Exercise hemodynamics as a predictor of myocardial recovery in LVAD patients

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Abstract

Mechanical circulatory support using left ventricular assist devices (LVADs) has been demonstrated to improve survival in patients with advanced heart failure. LVAD therapy also promotes reverse ventricular remodeling, which in some cases has led to sufficient myocardial recovery to allow LVAD removal. Identification of suitable patients for LVAD removal however remains challenging. We investigated the hypothesis that invasive assessment of exercise hemodynamics may provide added information in relation to the assessment of contractile reserve in potential candidates for LVAD explant.

Background

Left ventricular assist device (LVAD) implantation has revolutionized the management of advanced heart failure by improving survival, functional capacity and quality of life[1]. While principally utilized as destination therapy (DT) or bridge to cardiac transplantation (BTT)[2 3], LVAD is also recognized as providing a potential bridge to recovery *(BTR)* by ventricular unloading and reverse remodeling, thus obviating the need for cardiac transplantation[1 4]. BTT therapy remains relatively fixed due to a limited donor cohort[3], while DT and BTR are being increasingly utilized in patients either not appropriate for cardiac transplantation or not requiring transplant due to sufficient myocardial recovery[5]. Although successfully explantation rates vary widely[6], early recurrence of left ventricular failure has limited the durability of recovery[7]. Despite this, five-year survival rates are over 70% - similar to patients who undergo transplantation[3].

The benefits from LVAD implantation have previously been described and include improvements in resting systemic hemodynamics and reduced ventricular wall stress, together with reduced neurohormonal activation leading to reverse cardiac remodeling. In conjunction, LVAD therapy reverses end organ dysfunction by improved tissue perfusion[8]. At the cellular and tissue level, circulatory support improves cardiomyocyte calcium handling and restores myocyte size towards normal[9]. Despite these beneficial effects, the translation of these molecular and cellular changes into sufficiently stable cardiac recovery to allow LVAD removal is rare[6] and poorly understood.

Thus although varying degrees of cardiac recovery may be observed, there are no uniform systematic guidelines for assessing the extent of improvement in ventricular

performance, particularly in relation to the capacity to respond to stress. Exercise testing to assess inotropic reserve has been used in patients with heart failure in the absence of circulatory support[10]. In this study, we hypothesized that invasively measured indices of ventricular performance during exercise may provide added information in the assessment of myocardial recovery and in the suitability for device removal.

Methods

Between April 2012 and June 2015, a total of 53 patients underwent LVAD implantation, of whom 21 underwent detailed rest and exercise right heart catheterization. Haemodynamic parameters were assessed during incremental symptom-limited supine cycle ergometry. Statistical analysis was performed using SPSS 23.0 (IBM Corporation, Armonk, NY, USA). Quantitative group data are presented as mean ± SD, however due to small data sets with non-normally distributed data, differences between patients were analyzed using the non-parametric Mann-Whitney *U* test. Differences between groups were considered significant for two-sided P value <0.05.

4 of the 21 patients subsequently underwent uncomplicated LVAD explantation due to ventricular recovery. There were no significant differences in baseline characteristics, as shown in Table 1. During follow-up, 94% of non-explant patients underwent cardiac transplantation; the remaining patient continued destination therapy. Of those who were explanted, 1 patient suffered a right middle cerebral artery (MCA) infarct 4 months post device explantation. In the non-explant cohort, there were two deaths; one patient died of sepsis with multiorgan failure 4 months post transplant, and the other developed worsening cardiac failure following an episode of rejection 1 year post cardiac transplantation.

Results

Explant patients demonstrated a more robust haemodynamic response compared to non-explant patients, including a greater increment in cardiac output compared with that in the non-explant group 7.9±1.8 vs 3.4±2.22 L/min (p = 0.015). The rise in pulmonary capillary wedge pressure indexed to the amount of work performed was significantly lower in the explant group (0.15±0.09 vs. 0.32±0.18 mmHg/Watt, p=0.011).

Discussion

This brief report highlights the significantly higher augmentation in cardiac output and lower indexed filling pressures in patients who were successfully bridged to recovery from mechanical support. These results from a small cohort demonstrate the utility of exercise right heart catheterization as an additional modality to provide further information regarding the decision for VAD explantation.

LVAD support has been shown to facilitate reverse remodeling[1] through mechanical left ventricular unloading and cardiac reconditioning, with normalization of neurohormonal milieu[11]. Previous studies have demonstrated that exercise haemodynamics and overall performance are improved in patients on mechanical support compared to non-LVAD heart failure patients awaiting transplant[10]. The biochemical and molecular changes are well established, and lead to structural and functional improvements[12], with reversal of stress-related loading of the myocardium[8], alleviating LV pressure and volume loading and restoration of systemic blood flow[1 4]. Mechanical unloading promotes reverse remodeling by upregulation of a number of genes responsible for cell signaling pathways and mechanosensation, as well as promoting cell growth, DNA repair and reduced apoptosis[1]. Calcium reuptake and

storage is also promoted which improves cardiac contractility[9]. Molecular studies have demonstrated specific changes in sarcomeric and cytoskeletal proteins (including dystrophin) in the myocardium of patients with functional myocardial recovery[8], however despite the magnitude of these changes, numerous studies have concluded that molecular and histological changes are not necessarily consistent with clinical myocardial recovery[6].

