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ORIGINAL RESEARCH ARTICLE

Comparison of continuous-flow ventricular assist device therapy with intensive medical therapy in fixed pulmonary hypertension secondary to advanced left heart failure

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Abstract

Aims Both ventricular assist device (VAD) and pulmonary vasodilator therapy have been shown in uncontrolled studies to improve pulmonary hypertension secondary to advanced left heart failure (Group 2 PH). This study aimed to compare haemodynamic benefits and survival in patients with fixed Group 2 PH treated with continuous-flow VAD to intensive medical therapy.

Methods and results Ninety-five patients listed for heart transplantation with sequential right heart catheters were studied, 24 patients having fixed Group 2 PH (as defined by cardiac index < 2.8 L/min/m^2, pulmonary capillary wedge pressure ≥ 15 mmHg, and transpulmonary gradient ≥ 15 mmHg or pulmonary vascular resistance > 3.0 WU, unresponsive to vasodilator challenge). Ten patients received VAD therapy, and 14 patients received standard heart failure therapy with or without sildenafil, nitrates, or endothelin receptor antagonists.

At repeat right heart catheterization, patients treated with VAD therapy demonstrated significant improvement in both transpulmonary gradient (19 vs. 12 mmHg, $P = 0.046$) and pulmonary vascular resistance (6.5 vs. 2.9 WU, $P = 0.003$) compared with baseline, while those treated with medical therapy did not (20.9 vs. 20.3 mmHg and 6.5 vs. 6.4 WU, P = NS for both). Patients who received VAD therapy were significantly more likely to achieve normalized transpulmonary gradient (8/10 vs. 4/14, $P = 0.013$) and were more likely to be listed for orthotopic heart transplantation (7/10 vs. 4/14, $P < 0.05$). There were no significant differences between groups in terms of all-cause mortality.

Conclusions Continuous-flow VAD therapy more effectively reverses fixed Group 2 PH compared with medical therapy alone and may allow a higher rate of listing for orthotopic heart transplantation.

Keywords LVAD; Pulmonary hypertension; Heart transplantation; Hemodynamics

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Introduction

Pulmonary hypertension (PH) secondary to left heart failure, classified as Group 2 PH according to the Nice 2013 classification,[1] occurs in more than 60% of patients with moderate to severe systolic left heart failure and up to 80% of patients with heart failure with preserved ejection fraction.[2–4] In early stages, Group 2 PH is termed 'reactive' as elevated pulmonary pressures respond to acute vasodilators. Over time, passive venous congestion results in capillary and arterial remodelling and 'fixed' PH ensues, where pulmonary pressures become unresponsive to vasodilators during right heart catheterization (RHC).[5]

Fixed PH is a contraindication for orthotopic heart transplantation (OHTx) due to risks of post-transplant right heart failure, which is associated with increased mortality.[6–12]

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Uncontrolled case series have demonstrated that sustained medical therapy with the phosphodiesterase-5 inhibitor sildenafil reduces pulmonary vascular resistance (PVR) in some patients allowing successful heart transplantation.[13,14] However, most often fixed PH persists, and these patients have traditionally been listed for heterotopic heart transplantation or combined heart–lung transplantation, both associated with increased morbidity and mortality compared with isolated OHTx.[15–18]

Left ventricular assist device (LVAD) therapy has been demonstrated to reverse PH to varying degrees by chronically mechanically unloading left-sided pressures,[11,19–24] permitting listing for OHTx in some patients.[20–23,25] However, the absence of control arms in these studies makes determination of the specific contribution of LVAD therapy—as opposed to concurrent medical therapy—problematic. Further, data remain limited comparing the success of bridging fixed PH patients to listing for OHTx using ventricular assist device (VAD) and medical therapy and morbidity and survival outcomes post-transplant in these respective groups.

This study aimed to determine how successfully PH could be normalized with VAD therapy in fixed Group 2 PH patients, compared with a contemporaneous control group of patients treated with medical therapy alone. Secondly, the study aimed to analyse longer term outcomes such as successful bridge to OHTx and survival rates compared with medically treated patients. Group 2 PH was defined using haemodynamic criteria outlined by Mehra *et al*. in the 2016 guidelines on Listing Criteria for Heart Transplantation (described in the next section).[26] We hypothesized that VAD therapy would improve fixed Group 2 PH more effectively than medical therapy alone, leading to higher transplantation rates and improved survival.

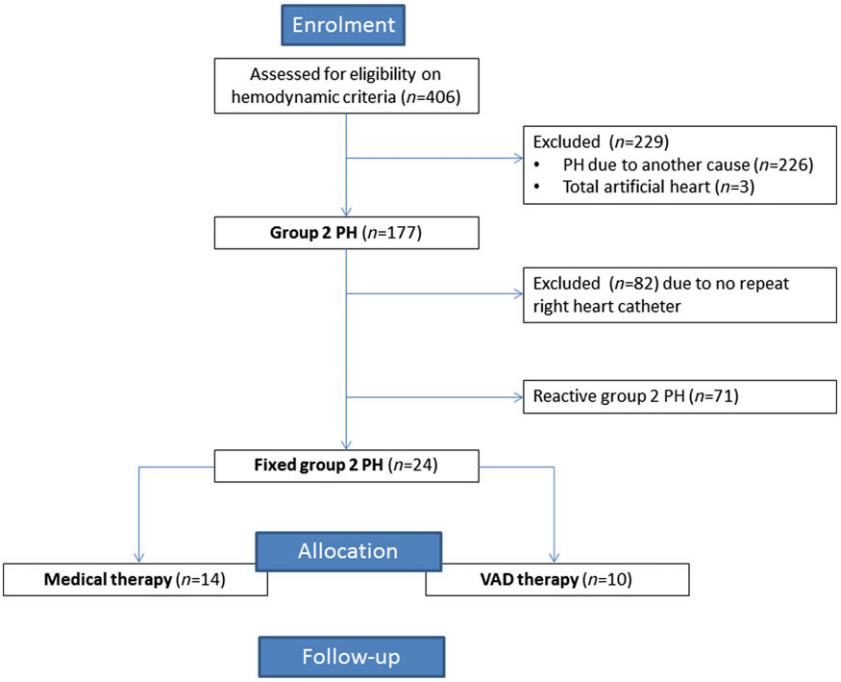
Methods

Patient population

Data from 177 consecutive patients with moderate to severe systolic or diastolic heart failure undergoing RHC at an academic transplant centre between June 2005 and October 2016 were analysed (*Figure 1*). Patients with sequential RHC were identified (n = 95). From that, those with fixed Group 2 PH on initial RHC classified on haemodynamic data were included. Patients were studied according to management strategy—intensive medical therapy or VAD therapy. In all patients who received VAD therapy, baseline RHC was performed prior to VAD insertion. This study was approved by the Institution's Human Research Ethics Committee (SVH HREC #13/206).

As described by Mehra *et al*.,[26] Group 2 PH was defined by thermodilution haemodynamic criteria of cardiac index (CI) < 2.8 L/min/m^2 with pulmonary capillary wedge pressure (PCWP) $>$ 15 mmHg and either transpulmonary gradient (TPG) $\geq$ 15 mmHg or PVR $>$ 3.0 WU. Fixed PH was defined by a failure to achieve TPG $\leq$ 15 mmHg and PVR $<$ 3.0 WU

Figure 1 Study outline. Group 2 PH, pulmonary hypertension secondary to left heart failure; PH, pulmonary hypertension; VAD, ventricular assist device.



despite a vasodilator challenge (*Figure 1*).[26] The choice of pulmonary vasodilator was determined by the procedural cardiologist and included intravenous glyceryl trinitrate, sodium nitroprusside, or inhaled nitric oxide either singly or additively.

Patients were excluded if PH was due to causes other than left heart failure (e.g. idiopathic pulmonary arterial hypertension, chronic thrombo-embolic PH, or PH due to respiratory disease or haemodynamically significant valvular heart disease without heart failure). All patients were treated with standard heart failure therapy with or without specific pulmonary vasodilating agents (oral nitrates, sildenafil, or endothelin receptor antagonists as tolerated), at the discretion of the treating physician.

Ventricular assist devices

Ventricular assist device therapy consisted of third generation centrifugal axial continuous-flow devices as outlined in *Table 2*. All patients were treated as bridge to transplantation.

Outcomes

Follow-up RHC data were analysed to determine the degree of reversal of PH, as measured by TPG and PVR. Successful reversal of PH was defined by mean pulmonary arterial pressure (mPAP) $\leq$25 mmHg, TPG $<$ 15 mmHg, and PVR $\leq$ 3.0 WU. Patient progress, the number of hospital admissions post-treatment (cardiovascular and all-cause), laboratory haemoglobin and creatinine at follow-up, VAD-related complications, transplantation status, length of stay in the intensive care unit, and 2-year survival were analysed.

Statistical analysis

Statistical analysis was performed using Prism 7.03 (GraphPad Software, Inc., SD) and Microsoft Excel. Continuous variables are expressed as mean ± standard deviation and categorical variables as the number and percentage. Continuous variables were analysed using repeated-measures ANOVA or the Student's *t*-test as appropriate. Categorical variables were analysed using χ^2 or Fisher's exact test. mPAP, TPG, and PVR at follow-up were compared with baseline values using the paired *t*-test. Patients were censored at the study end date or the last visit if lost to follow-up. A *P*-value $<$0.05 was considered statistically significant.

Results

We identified 406 patients in our database who met haemodynamic criteria for Group 2 PH. After review of medical and echocardiogram reports, 226 patients were excluded because PH was due to causes other than left heart failure (idiopathic pulmonary arterial hypertension, chronic thrombo-embolic PH, respiratory disease, or valvular heart disease), and three patients were excluded because of treatment with total artificial hearts. Of the 177 patients with PH due to left heart failure, 82 did not undergo repeat RHC and were excluded. Of the remaining 95 patients, 24 had fixed PH and were included in the analysis (*Figure 1*). Of these patients, 10 were managed with VAD therapy, while 14 were managed with medical therapy alone.

Functional class and comorbidities

There were no significant differences between groups in terms of age, gender, or body mass index. Patients in the VAD group had higher median New York Heart Association functional class and higher Interagency Registry for Mechanical Assisted Circulatory Support (INTERMACS) class but lower serum creatinine compared with the medical group. Patients in the VAD group had significantly lower left ventricular ejection fraction and demonstrated a non-significant trend towards impairment of right ventricular function (*Table 1*). There were no significant differences in cerebrovascular accidents, chronic obstructive pulmonary disease, or prior cardiac surgery (data not shown).

Treatment

Two patients in the VAD group received biventricular support because of severe right ventricular dysfunction. All VAD patients received warfarin (target international normalized ratio 2.0–3.0) and antiplatelet therapy (either aspirin 100 mg or clopidogrel 75 mg daily or in combination at the discretion of the treating physician) after device implantation. More patients in the medical group than the VAD group received beta-blocker therapy. Otherwise, there were no significant differences between groups in terms of standard heart failure therapy. Similar numbers of patients in each group were administered pulmonary vasodilator therapy. The mean duration from commencement of pulmonary vasodilator therapy to follow-up RHC was also similar across the two groups (*Table 1*).

Haemodynamic profile

There were no significant differences in mPAP, PCWP, TPG, CI, or PVR between groups at baseline (*Table 2*). At follow-up RHC, patients in the VAD group had significantly lower mPAP, PCWP, TPG, and PVR and a significantly higher CI compared with baseline. Patients in the medical therapy group demonstrated no significant change compared with baseline across these variables. As a result, patients in the VAD group

Table 1 Patient demographics

		VAD therapy (n = 10)	Medical therapy (n = 14)	P-value
Age (years)		49.9 ± 10.8	52.1 ± 11.0	0.62
Male [number (%)]		8/10 (80)	10/14 (71)	0.63
Aetiology of HF [number (%)]	Dilated CM	4/10 (40)	7/14 (50)	
	Ischaemic CM	2/10 (20)	3/14 (21)	
	Hypertrophic CM	1/10 (10)	0/14 (0)	
	Other	3/10 (30)	4/14 (29)	
LVEF (%)		20.56	27.9	0.048
RV moderately or severely impaired [number (%)]		6/10 (60)	3/14 (21)	0.054
Median INTERMACS class		2	5	
Median NYHA class		4	3	
BMI (kg/m^2)		25 ± 4.7	27 ± 4.1	0.17
Haemoglobin (g/L)		127 ± 27.4	137 ± 20.6	0.40
Creatinine (μmol/L)		110 ± 20.7	139 ± 29.8	0.012
Serum sodium (mmol/L)		138.7 ± 4.2	138.7 ± 3.7	0.99
Serum albumin (g/L)		38.9 ± 8.6	43.2 ± 7.0	0.20
Time RHC 1 to 2 (months)		8.5 ± 4.3	10.9 ± 19.1	0.67
Time VAD to RHC 2 (months)		5.1 ± 3.3	N/A	
Type of mechanical support [number (%)]	HeartWare LVAD	8/10 (80)	N/A	
	HeartWare BiVAD	2/10 (20)	N/A	
Heart failure therapy [number (%)]	ACE-Inhibitor	6/10 (60)	10/14 (71)	0.56
	Beta-blocker	3/10 (30)	11/14 (79)	0.017
	Diuretic therapy	8/10 (80)	14/14 (100)	0.08
Pulmonary vasodilator therapy [number (%)]	Any	6/10 (60)	11/14 (79)	0.32
	PDE-5 inhibitor	6/10 (60)	9/14 (64)	
	ERA	1/10 (10)	3/14 (21)	
	Nitrate	0/10 (0%)	2/14 (14)	
Time from commencement of pulmonary vasodilator to RHC 2 (months)		5.7 ± 4.9	5.0 ± 5.2	0.80

ACE, angiotensin-converting enzyme; BiVAD, biventricular assist device; BMI, body mass index; CM, cardiomyopathy; ERA, endothelin receptor antagonist; HF, heart failure; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; N/A, not applicable; NYHA, New York Heart Association; PDE-5, phosphodiesterase-5; RHC, right heart catheterization; RV, right ventricle; VAD, ventricular assist device.
Data are presented as mean ± standard deviation unless otherwise specified.

Table 2 Haemodynamic parameters at baseline (RHC 1) and post-treatment (RHC 2)

	RHC 1			RHC 2			RHC 1 vs. 2 (P-value)	
	LVAD group	Med group	P-value	LVAD group	Med group	P-value	LVAD group	Med group
mPAP	47.7 ± 4.8	46.5 ± 9.7	0.70	28.0 ± 8.2	45.8 ± 6.9	<0.001	<0.001	0.71
PCWP	28.7 ± 4.9	26.0 ± 6.8	0.27	16.0 ± 3.6	25.6 ± 7.6	<0.001	<0.001	0.85
TPG	19.0 ± 5.8	20.9 ± 7.0	0.49	12.0 ± 5.2	20.3 ± 8.4	0.009	0.046	0.54
DPG	7.9 ± 7.1	7.3 ± 7.1	0.84	3.2 ± 2.9	7.4 ± 6.6	0.09	0.10	0.85
CI	1.6 ± 0.3	1.8 ± 0.5	0.23	2.5 ± 0.5	1.7 ± 0.6	0.002	<0.001	0.60
PVR	6.5 ± 1.8	6.4 ± 1.8	0.88	2.9 ± 1.6	6.5 ± 3.2	0.002	0.003	0.88

CI, cardiac index; DPG, diastolic pulmonary gradient; LVAD, left ventricular assist device; mPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RHC, right heart catheterization; TPG, transpulmonary gradient.

had significantly lower TPG and PVR compared with patients in the medical therapy group at follow-up RHC (*Table 2*, *Figure 2*). Furthermore, patients who received VAD therapy were significantly more likely to achieve normalized TPG at repeat RHC (8/10 vs. 4/14, P = 0.013).

