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Systemic perfusion at peak incremental exercise in left ventricular assist device recipients: Partitioning pump and native left ventricle relative contribution

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ABSTRACT

Background: In continuous-flow left ventricular assist device (LVAD) recipients, little is known about the relative pump- and left ventricle-generated blood flow (PBF and LVBF, respectively) contribution to peak systemic perfusion during incremental exercise and about how PBF/LVBF interplay and exercise capacity may be affected by pump speed increase.

Methods: Twenty-two LVAD recipients underwent ramp cardiopulmonary exercise tests at fixed and increasing pump speed (+1.5% of baseline speed/10 W workload increase), echocardiography and NT-proBNP dosage. Peak systemic perfusion was peak VO_2/estimated peak arterio-venous O_2 difference, and LVBF was systemic perfusion minus PBF provided by LVAD controller. A change of peak percentage of predicted VO_{2max} (Δpeak%VO_2) $\geq$3 in increasing- vs. fixed-speed test was considered significant.

Results: Tricuspid annular plane systolic excursion (TAPSE) and NT-proBNP were significantly lower and higher, respectively, in Δpeak%VO_2 < 3 than $\geq$3. A LVBF contribution to systemic perfusion significantly larger than that of PBF was observed in Δpeak%VO_2 $\geq$ 3 vs. <3 in fixed-speed test, which was further amplified in increasing-speed test (2.4 ± 1.7 l/min vs. 2.0 ± 1.5 l/min and 0.8 ± 2.2 l/min vs. 1.3 ± 2.3 l/min, respectively, p for trend <0.0005). Among several clinical-instrumental parameters, logistic regression selected only TAPSE >13 mm as a predictor of Δpeak%VO_2 $\geq$ 3.

Conclusions: A significant LVBF contribution to peak systemic perfusion and pump speed increase-induced peak VO_2 improvement was detectable only in patients with a more preserved right ventricular systolic function and stable hemodynamic picture. These findings should be taken into consideration when designing LVAD controllers aiming to increase pump speed according to increasing exercise demands.

1. Introduction

Continuous-flow left ventricular assist devices (LVADs) are increasingly used as destination therapy in end-stage chronic heart failure (CHF), and patients can be supported by LVADs in their habitual activities even for some years [1,2]. In such a clinical setting, knowledge of exercise pathophysiology plays an important role. LVAD implantation determines a peculiar exercise hemodynamic picture, where two pumps, i.e., LVAD and native left ventricle, can act in parallel to generate systemic perfusion [3]. Even in the presence of a fixed pump speed, some increase of PBF is actually detectable during exercise testing and habitual activities [3–6], as both exercise-induced tachycardia and augmentation of telediastolic left ventricular pressure do reduce the pressure gradient across the pump [3,5]. The contribution of native left ventricle to systemic perfusion can also increase during exercise, due to augmented venous return, decrease of peripheral resistances and activation of sympathetic drive [3]. However, notwithstanding the device boost to O_2 delivery, LVAD-implanted patients often suffer from a reduced exercise capacity [3,7,8], due to the limited ability of both the LVAD and the dysfunctioning left ventricle to adapt to increasing energetic demands. In this regard, scant data are available as to the relative contribution of PBF and left ventricle-generated blood flow (LVBF) to

Abbreviations: LVAD, left ventricular assist device; PBF, pump-generated blood flow; LVBF, left ventricle-generated blood flow; TAPSE, tricuspid annular plane systolic excursion; CHF, chronic heart failure; NYHA, New York Heart Association; CaO_2, resting arterial O_2 content; Hb, hemoglobin; PASP, pulmonary arterial systolic pressure.

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peak systemic perfusion [3], nor is it known how such an interplay may be affected by pump speed increase. In addition, few studies have evaluated the effects of pump speed increase on exercise capacity in LVAD-implanted patients, showing either no change or a significant increase [9–11].

The aim of this study was to evaluate the relative contribution of PBF and LVBF to peak systemic perfusion in a group of LVAD recipients with severely reduced exercise capacity, tested at two different pump speeds during incremental exercise. In addition, we evaluated the effects of pump speed increase on peak aerobic power (peak VO_2) in this population and sought for possible clinical–instrumental predictors of peak VO_2 increase in response to changes in pump speed.

2. Methods

2.1. Study population

Twenty-two patients implanted with LVAD were studied. Inclusion criteria were: 1) clinical stability, defined as no change in NYHA class, absence of hospitalization and stable medical treatment during the month prior to evaluation; 2) LVAD implanted ≥30 days prior to evaluation; 3) cardiopulmonary exercise tests stopped for fatigue and/or dyspnea with peak respiratory exchange ratio of ≥1.05; 4) absence of angina and/or instrumentally inducible myocardial ischemia and/or evidence of complex ventricular arrhythmias. Indication for LVAD implantation was persistent hemodynamic decompensation not responsive to intensive medical therapy. No patient had undergone aortic valve suturing at LVAD implantation. The protocol was approved by the Central Ethics Committee of the S. Maugeri Foundation, IRCCS and informed written consent was obtained from all participants in the study.

2.2. Echocardiographic evaluation

Within 7 days prior to ergometric evaluation, all participants underwent an echocardiogram according to reported standards in patients with LVAD [12]. Left ventricular cavity areas at end-diastole and end-systole from the apical 4- and 2-chamber views were obtained. The modified Simpson's rule was used to obtain biplane left ventricular volumes, and left ventricular ejection fraction was derived from the standard equation. Tricuspid annular plane systolic excursion (TAPSE) was used as a descriptor of right ventricular systolic function. To obtain TAPSE, the apical 4-chamber view was used, and an M-mode cursor was placed through the lateral tricuspid annulus in real time. Offline, the brightness was adjusted to maximize the contrast between the M-mode signal arising from the tricuspid annulus and the background. TAPSE was measured as the peak excursion of the tricuspid annulus (mm) from the end of diastole to the end of systole, with values representing TAPSE being averaged over 3 to 5 beats. Right ventricular systolic pressure was determined from the tricuspid regurgitation jet velocity using the simplified Bernoulli equation, and this value combined with an estimate of the right atrial pressure by the diameter and collapsibility of the inferior vena cava to yield pulmonary arterial systolic pressure (PASP).

2.3. Ergometric evaluation

All tests were performed on an electromagnetic bicycle ergometer (Ergo-metrics 800S; Sensormedics; Yorba Linda, CA, USA). Each patient underwent two ramp cardiopulmonary exercise tests, one with fixed LVAD speed (as set soon after implantation by the cardiac surgery team to allow maximum hemodynamic support at rest while avoiding suction events) and one with increasing LVAD speed. The two tests were separated by 48 h and their sequence was randomized. Brassard et al. [9] recently used a 400 rpm/30 W increase of pump speed during incremental exercise, equal to an average percent increase of 1.5%/10 W with respect to baseline. The latter figure was used as the criterion for pump speed increase in the present study, given the presence of 3 types of LVAD (Table 1) with different baseline pump speeds (HeartWare, range 2400–2800 rpm; HeartMate II, range 8600–9400 rpm; Incor, range 6850–7500 rpm). Heart rate and 12-lead ECG were monitored continuously during the test (CASE; GE Healthcare; Fairfield, CT, USA). After a 1-min 20 W warm-up period, a ramp protocol of 5, 7, or 10 W/min at a pedaling rate of 60 rev/min was started, and respiratory gas exchange measurements were obtained breath-by-breath (Vmax29; SensorMedics; Yorba Linda, CA, USA). Peak VO_2 was the mean VO_2 value observed during the last 30 s of the exercise period.

Table 1
Demographic and clinical characteristics.

	Total group (n = 22)	Δpeak%VO_2 ≥ 3 (n = 13)	Δpeak%VO_2 < 3 (n = 9)
Age (years)	57 ± 9	56 ± 8	57 ± 10
Male gender (n, %)	21 (95)	13 (100)	8 (89)
BMI (kg/m^2)	24.99 ± 3.71	25.74 ± 3.27	23.90 ± 4.22
LVAD type (n, %)	HM 9 (41)	HM 6 (46)	HM 3 (33)
	HW 8 (36)	HW 3 (23)	HW 5 (55)
	INC 5 (23)	INC 4 (31)	INC 1 (12)
Indication for LVAD implantation (n, %)	BR 15 (68)	BR 11 (85)	BR 5 (55)
	DT 6 (32)	DT 2 (15)	DT 4 (45)
Time since implantation (days)	156 ± 186	168 ± 171	138 ± 215
Etiology	I 14 (64)	I 8 (61)	I 6 (66)
	D 8 (36)	D 5 (39)	D 3 (34)
β-Blockers (n, %)	21 (95)	12 (92)	9 (100)
LVEF (%)	26 ± 8	26 ± 3	25 ± 12
TAPSE (mm)	12.3 ± 2.7	13.4 ± 2.3	10.7 ± 2.3[a]
PASP (mm Hg)	32 ± 8	28 ± 4	38 ± 9[a]
Hematocrit (%)	36 ± 3	37 ± 4	34 ± 2
NT-proBNP (pg/ml)	2825 ± 2907	1961 ± 1889	4073 ± 3724[b]

Values are n (%) or mean ± standard deviation.
Δpeak%VO_2 ≥ 3 = increase of peak % predicted VO_{2max} between fixed and increasing pump speed tests ≥3; Δpeak%VO_2 < 3 = increase of peak % predicted VO_{2max} between fixed and increasing pump speed tests <3; BMI = body mass index; LVAD = left ventricular assist device; HM = HeartMate II; HW = HeartWare; INC = Incor; BR = bridge to transplantation/decision/recovery; DT = destination therapy; I = ischemic cardiomyopathy; D = dilative cardiomyopathy; LVEF = left ventricular ejection fraction; TAPSE = tricuspid annular plane systolic excursion; PASP = pulmonary arterial systolic pressure.
[a] $P < 0.05$ vs. Δpeak%VO_2 ≥ 3.
[b] $P < 0.08$ vs. Δpeak%VO_2 ≥ 3.

The slope of the ventilation vs. VCO_2 relationship (VE/VCO_2 slope) was evaluated excluding, when present, its final nonlinear portion due to acidotic ventilatory drive.

2.4. Hemodynamic evaluation

Systemic perfusion was calculated by the Fick's principle using measured VO_2 and estimated arterio-venous O_2 difference values. Resting arterial O_2 content (CaO_2) was

$$\text{Resting } CaO_2\ (\text{ml/dl}) = Hb * 1.34 * SaO_2$$

were Hb is hemoglobin concentration in g/dl, 1.34 is hemoglobin O_2 binding capacity in ml O_2/g Hb and SaO_2 is hemoglobin oxygen saturation (assumed equal to 98%). Due to the exercise-induced hemoconcentration, a value of Hb increased by 0.5 g/dl with respect to baseline [Mezzani A, unpublished data, 2013] was used to calculate peak CaO_2. According to available data [13], resting and peak exercise O_2 extraction in advanced CHF is around 40% and 80%, respectively; in addition, a similar peak O_2 extraction has been reported in LVAD patients [3]. These values were thus adopted to calculate resting and peak systemic perfusion in l/min using the Fick's principle. PBF values in l/min were obtained by the device controller and LVBF was the difference between systemic perfusion and PBF values.

2.5. Blood sampling procedures and hormonal assays

All patients had a measurement of plasma NT-pro-BNP. Venous blood samples were obtained after at least 30 min of rest and collected in tubes containing an ethylenediamine tetraacetic acid buffer. They were immediately placed on ice and centrifuged at 4 °C. Plasma samples were stored at −20 °C until assay. The time between NT-pro-BNP and ergometric evaluation was 4 ± 3 days.

2.6. Statistics

Unpaired and paired t-tests and repeated measures ANOVA were used to compare the means of quantitative variables, whereas the chi-squared test with Fisher's exact test was employed for qualitative data. Stepwise logistic regression analysis was used to assess predictors of peak VO_2 change between increasing- and fixed-speed tests. Given the quite wide age range of the study population (35–69 years), change of peak VO_2 expressed as a percentage of predicted VO_{2max} ($\Delta peak\%VO_2$), i.e. corrected for sex and age, was used as categorical dependent variable. A 3% cutoff value (≥3% / <3%) was chosen because equal to the median of the study population and larger than our laboratory's repeated-test variability in CHF patients with severely depressed peak VO_2 [14]. The independent variables forced into the model included time since LVAD implantation (≤180 days / >180 days), left ventricular ejection fraction, hematocrit, NT-proBNP, peak heart rate and PBF at increasing-speed test, LVAD type (HeartMate II yes/no, HeartWare yes/no, Incor yes/no) and TAPSE (≤13 mm / >13 mm). The 13 mm TAPSE cutoff was the median value of the study population, and corresponds to the value separating light from moderate-to-severe depression of right ventricular systolic function [15].

The level of statistical significance was set at a 2-tailed *P*-value of ≤0.05. The StatView® 5.0.1. (SAS Institute, Inc.; Cary, NC) software package was used for statistical calculations.

3. Results

Demographic and clinical characteristics of the study population are shown in Table 1. HeartWare LVADs were relatively more represented in the $\Delta peak\%VO_2 < 3$ group, even if the difference was not statistically significant. TAPSE was significantly lower and PASP and NT-proBNP significantly higher, respectively, in $\Delta peak\%VO_2 < 3$ than in $\Delta peak\%VO_2 \geq 3$, testifying to a more compromised hemodynamic picture in the former group (Table 1).

3.1. Contributors to systemic perfusion at fixed vs. increasing pump speed

No patient suffered from suction episodes and/or complex ventricular arrhythmias during exercise tests. By design, the pump speed increase during the increasing-speed test was on average equal to 7% and 6% in $\Delta peak\%VO_2 \geq 3$ and <3, respectively.

In the whole study group, resting systemic perfusion was similar to resting PBF irrespective of pump speed, peak $\%VO_2$ values and LVAD type (Table 2). As expected, the PBF increase at peak exercise was significantly larger in increasing- than in fixed-speed tests (1.6 ± 0.7 l/min vs. 1.2 ± 0.7 l/min, +33%, $P < 0.005$), with a similar behavior in $\Delta peak\%VO_2 \geq 3$ and <3 irrespective of LVAD type (P for trend = 0.42) (Fig. 1). On the contrary, a different trend of change of LVBF was evident between the 2 groups, with LVBF increasing by 20% at increasing- vs. fixed-speed test in $\Delta peak\%VO_2 \geq 3$ and decreasing by 39% in $\Delta peak\%VO_2 < 3$ (2.4 ± 1.7 l/min vs. 2.0 ± 1.5 l/min and 0.8 ± 2.2 l/min vs. 1.3 ± 2.3 l/min, respectively, P for trend <0.0005) (Fig. 1). In the increasing-speed test, this made LVBF provide around one fourth of peak systemic perfusion in $\Delta peak\%VO_2 \geq 3$, but only less than one tenth in $\Delta peak\%VO_2 < 3$ (Table 2). Accordingly, peak systemic perfusion increase in increasing- vs. fixed-speed tests

Table 2
Haemodynamic parameters.

		Total group ($n = 22$)		$\Delta peak\%VO_2 \geq 3$ ($n = 13$)		$\Delta peak\%VO_2 < 3$ ($n = 9$)	
		Fixed speed test	Increasing speed test	Fixed speed test	Increasing speed test	Fixed speed test	Increasing speed test
Resting pump speed (rpm)	HM	9156 ± 240	9156 ± 240	9133 ± 301	9133 ± 301	9200 ± 0	9200 ± 0
	HW	2628 ± 133	2628 ± 133	2620 ± 203	2620 ± 203	2632 ± 100	2632 ± 100
	INC	7230 ± 277	7230 ± 277	7162 ± 269	7162 ± 269	7500 ± 0	7500 ± 0
Peak pump speed (rpm)	HM	9156 ± 240	9622 ± 307	9133 ± 301	9566 ± 344	9200 ± 0	9733 ± 231
	HW	2628 ± 133	2779 ± 123	2620 ± 203	2743 ± 212	2632 ± 100	2800 ± 51
	INC	7230 ± 277	8090 ± 296	7162 ± 269	8112 ± 268	7500 ± 0	8000 ± 0
Resting PBF (l/min)		4.2 ± 0.8	4.2 ± 0.8	4.2 ± 0.9	4.3 ± 0.9	4.1 ± 0.6	4.2 ± 0.6
Resting systemic perfusion (l/min)		3.9 ± 0.9	4.0 ± 1.0	4.0 ± 0.9	4.1 ± 1.0	3.9 ± 0.9	3.8 ± 1.0
Peak PBF (l/min)		5.4 ± 0.8	5.9 ± 0.8[a]	5.3 ± 0.8	5.8 ± 0.7[a]	5.7 ± 0.8	6.0 ± 1.0[a]
Peak systemic perfusion (l/min)		7.1 ± 1.8[b]	7.6 ± 1.9[a,b]	7.2 ± 1.9[b]	8.1 ± 2.0[a,b]	6.9 ± 1.8	6.8 ± 1.7

Values are mean ± standard deviation.
$\Delta peak\%VO_2 \geq 3$ = increase of peak % predicted VO_{2max} between fixed and increasing pump speed tests ≥3; $\Delta peak\%VO_2 < 3$ = increase of peak % predicted VO_{2max} between fixed and increasing pump speed tests <3; HM = HeartMate II; HW = HeartWare; INC = Incor; PBF = pump blood flow.
[a] $P < 0.005$ vs. fixed pump speed.
[b] $P < 0.001$ vs. peak PBF.