Right heart catheterization under resting conditions has been utilized to assist with VAD weaning, and stable hemodynamic parameters are necessary to consider VAD explantation. Although pulmonary pressures are critical to the decision immediately prior to explant with the off pump trial, they have not been predictive of long term cardiac stability. Exercise capacity has been assessed extensively in the advanced heart failure population, and has been shown to be a powerful prognostic indicator in regards to cardiovascular mortality and hospitalization[13].

In VAD patients, peak VO_2 does not change significantly post implantation, however exercise time does increase[7]. Previous use of exercise hemodynamic parameters has been limited to small numbers with heterogeneous explant cohorts, however did suggest a potential role for exercise as a predictor of explantation[13]. At rest, the LVAD may provide nearly all of the cardiac output[14], while exercise testing has demonstrated that the native myocardium contributes at least modestly to augmenting the cardiac response to exercise[15 16].

Elevated filling pressures are a key determinant in the pathophysiology of heart failure, regardless of systolic function. VAD therapy has been demonstrated to improve filling pressures predominantly through adequate mechanical ventricular unloading, which leads to improved left ventricular output and may reflect improvements in diastolic function.

A small number of prospective studies have utilized echocardiographic parameters to predict potential candidates for device removal, with reductions in ventricular size and end-diastolic dimension correlating well with improved cardiac function[18]. In this study, patients who were explanted showed an improved, but still severely reduced ejection fraction compared with the non-explant group. Ejection fraction is an important predictive variable in this population, however exercise hemodynamics provide novel incremental information in regards to augmentation of cardiac output. Although stress echocardiography is theoretically of use, non-invasive assessment of pulmonary pressures and ventricular function is often challenging in LVAD patients, due to pump position and limited imaging, particularly during exercise. Invasive haemodynamics provide accurate real time information on cardiac inotropic reserve that can be combined with existing data to facilitate decision making.

Conclusion

The present study demonstrates the adjunctive value of invasive exercise hemodynamic evaluation to assess ventricular recovery after VAD placement. Larger studies should be conducted to establish the broad utility of this approach.

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Baseline Characteristics		Explant N = 4	Non-Explant N = 17
Age (years)		46.5 ±10.7	45.7 +/- 16.6
Male gender, no. (%)		4/4 (100%)	15/17 (88%)
Aetiology, no. (%)			
	Idiopathic	4/4 (100%)	8/17 (47%)
	Dilated	0/4 (0%)	5/17 (29%)
	Ischaemic	0/4 (0%)	1/17 (6%)
	Other (Familial, hereditary)	0/4 (0%)	2/17 (12%)
Therapy			
	Destination, no. (%)	0/4 (0%)	1/17 (6%)
	Explant, no. (%)	4/4 (100%)	0/17 (0%)
	Transplant, no. (%)	0/4 (0%)	16/17 (94%)
Type of VAD, no. (%)			
	Heartmate II	0/4 (0%)	6/17 (35%)
	Heartware	4/4 (100%)	11/17 (65%)

Data are presented as mean+/- SD. VAD, ventricular assist device.

Table 2. Rest and exercise hemodynamics

RHC PARAMETERS	REST		p value	EXERCISE		p value
	Explant N = 4	Non-explant N = 17		Explant N = 4	Non-explant N = 17	
CO, L/min	4.9 ± 0.6	5.3 ± 1.1	0.382	12.8 ± 2.1	8.7 ± 2.6	0.027*
VAD CO, L/min	4.4 ± 1.5	5.3 ± 0.9	0.247	5.5 ± 1.5	6.0 ± 0.9	0.198
MAP, mmHg	79 ± 20	71 ± 13	0.341	93 ± 23	86 ± 16	<0.005*
Mean PAP, mmHg	18 ± 2	22 ± 5	0.160	32 ± 8	35 ± 8	0.749
Mean PCWP, mmHg	8.8 ± 4.0	12.2 ± 5.2	0.196	19.8 ± 11.1	27.8 ± 5.6	0.314
Peak work, watts	-	-		84.8 ± 35.4	57.8 ± 25.3	0.148
Exercise duration, mins	-	-		10 ± 4.6	7 ± 2.3	0.25

	EXPLANT	NON-EXPLANT	
ΔCO (L/min)	7.9 ± 1.81	3.4 ± 2.22	0.015*
ΔPCWP, mmHg	11.0 ± 8.49	15.7± 6.55	0.408
Index **Δ**CO, (L/min/W)	0.10± 0.02	0.07± 0.04	0.035*
Index **Δ**PCWP (mmHg/W)	0.11± 0.09	0.31± 0.18	0.011*

Results are given as mean +/- SD. RHC: right heart catheterization; CI: cardiac index; CO: cardiac output; LVSWI: left ventricular stroke work index; MAP: mean arterial pressure; PAP: pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance.