01
HR (bpm)	79 ± 17	50–125	73 ± 19	77 ± 18	n.s.
sPAP (mmHg)	46 ± 16	16–86	51 ± 15	43 ± 16	n.s.
dPAP (mmHg)	25 ± 9	9–53	28 ± 10	23 ± 8	<0.05
mPAP (mmHg)	33 ± 10	12–65	36 ± 10	31 ± 11	n.s.
TPG (mmHg)	8.9 ± 4.4	1–22	10.4 ± 5.5	8.0 ± 3.5	n.s.
PAWP (mmHg)	23 ± 8	6–40	26 ± 7	22 ± 8	n.s.
CVP (mmHg)	13 ± 6	3–34	13 ± 6	13 ± 6	n.s.
CO (L/min)	3.5 ± 1.0	1.8–5.4	3.6 ± 0.7	3.3 ± 0.8	n.s.
CI (L/min/BSA)	1.8 ± 0.4	1.0–2.6	1.8 ± 0.3	1.7 ± 0.3	n.s.
SAO2 (%)	95 ± 3	82–99	94 ± 5	95 ± 2	n.s.
PVR (WU)	2.6 ± 1.2	0.3–6.0	2.8 ± 1.3	2.5 ± 1.1	n.s.
RVSWI (mmHg mL m^{-2})	423 ± 243	136–1274	534 ± 278	367 ± 205	<0.05
sPAP > 50 mmHg (n)	14	—	7	7	NA
TPG > 15 mmHg (n)	2	—	1	1	NA
PVR > 5 WU (n)	1	—	0	1	NA

CI, cardiac index; CO, cardiac output; CVP, central venous pressure; dAP, diastolic arterial pressure; dPAP, diastolic pulmonary artery pressure; HR, heart rate; mAP, mean arterial pressure; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure, PVR, pulmonary vascular resistance; RVSWI, right ventricular stroke work index; SAO_2, arterial oxygen saturation; sAP, systolic arterial pressure, sPAP, systolic pulmonary artery pressure; TPG, trans pulmonary gradient.
P values derived from independent sample t-test represent the difference between the LVAD and the non-LVAD group when applicable.

PAP), and PAWP were recorded as mean over several heart beats at free breathing. CO was calculated by thermodilution, and PVR was calculated as (mPAP − PAWP)/CO and reported as WU throughout. Pulmonary effective arterial elastance (Ea) was calculated as RV-systolic pressure/stroke volume (SV). Cardiac index was used to calculate right ventricular stroke work index by the formula: (mPAP − mRAP) × SVI. Systemic blood pressure was measured using a cuff and sphygmomanometer.

Statistical analysis

Statistical analysis was performed using the commercially available software SPSS Statistics 25.0 (IBM, Chicago, IL). All continuous data conforming to a normal distribution are presented as mean (±SD) and as percentage for categorical variables. Assumptions of normality were confirmed by visual inspection of histograms. Differences between the LVAD and non-LVAD group were tested with independent samples t-tests at each time point. Unequally distributed parameters were compared using Mann–Whitney U-test. Categorical variables were compared using Pearson χ^2 test. Comparison of RHC parameters within the LVAD subgroup prior to OHT was conducted using dependent sample t-test. Correlation between continuous variables and haemodynamic parameters at each time point were explored using Pearson's correlation coefficients. Findings were considered statistically significant when $P < 0.05$.

Results

Haemodynamic evaluation while on left ventricular assist device support

Re-evaluation with RHC was performed in a subgroup of the LVAD patients while on LVAD support (n = 8, median time between initial RHC and RHC on LVAD support was 5 months, range 2–34 months). In these patients, a significant reduction in sPAP (50 ± 19 mmHg vs. 30 ± 11 mmHg), diastolic pulmonary artery pressure (dPAP) (29 ± 14 mmHg vs. 15 ± 7 mmHg), mPAP (37 ± 13 mmHg vs 21 ± 8 mmHg), PAWP (26 ± 11 mmHg vs. 13 ± 7 mmHg), and PVR (3.2 ± 1.4 WU vs. 1.8 ± 0.7 WU) was detected ($P < 0.05$ for all parameters).