Clinical outcomes

At the end of the study period, 5/10 (50%) of VAD patients and 6/14 (43%) of medical therapy patients remained alive (*Table 3*, *Figure 3*). The deaths in the VAD group were due to LVAD thrombus (one patient), intracerebral haemorrhage (two patients), pulmonary haemorrhage (one patient), and sepsis (one patient). The deaths in the medical therapy group were due to end-stage heart failure (six patients) and unknown causes (two patients).

Significantly, more VAD managed patients were listed for OHTx (7/10) compared with medically managed patients (4/14), P = 0.045. Of these, four patients successfully underwent cardiac transplantation, and all remained alive at the conclusion of the study (mean 416 days post-transplantation). One patient

Figure 2 Comparison of mean pulmonary arterial pressure (mPAP), mean pulmonary capillary wedge pressure (mPCWP), cardiac index, transpulmonary gradient (TPG), and pulmonary vascular resistance (PVR) at baseline and follow-up, stratified by therapy. Values are displayed as the mean and upper 95% confidence limit. *$P < 0.05$ vs. baseline; **$P < 0.01$ vs. baseline; ***$P < 0.01$ vs. ventricular assist device (VAD) therapy.

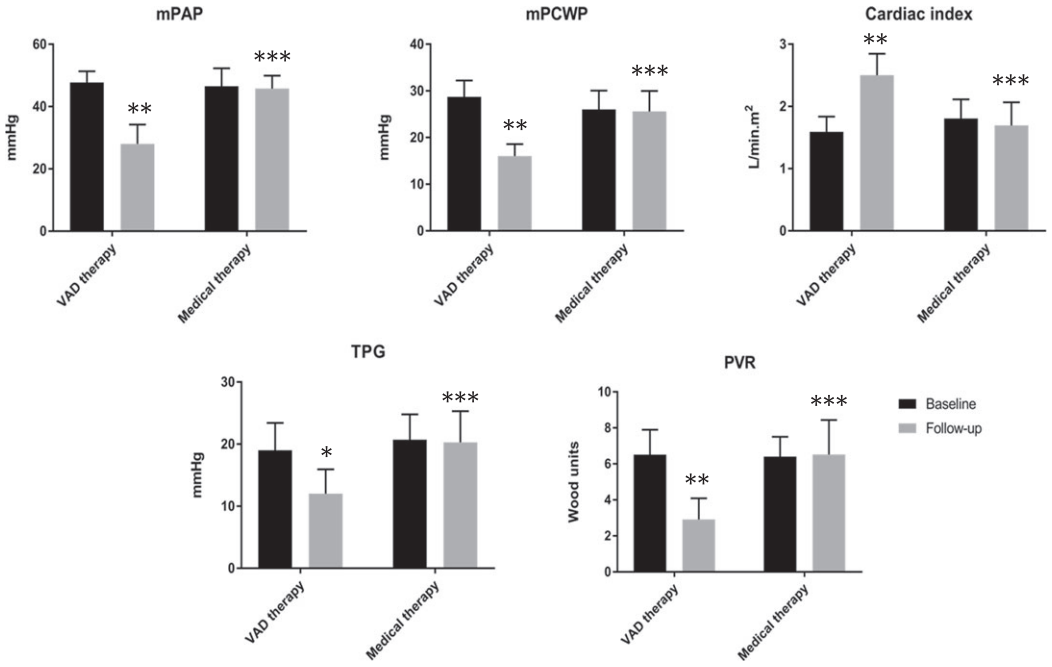
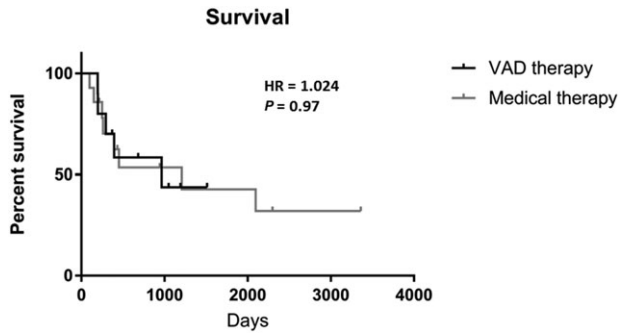


Table 3 Clinical outcomes

	VAD therapy	Medical therapy	*P*-value
Length of follow-up (years)	1.9 ± 1.3	2.8 ± 2.9	0.36
Length of stay post-VAD (days)	60.3 ± 50.8	N/A	
Alive at study end	5/10 (50%)	6/14 (43%)	0.72
Alive at 1 year post initial RHC	7/10 (70%)	10/14 (71%)	0.93
Listed for OHTx	7/10 (70%)	4/14 (28%)	0.044
Died while on OHTx waiting list	3/7	1/4	
Transplanted	4/10 (40%)	2/14 (14%)	0.15
Alive, not transplanted	1/10 (10%)	4/14 (28%)	0.26

OHTx, orthotopic heart transplantation; N/A, not applicable; RHC, right heart catheterization; VAD, ventricular assist device.

Figure 3 Kaplan–Meier curve showing survival following initial right heart catheterization. Patients were censored at the study end date or last visit if lost to follow-up. Differences between groups were calculated using log-rank test. HR, hazard ratio; VAD, ventricular assist device.



in the VAD group remained alive with VAD *in situ*. Five patients in the VAD group died without undergoing transplantation, three of whom were on the waiting list for OHTx. Four out of 14 patients in the medical therapy group were actively listed for OHTx. Of these, two patients successfully underwent cardiac transplantation, and both remained alive at the conclusion of the study (mean 1490 days post-transplantation). One patient was listed for OHTx but subsequently de-listed due to improved functional status, while one patient died while on the active waiting list. Ten patients in the medical therapy group were not listed for OHTx (three did not require transplant listing; three died during the workup process; two were listed for combined heart–lung transplantation; two were listed for heterotopic transplantation). The four patients managed with intensive medical therapy listed for combined heart–lung or heterotopic transplantation all died while awaiting transplant.

Discussion

Patients with fixed PH due to advanced left heart failure are a very high-risk cohort. Rates of heterotopic heart transplantation and heart–lung transplantation—the only available options when orthotopic heart transplant is rendered unfeasible due to fixed PH—have declined significantly in recent years, and these procedures are associated with a worse prognosis than orthotopic heart-only transplant.[27] Reversing fixed PH is clearly, therefore, of paramount importance. Uncontrolled studies to date have shown that VAD therapy can normalize PH in these patients, with successful bridging to OHTx.[11,18,20–22,28] However, uncontrolled case series have also demonstrated the efficacy of pulmonary vasodilators in similar patients,[13,14] raising doubts as to the specific contribution of each therapy.

This study aims to resolve this by assessing the haemodynamic effects of continuous-flow VAD therapy on fixed PH using a medical therapy group for comparison. Our data demonstrate that continuous-flow VAD therapy is more effective at reversing fixed PH than medical therapy alone. Despite the increased cardiac output resulting from VAD support, there was a significant overall reduction in TPG, reflecting markedly reduced PVR. Eight out of 10 patients in the VAD therapy group demonstrated reduction of TPG to $<$15 mmHg, a gradient that would permit OHTx. In contrast, only four out of 14 patients in the medical therapy group demonstrated TPG $<$ 15 mmHg at repeat RHC, resulting in significantly lower rates of listing for heart transplantation in this study.

There was no significant difference between groups in terms of the number of patients administered pulmonary vasodilators, rendering this an unlikely source of confounding. Furthermore, both patients in the VAD group who did not achieve a TPG $<$ 15 mmHg were on pulmonary vasodilators, compared with only four out of the eight VAD patients who achieved reversal of PH. In the medical therapy group, pulmonary vasodilators were administered to nine out of the 10 patients who did not demonstrate reversal of PH, compared with two out of four patients who did demonstrate reversal. Taken together, these data represent convincing evidence as to the lack of efficacy of pulmonary vasodilators alone in reversing fixed PH in the setting of advanced left heart failure. Further, while this study is not designed to specifically assess the use of pulmonary vasodilators following VAD insertion, our data nevertheless fail to present a convincing case for their efficacy in this context. This question will be specifically addressed in the SOPRANO trial (clinicaltrials.gov NCT02554903), comparing the effects of macitentan with placebo on PVR following LVAD insertion.

Despite the haemodynamic benefits of VAD therapy, there were no significant differences between groups in terms of survival. Only four out of the 10 patients in the VAD group have thus far successfully undergone transplantation, with five out of 10 patients having died prior to transplantation. All deaths occurred greater than 30 days post-VAD insertion, suggesting that the high mortality in this group may have been related to the inherent risks associated with VAD therapy in this high-risk patient population rather than operative factors. The similar survival rates demonstrated in the medical therapy group —despite relative lack of haemodynamic improvement— likely reflect a lesser severity of heart failure in this group. The high mortality even in patients without VAD in this cohort attests to the high-risk nature of fixed PH in the setting of advanced heart failure This is supported by baseline differences between groups in terms of ejection fraction, New York Heart Association class, and INTERMACS class. As a result, any conclusions from this data regarding clinical decision-making should be made with caution: the implication is not that all patients with fixed Group 2 PH should undergo VAD insertion, rather that in selected patients within this group who require advanced therapy, VAD may be considered as a bridge to candidacy. An alternative—long-term inotrope therapy—was examined by Al-Kindi *et al*. in a retrospective analysis of patients with Group 2 PH in the United Network for Organ Sharing registry.[29] There were similar rates of PH reversal in patients treated with LVAD and inotrope therapy prior to heart transplantation, highlighting the potential role of the latter therapy, as well as the need for individualized decision-making in the absence of convincing evidence for one approach over the other.

To add a further note of caution, post-VAD complications were high, such as bleeding, take-back to theatre, VAD thrombosis, deconditioning, and prolonged hospital stays. Fixed PH patients in more critical INTERMACS classes may therefore be a group with more chronic and severe stages of advance heart failure, with resultant cardiac cachexia and generalized frailty, placing them at significantly higher risk of morbidity and mortality despite VAD therapy. It may therefore be necessary to use tools, such as 'frailty indices' to determine the suitability of these patients for VAD and transplantation.[30] These considerations need to be balanced against the high mortality associated with not implanting LVAD in the group of fixed PH patients waitlisted for heterotopic or combined heart–lung transplantation. In our study, all such patients died prior to transplantation.

Limitations

The inclusion of a retrospectively identified control group raises the possibility of confounding, particularly given the baseline differences between the two groups in WHO functional and INTERMACS class, variable intervals between RHCs, and differences in medical therapy regimens between the two groups. Most of these differences would have favoured the medical therapy group in severity however. However, the two groups demonstrated very similar haemodynamics at baseline. In addition, a number of patients in the VAD

group were treated with pulmonary vasodilators. However, given these agents were employed in both groups, the ultimate difference in pulmonary haemodynamic outcomes must logically be ascribed to VAD, rather than medical therapy. This study is hypothesis-generating in nature, and as stated, any conclusions should be drawn with caution and bearing in mind its limited scope.

Conclusions

This study demonstrates that continuous-flow VAD therapy provides significant haemodynamic benefits in patients with fixed Group 2 PH, with a significantly higher rate of listing for OHTx in this cohort, allowing the use of this therapy as a 'bridge to candidacy'. LVAD therapy should therefore be actively considered in those waiting for dual organ or heterotopic heart transplantation. Further prospective studies are warranted to determine whether these haemodynamic benefits translate to improved clinical outcomes.

Conflict of interest

None declared.

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