REST AND EXERCISE ADAPTATION OF THE RIGHT VENTRICULAR FUNCTION IN LONG-TERM LEFT VENTRICULAR ASSIST DEVICE PATIENTS: A PROSPECTIVE, PILOT STUDY

Short title: *Right ventricular adaptation on exercise in LVAD patients*

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Left Ventricular Assist Device (LVAD) therapy improves survival, functional status, and quality of life in end-stage heart failure (1). However exercise capacity, as assessed by cardiopulmonary exercise testing, remains altered after continuous-flow LVAD implantation (2-4). Right ventricular (RV) function is known to be strongly related to exercise performance in many pathophysiological conditions but has never been investigated in this clinical setting (5, 6). We sought to investigate the feasibility of RV assessment by stress echocardiography in long-term LVAD-supported patients in order to characterize the RV during exercise.

All continuous flow LVAD recipients followed at Rennes University Hospital, with at least 6-months of device support (Heartmate-II, Thoratec Corporation, Pleasanton, CA, USA), and with no RV dysfunction at rest, were eligible for the prospective REVADE study (7). All echocardiographic examinations were performed with a Vivid E9 ultrasound system (GE Medical Systems, Milwaukee, WI, USA). RV dimensions were obtained from a RV-focused apical 4-chamber view at end-diastole (8). The right ventricular fractional area change (RVFAC) was measured as the percentage of area change between RV end-diastolic area and end-systolic area. Tricuspid annular plane systolic excursion (TAPSE) was calculated as the difference between the systolic and diastolic lengths between the RV apex and the tricuspid annulus. RV systolic excursion velocity (S’) was obtained with pulsed Doppler sample volume placed in the lateral part of the tricuspid annulus. The RVOT velocity-time integral (VTI) was measured from pulse-wave Doppler from a parasternal short-axis view. RV flow was calculated as: RVOT VTI x RVOT area x heart rate. RV myocardial performance index (RVMPI) was measured using pulsed Doppler as the ratio of sum of isovolumic contraction and relaxation time over ejection time. Informed consent was obtained from all participants. The study was approved by the local institutional review board and registered on clinicaltrials.gov (NCT 02067455).

The protocol consisted of two exercise tests associated with clinical follow-up: bicycle stress echocardiography (45 Watts) and maximal cardiopulmonary exercise testing (CPET). The rotational speed of the device was not modified during the investigations.

Ten patients were prospectively enrolled between April and September 2014 (100% men, mean age 60.6 years). No adverse event occurred. The table displays the main results of echocardiographic assessment and of cardiopulmonary exercise tests.

We found a significant increase in RV flow and in the SPAP on slight exercise, while systolic function parameters (TAPSE, 2D RV FAC, S’, RVMPI) remained unchanged. Mean RV flow improved with a relative increase of 43% associated with a mean relative increase of 56% for SPAP. We did not find any difference between rest and exercise in conventional measures of RV systolic function (TAPSE, 2D RV FAC, S’, RVMPI).

In normal subjects, S’ and TAPSE have been shown to significantly increase on maximal exercise.(9) The lack of improvement in our cohort may be due to the submaximal threshold of exercise testing, the blunted response to the increase in load during exercise and to intrinsic cardiomyopathy progression. RVFAC and RVMPI were within normal ranges, whereas TAPSE was slightly reduced and S’ severely impaired as compared to normal values. There is growing evidence in the literature that the RV contractile pattern changes after cardiac surgery. Raina et al recommend the use of more global measures of RV function after cardiac surgery or lower normative values when longitudinal measures are used.(10) Our echocardiographic data suggest that the RV flow adapts on slight exercise, even if we cannot say that the systolic function of the RV improves on exercise. Exercise capacity remained altered in LVAD patients. Several factors may explain this finding. First, the relatively fixed cardiac output provided by the continuous-flow LVADs may limit exercise capacity.(2) Indeed, we found a modest increase in pump flow (average 1L/min) irrespective of the workload sustained (45W during echocardiography, 80W during CPET). Peripheral factors may also be involved for patients in whom muscular deconditioning persists.

Limitations: This is a single center pilot study that sought to evaluate the feasibility of RV function assessment on exercise with stress echocardiography so the overall number of patients included is small, limiting our ability to detect differences between observations at rest and on exercise.

In conclusion, exercise capacities of LVAD patients remain limited. In stable LVAD patients, with no RV dysfunction at rest, we could demonstrate an increase in RV flow on slight exercise. The limitation seems to originate from the limited ability of the continuous flow device to significantly increase its flow, but also to the chronic insufficiency of the peripheral muscle to extract oxygen, which is likely to persist after LVAD implantation.

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Table 1. Right heart parameters and ventilatory parameters at rest and on exercise.

	Rest	Exercise (45W)	p	Feasibility of measures at rest	Feasibility of measures on exercise	Peak exercise
Echocardiographic parameters						
RV dimensions (mm)						
- **basal**	39.3±6.4	40.9±11.3	NS	9/10	8/10	-
- **mid-cavity**	34.7±6.6	35.5±5.9	NS	9/10	8/10	-
- **longitudinal**	65.2±8.2	64.0±9.4	NS	9/10	8/10	-
RV FAC (%)	0.4±0.1	0.4±0.1	NS	9/10	8/10	-
RV flow (L/min)	3.8±1.4	5.6±2.5	0.03	9/10	7/10	-
SPAP (mmHg)	32.3±4.9	51.4±13.8	0.01	8/10	7/10	-
TR (/4)	0.9±0.7	1.4±0.6	NS	9/10	7/10	-
RIMP	0.4±0.1	0.3±0.0	NS	7/10	5/10	-
TAPSE (mm)	13.9±1.6	14.4±2.4	NS	9/10	8/10	-
RV systolic excursion velocity S' (cm/s)	6.3±1.7	6.7±1.4	NS	9/10	7/10	-
Ventilatory parameters						
HR (bpm)	68.1 ± 10.4	96.9±19.5	-	-	-	112.3 ± 19.5
% predicted	-	-				69.8 ± 10.4
Pump flow (L/min)	4.7 ± 0.9	5.7±0.9	-	-	-	5.7 ± 1.0

Workload (W) **% predicted**	-	-	-	-	-	80.6±23.2 50.1±12.2
Peak VO_2 (ml/kg/min) **% predicted**	-	-	-	-	-	12.6 ± 2.5 49.2 ± 9.2
Slope VE/VCO_2	-	-	-	-	-	39.4 ± 8.2
AT (ml/kg/min) **% predicted**	-	-	-	-	-	9.3 ± 0.9 34.6 ± 2.1

RV : Right Ventricle; RVFAC : Right Ventricular Fractional Area Change ; SPAP : systolic pulmonary arterial pressure; TR : tricuspid regurgitation; RIMP : right ventricular index of myocardial performance; TAPSE : Tricuspid Annular Plane Systolic Excursion; HR : heart rate; VO2 : oxygen consumption; slope VE/VCO_2 : ventilator efficiency slope; AT : anaerobic threshold