Clinical findings pre-operative and during early intensive care

No difference was detected in occurrence of severe primary graft dysfunction (i.e. need of circulatory support; extracorporeal membrane oxygenation), time in intensive care or duration of inotropic support between the groups (n.s.). A trend towards higher amount of intraoperative bleeding (P = 0.09) and need of blood transfusion intraoperatively (P = 0.09), or during intensive care (P = 0.07) was seen in the LVAD group (*Table 1*).

Table 3 Right ventricular function parameters assessed with echocardiography for both groups at all time points

	1 month (mean ± SD)		6 months (mean ± SD)		12 months (mean ± SD)		*P* value	*P* value
	LVAD	Non-LVAD	LVAD	Non-LVAD	LVAD	Non-LVAD	LVAD	Non-LVAD
TAPSE (mm)	14.5 ± 2.9***	11.7 ± 2.4	13.6 ± 2.8	13.2 ± 3.6	14.1 ± 3.8	14.5 ± 4.2	n.s.	<0.001
S′ (cm/s)	7.9 ± 1.6	8.2 ± 2.1	8.9 ± 2.0	8.9 ± 2.7	9.2 ± 2.4	9.5 ± 2.7	n.s.	<0.01
RV FAC (%)	39 ± 5	36 ± 8	38 ± 7	39 ± 7	41 ± 9	40 ± 7	n.s.	<0.05
RVGLS (%)	−19.8 ± 2.1 ***	−14.3 ± 2.8	−17.2 ± 4.4	−17.2 ± 3.1	−18.2 ± 2.4	−18.1 ± 2.8	n.s.	<0.001
RVfree (%)	−19.8 ± 2.3***	−14.1 ± 2.9	−17.8 ± 4.3	−17.0 ± 2.9	−18.9 ± 2.2	−18.2 ± 2.9	n.s.	<0.001

RV FAC, right ventricular fractional area change, RVfree, right ventricular strain of the lateral wall; RVGLS, right ventricular global longitudinal strain; S′, tricuspid annular systolic velocity; TAPSE, tricuspid annular plane systolic excursion.
P values are derived from paired *t*-test and represent the difference within the group between 1 and 12 months. Significant differences between the two groups derived from independent sample *t*-test at a given time point are denoted by asterisks in the LVAD group.
*$P < 0.05$,
**$P < 0.01$,
***$P < 0.001$.

One month post-transplantation

Right ventricular function assessed with TTE was better in the LVAD group than in the non-LVAD group at 1 month post-OHT: TAPSE (15 ± 3 mm vs. 12 ± 2 mm, $P < 0.01$), RVGLS (−19.8 ± 2.1% vs. −14.3 ± 2.8%, $P < 0.001$), and RVfree (−19.8 ± 2.3% vs. −14.1 ± 2.9%, $P < 0.001$), *Table 3*. The remaining RV function parameters (i.e. S′ and FAC) were similar between the groups. The subgroup of patients with sPAP > 50 mmHg (including the patients with TPG > 15 mmHg and PVR > 5 WU) when evaluated for OHT did not differ significantly from the rest of the cohort in any echocardiographically measured RV function parameter at any time point during follow up. At 1 month, PAWP was slightly higher (11 ± 5 mmHg vs. 9 ± 4 mmHg, $P < 0.05$) and PVR was lower (1.2 ± 0.4 WU vs. 1.6 ± 0.6 WU, $P < 0.05$) in the LVAD group compared with the non-LVAD group, whereas all other invasive measures were comparable between the groups, *Table 4*. Exclusion of patients transplanted within 1 month of formal acceptance for OHT (non-LVAD $n = 5$ and LVAD $n = 1$) did not affect the absolute values obtained, nor the differences observed between the groups.

Difference between 1 and 12 months post-transplantation

Between 1 and 12 months, all parameters of RV function improved significantly in the non-LVAD group: TAPSE (12 ± 2 mm vs. 15 ± 4 mm, $P < 0.001$), S′ (8.3 ± 2.1 cm/s vs. 9.4 ± 2.6 cm/s, $P < 0.01$), FAC (36 ± 8% vs. 41 ± 7%, $P < 0.05$), RVGLS (−14.3 ± 2.8% vs. −18.1 ± 2.8%, $P < 0.001$), and RVfree (−14.1 ± 2.9% vs. −18.2 ± 2.9%, $P < 0.001$). No difference in RV function parameters between 1 and 12 months was observed in the LVAD group, and at 12 months, no difference between the LVAD and non-LVAD group was detectable. Echocardiographic parameters for both groups at all time points are listed in *Table 3* and depicted in *Figure 1*.

For both LVAD and non-LVAD group, blood pressure increased between 1 and 12 months ($P < 0.001$). No difference in blood-pressure between the groups was found at any timepoint (n.s.). During the same time period, sPAP, dPAP, and mPAP decreased significantly (27 ± 9 mmHg vs. 23 ± 6 mmHg, $P < 0.01$, 11 ± 5 mmHg vs. 9 ± 3 mmHg, $P < 0.01$ and 17 ± 6 mmHg vs. 15 ± 4 mmHg, $P < 0.05$) for the non-LVAD group while the LVAD group only showed significant decrease in dPAP and mPAP (13 ± 4 mmHg vs. 8 ± 4 mmHg, $P < 0.01$ and 18 ± 5 mmHg vs. 14 ± 5 mmHg, $P < 0.05$, respectively). For the non-LVAD group, CVP and Ea were also found to be lower at 12 months compared with 1 month (2.9 mmHg ± 1.7 mmHg vs. 5.5 mmHg ± 3.3 mmHg, $P < 0.001$ and 0.33 ± 0.08 mmHg/mL vs. 0.42 ± 0.12 mmHg/mL, $P < 0.001$), while the reduction in the LVAD group were more modest (2.6 mmHg ± 2.9 mmHg vs. 6.9 mmHg ± 4.7 mmHg, $P < 0.05$ and 0.33 ± 0.18 mmHg/mL vs. 0.46 ± 0.12 mmHg/mL, $P < 0.05$). Haemodynamic data for all time points are depicted in *Table 4*.

Comparison between echocardiographic findings and invasive haemodynamic measures

At 1 month post-OHT, a weak negative linear correlation was detected for RVGLS and RVfree to PAWP ($R = -0.28$ and -0.31, $P < 0.05$ for both). RVfree also showed a weak negative correlation to CVP ($R = 0.28$, $P < 0.05$) and TAPSE showed correlation to PVR ($R = 0.28$, $P < 0.05$).

Discussion

Adaptation to functional demands and pulmonary pressures in the recipient may affect RV size and function, primarily

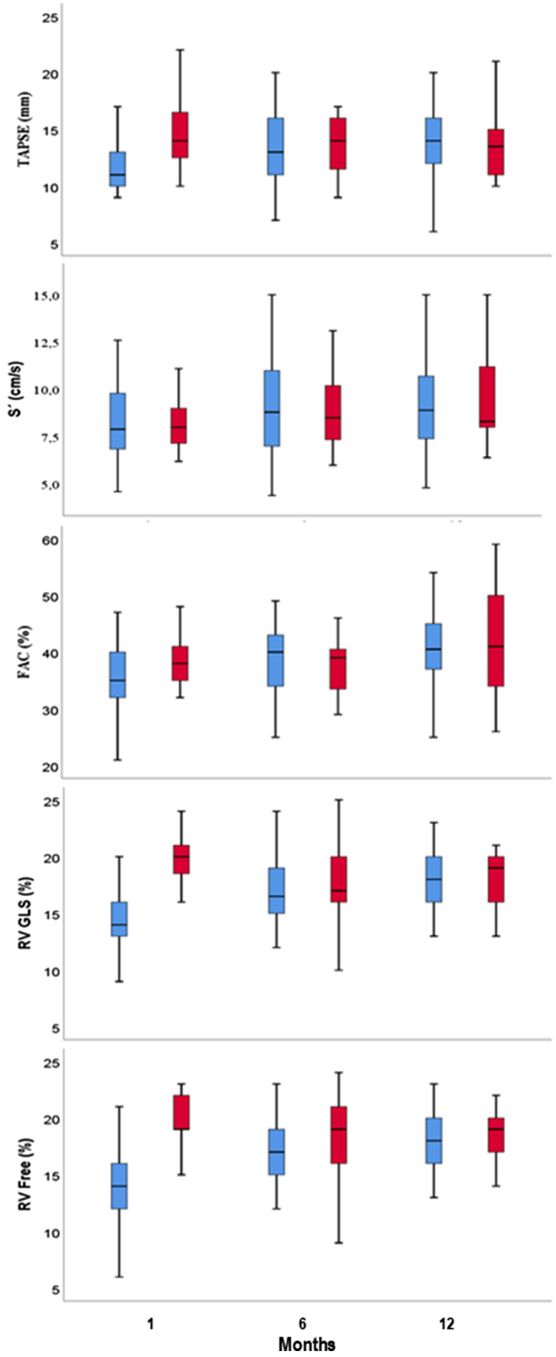
Table 4 Haemodynamic assessment with RHC for both groups at all time points

	1 month (mean ± SD)		6 months (mean ± SD)		12 months (mean ± SD)		*P* value	*P* value
	LVAD	Non-LVAD	LVAD	Non-LVAD	LVAD	Non-LVAD	LVAD	Non-LVAD
sAP (mmHg)	120 ± 18	120 ± 14	145 ± 17	139 ± 14	140 ± 18	134 ± 13	<0.001	<0.001
dAP (mmHg)	70 ± 10	73 ± 10	90 ± 12	87 ± 10	87 ± 11	85 ± 9	<0.001	<0.001
mAP (mmHg)	86 ± 10	89 ± 10	108 ± 13	104 ± 10	105 ± 12	101 ± 9	<0.001	<0.001
HR (bpm)	88 ± 13	91 ± 10	79 ± 15	79 ± 7	78 ± 12	81 ± 8	<0.05	<0.001
sPAP (mmHg)	30 ± 6	27 ± 9	24 ± 7	25 ± 7	24 ± 7	23 ± 6	n.s.	<0.01
dPAP (mmHg)	13 ± 4	11 ± 5	9 ± 5	9 ± 3	8 ± 4	9 ± 3	<0.01	<0.01
mPAP (mmHg)	18 ± 5	17 ± 6	15 ± 5	16 ± 4	14 ± 5	15 ± 4	<0.05	<0.05
TPG (mmHg)	7 ± 2	9 ± 3	7 ± 3	8 ± 3	7 ± 3	8 ± 3	n.s.	n.s.
PAWP (mmHg)	11 ± 5*	9 ± 4	8 ± 4	8 ± 4	7 ± 5	7 ± 3	n.s.	n.s.
CVP (mmHg)	7 ± 5	6 ± 3	3 ± 3	2 ± 2	3 ± 3	3 ± 2	<0.05	<0.001
CO (L/min)	6.1 ± 1.6	5.8 ± 1.1	5.8 ± 1.4	5.5 ± 0.9	5.8 ± 1.0	5.8 ± 1.2	n.s.	n.s.
CI (L/min/BSA)	3.0 ± 0.7	3.1 ± 0.6	2.8 ± 0.6	2.9 ± 0.5	2.8 ± 0.4	3.0 ± 0.6	n.s.	n.s.
SAO_2 (%)	94 ± 3	95 ± 2	97 ± 1	97 ± 2	97 ± 2	97 ± 2	<0.001	<0.001
Ea (mmHg/mL)	0.5 ± 0.1	0.4 ± 0.1	0.3 ± 0.1	0.4 ± 0.1	0.3 ± 0.2	0.3 ± 0.1	<0.05	<0.001
PVR (WU)	1.2 ± 0.4*	1.6 ± 0.6	1.2 ± 0.5	1.5 ± 0.6	1.2 ± 0.4	1.4 ± 0.5	n.s.	n.s.
RVSWI (mmHg mL m^{-2})*	407 ± 200	434 ± 216	421 ± 228	500 ± 197	433 ± 141	445 ± 167	n.s.	n.s

CI, cardiac index; CO, cardiac output; CVP, central venous pressure; dAP, diastolic arterial pressure; dPAP, diastolic pulmonary artery pressure; Ea, pulmonary effective arterial elastance; HR, heart rate; mAP, mean arterial pressure; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RVSWI, right ventricular stroke work index; sAP, systolic arterial pressure; $SAO^{2,}$ oxygen saturation, sPAP, systolic pulmonary artery pressure; TPG, transpulmonary gradient.
P values are derived from paired *t*-test and represent the difference within the group between 1 and 12 months. Significant differences between groups derived from independent sample *t*-test at any given time point are denoted by asterisks in the LVAD group.

$^{*}P < 0.05$,
$^{**}P < 0.01$,
$^{***}P < 0.001$.

Figure 1 Prospective longitudinal follow up of right ventricular function assessed with echocardiography between 1 and 12 months after heart transplantation. Box plot illustrating unaltered right ventricular function parameters between 1 and 12 months after transplantation in the LVAD group compared with gradually improved RV function parameters over the first year following OHT in the non-LVAD group. Results indicate a more rapid RV adaptation in patients pre-treated with a left ventricular mechanic assist. LVAD patients are represented by red boxes and non-LVAD group by blue boxes. Black lines in the box represent median, boxes represent interquartile range (25–75 percentile), and whiskers represent the range. FAC, fractional area change; RVfree, right ventricular strain of the lateral wall; RV GLS, right ventricular global longitudinal strain; S′, tricuspid annular systolic velocity; TAPSE, tricuspid annular plane systolic excursion.



early after transplantation. Right ventricular recovery is crucial following heart transplantation. Early RV dysfunction following OHT is a common clinical challenge resulting in prolonged time in intensive care and risk of complications due to negative effects on other organs.[14] Consequently evaluating treatments to facilitate RV to adapt to the recipient

are warranted. However, evaluation of possible impact of pre-LVAD treatment post-OHT has received limited attention.

The main findings of the current study are that (i) LVAD pre-treatment result in initially better RV function assessed with echocardiography 1 month post-OHT. Albeit within normal range, RHC revealed slightly lower mean PVR at 1 month in OHT patients pre-treated with LVAD. (ii) During 1 year follow up in OHT patients without prior LVAD treatment, the RV function parameters recovered whereas for LVAD pre-treated patients function parameters remained unaltered. Consequently, no difference between groups was detectable at 12 months.

Normal adaptation following orthotopic heart transplantation

It is not controversial that thoracic surgery affects longitudinal ventricular function. RV contractility might be affected by the explantation process including preservation leading to pan-ischaemia and myocardial stunning of the donor heart as well as factors such as ischaemic time and cause of donor death.[15–18] Moreover, it is also possible that the morphology of the RV renders it more vulnerable to ischaemia–reperfusion injury when perfusion is restored.

It has previously been shown that LV function reach a steady state already 1 month after transplantation, whereas RV function continuously improve during the first year following OHT and is normalized at 12 months. The authors could not explain the improvement in RV function parameters by changes in pulmonary pressures over time.[19] Similar findings regarding severely abnormal RV strain the first 3 months with improvement at 1 to 5 years follow up has also been reported by another group.[20] On the contrary, in another cohort, adaptation time of the RVfree was found to be close to normal 2 months after OHT and continue to increase during the first year.[21] Neither of the studies has validated the potential impact of pre-treatment with mechanical assist on RV function parameters.

Impact of LVAD pre-treatment on ventricular function following orthotopic heart transplantation

In this study, the LVAD group had almost normal echocardiographic RV function parameters at 1 month post-OHT, while in the non-LVAD group, echocardiographically derived parameters of RV function were significantly decreased. However, since echocardiographic data implying reduced RV function was not confirmed by differences in RHC (i.e. CVP and CO) between the two groups, it may not accurately reflect clinical RV dysfunction. This discrepancy between echocardiographic and RHC derived data may partly be explained methodologically because the echocardiographic measurements included in this study mostly reflect the longitudinal component of RV function. Clinical factors (e.g. intraoperative bleeding, duration of inotropic support, and occurrence of severe primary graft dysfunction) were similar between the two groups and could not explain the difference observed in RV-function parameters. The presence of pre-existing PH or increased PVR is described as disadvantageous for RV function in the non-adapted donor heart.[5,8,9] Although within normal range, at 1 month, PVR was lower in the LVAD group, which may partly explain the difference in longitudinal RV function. Interestingly, at 1 month, the LVAD group revealed slightly higher PAWP. The reason for this finding is uncertain, but, if not just a random finding, could relate to differences in RV improvement between the groups. This theory is partly supported by the tendency of slightly higher CO in the LVAD group.

Differences detected in echocardiographic parameters might be associated with selection bias related to differences in patient characteristics pre transplantation. However, haemodynamic parameters, including CVP, were comparable between the groups when accepted for OHT. This reduces the likelihood that there were significant differences in clinical RV function. It would, of course, be interesting to compare RHC pressures obtained directly before OHT between the two groups. Unfortunately, such data are not available because RHC is not performed in clinical practice in the acute setting when the patient is scheduled for OHT. Consequently, pre-transplant RHC data merely reflect baseline characteristics when evaluated for OHT and before decision of LVAD support. This study could not detect any differences, based on pre-existing sPAP $>$ 50 mmHg, TPG $>$ 15 mmHg, or PVR $>$ 5 WU, in RV function parameters at any time point post-OHT in either of the study groups. In the LVAD group, a possible explanation for this finding could be that catheterization data were obtained prior to LVAD support, thus pulmonary pressures may have been altered before OHT. However, this hypothesis does not explain why no difference was detected within the non-LVAD group. While we are unable to correct for selection bias, decision to utilize LVAD 'bridging' will reflect broadly more severe disease and therefore would not be expected to be associated with better early RV function in the allograft heart.

Left ventricular assist device treatment has been demonstrated to reduce mPAP and sPAP with sustained effect three to 5 years following OHT.[22] Moreover, in a small study, LVAD support has been shown to progressively increase CO and decrease PAWP in the early period following LVAD implantation. Furthermore, markers of RV adaptation (i.e. right ventricular stroke work index, RAP, and RAP/PAWP) were unaltered acutely after implantation but progressively improved during continued LVAD support. The authors also found that the total RV load (i.e. Ea) as well as PVR declined progressively.[23] This is in line with our findings where a small

subgroup of our LVAD patients was re-evaluated with RHC while on LVAD support. In this subgroup, we demonstrated a significant reduction in pulmonary pressures, PVR and PAWP. Therefore, we find it plausible that the reduction in PVR occurring during LVAD support had a positive impact on RV function parameters post-OHT.

In our material, the timespan between initial RHC and transplant varied from 6 days to almost 3 years. The time between OHT decision and transplant were significantly higher for patients on LVAD support. This is not surprising because LVAD treatment is used not only to bridge but also to recondition the patient before transplantation. Prolonging the time before receiving an allograft could be postulated to negatively affect the pulmonary vascular circuit. According to our results, the positive impact on pulmonary pressures and PVR accomplished by LVAD treatment is potentially an important consideration in the risk–benefit evaluation of LVAD implantation pre-OHT.

Six patients (LVAD $n = 1$) were transplanted within 1 month from RHC. It could be hypothesized that some of these patients were transplanted related to urgent circumstances and may have received a less compatible allograft although others were simply fortunate to find an early good match. Additionally, it is reasonable to believe that LVAD treatment for less than 1 month might not be sufficient to cause a clinically relevant decrease in pulmonary pressures. It has previously been demonstrated that PVR and mPAP is decreased 6 months after LVAD implantation, after which no additional reduction was detected.[24] In our study, however, we could not detect any differences between the small sample of six patients compared with the rest of the cohort.

Despite considering that echocardiographically derived RV function parameters may not reflect global RV function or properly reveal clinical RV dysfunction, it is noteworthy that these parameters were stable in the LVAD group during follow up while a gradual improvement was observed in the non-LVAD treatment group. In neither of the two groups could enlargement in RV size or augmented CVP be detected, supporting that no clinically important RV dysfunction was present in our cohort during follow up. A reduction in mPAP, mRAP, and Ea were detected in both groups at 12 months compared with 1 month. The improvement seen in non-LVAD group can therefore not solely be explained by differences in RHC parameters but may be a result of a prolonged adaptation period. Even though the design of this study does not allow formal conclusions, a plausible explanation to our findings is that bridging with LVAD results in better RV-pulmonary artery coupling. Our results suggests that pre-treatment with LVAD initialize a beneficial conditioning-process that may positively affect the RV of the allograft and thereby accelerate the potential normalization process.

Our study of OHT patients revealed initially better echocardiographic RV function parameters accompanied by a lower PVR in patients pre-treated with LVAD. During the first year of follow up RV function parameters increased in the non-LVAD group and at 1 year, the groups were comparable. The results of our study support that LVAD treatment while awaiting OHT appears to expedite early improvement of RV function following transplantation and is potentially a very important consideration in the risk–benefit evaluation for LVAD implantation pre-OHT. The finding that measures of RV function improvement occur more rapidly in patients with bridging LVAD may also have clinical impact when evaluating patients suitable for transplantation.

To summarize, our results indicate that pre-treatment with LVAD is associated with significantly better RV function early following OHT and that RV function progressively improved in the non-LVAD the first year. The most plausible potential mechanisms, involved in how LVAD pre-treatment might affect RV function post-OHT, that may explain our observations are as follows: (i) through decreased PVR and pulmonary pressures and (ii) Through better RV-pulmonary artery coupling. (iii) Although less likely, possible differences between the groups regarding haemodynamic parameters pre-OHT might have impacted on the results. The clinical implication of our findings is uncertain at the present stage because the impact on long-term morbidity or mortality has not been explored. Nevertheless, we find it reasonable to believe that an accelerated improvement after surgery is beneficial and desirable.

Study limitations

We wish to point out that the study has limitations that merit consideration. The RHC values reported in *Table 2* pre-OHT are challenging to interpret because the timespan between evaluation and OHT varies from 6 days to 2.8 years and were all performed before LVAD implantation. This account for the fact that evaluation of features like pre-transplant PH may be difficult to interpret. Moreover, parameters that are not reported pre-OHT were not routinely assessed in the haemodynamic evaluation and therefore not possible to retrieve.

Concerns could be raised about the limited sample size. However, given that OHT cohorts often are quite limited in single-centre studies, we regard the sample size large enough to adequately reflect differences between the groups. There is an obvious consideration of population differences based upon selection bias in receiving an LVAD. This has been discussed within the text.

A well-known disadvantage of STE is the limited comparability for absolute values between different software and differences between vendors is not fully solved. Our study was performed using Philips software and the absolute values reported may only be applicable to patients examined with the same system. However, the difference reported between

groups should not be influenced by this matter. Furthermore, it should be noted that the Philips software used in the study for RV strain analyses is developed and validated for the LV and no validation against RV dedicated software has been conducted. Radial strain and strain rate as well as torsion and 3D parameters were not included in our analysis due to the initial study design.

A minor concern is that allografts where donor death was due to cardiac arrest (n = 3) were only present in the non-LVAD group. The possible impact of cardiac arrest on RV function pre-explantation is not validated, but the transplant coordinates routinely only accept donor hearts with ventricular function that are normal or at most mildly reduced. In this study, the mean value of RV-function parameters in these three patients was similar to the rest of the group.

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Conflict of interest

All authors have no conflicts of interest to declare.

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