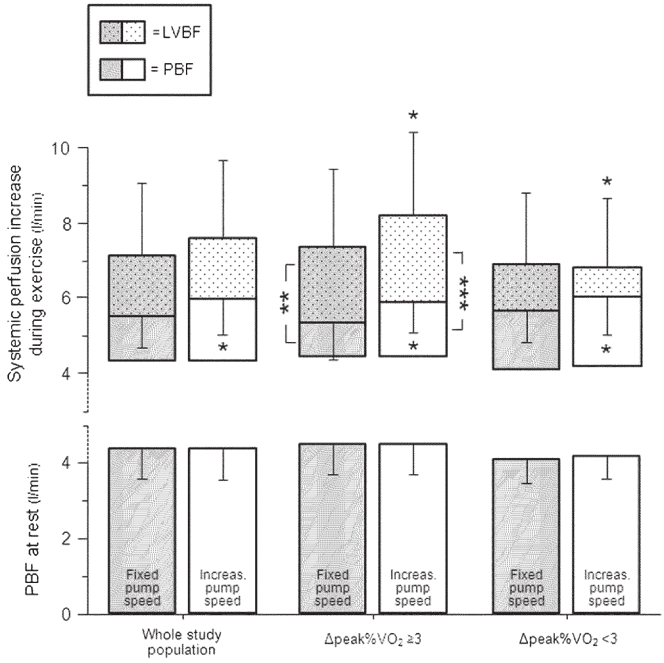

Fig. 1. Partitioning of contributors to systemic perfusion increase during incremental exercise in left ventricular assist device recipients. Peak pump blood flow (PBF) increased significantly during increasing-speed exercise in both $\Delta peak\%VO_2 \geq 3$ and <3, whereas peak left ventricular blood flow (LVBF) was significantly increased in $\Delta peak\%VO_2 \geq 3$ and decreased in $\Delta peak\%VO_2 < 3$. See text for further details. * = $P < 0.05$ vs. fixed speed; ** = $P < 0.05$; *** = $P < 0.11$.

was provided only by the $\Delta peak\%VO_2 \geq 3$ group (+11%) and not by $\Delta peak\%VO_2 < 3$ (−2%) (P for trend <0.001 — Fig. 1 and Table 2). These findings did not differ between different LVAD types.

3.2. Peak VO_2 at fixed vs. increasing pump speed

In the whole study population, peak VO_2 and peak $\%VO_2$ were significantly higher in increasing- than in fixed-speed tests, irrespective of LVAD type; by design, such an increase was present in $\Delta peak\%VO_2 \geq 3$ but not in $\Delta peak\%VO_2 < 3$ (P for trend <0.0001) (Table 3). VE/VCO_2 slope and peak heart rate were not affected by pump speed changes (Table 3).

At stepwise logistic regression analysis testing $\Delta peak\%VO_2 \geq 3$ predictors, LVAD type did not enter the model due to colinearity and only TAPSE >13 mm was significantly associated with the dependent variable (Table 4).

Table 4
Predictors of $\Delta peak\%VO_2 \geq 3$ at logistic regression analysis. $\Delta peak\%VO_2 \geq 3\%$ = difference of peak % predicted VO_{2max} between fixed and increasing pump speed tests ≥3; CI = confidence interval; LVEF = left ventricular ejection fraction; PBP incr. = pump blood flow at increasing-speed test; Peak HR = peak heart rate at increasing-speed test; TAPSE = tricuspid annular plane systolic excursion.

	Chi-square	*P*-value	Odds ratio (95% CI)
LVEF (%)	0.01	0.90	0.99 (0.77–1.25)
Peak PBP incr. (l/min)	0.01	0.76	1.40 (0.14–13.7)
Time since LVAD implantation ≤180 days	0.26	0.61	6.97 (0.00–120.21)
Peak HR incr. (bpm)	0.36	0.55	1.04 (0.92–1.17)
NT-proBNP (pg/ml)	0.75	0.39	1.00 (0.99–1.00)
Hematocrit (%)	0.97	0.32	1.41 (0.71–2.80)
TAPSE >13 mm	3.29	0.05	34.65 (0.75–159.98)

4. Discussion

Our results show that a significant LVBF contribution to peak exercise systemic perfusion can be observed in LVAD recipients. In patients with quite a preserved right ventricular systolic function and lower neurohormonal activation, such a contribution is significantly larger than that provided by the LVAD. In addition, these patients are able to increase both their LVBF and peak VO_2 to a larger extent than those more hemodynamically compromised in response to pump speed increase. These findings let hypothesize a better management of systemic venous return during incremental exercise in LVAD-implanted patients with a more preserved right ventricular function and hemodynamic balance.

4.1. Contributors to systemic perfusion at fixed vs. increasing pump speed

Resting PBF is known to be dictated by the pump speed and the pressure head across the pump [16]. In our population, PBF did not differ from systemic perfusion at rest (Table 2), with values consistent with resting cardiac output of elderly beta-blocked CHF patients [17]. Moreover, our findings are in agreement with previously reported data indicating no differences between resting PBF and systemic perfusion measured by thermodilution technique [3,18]. During exercise, a spontaneous increase of PBF is usually observed due to the reduction of the pressure gradient across the pump. This occurs due to tachycardia-induced prolongation of the time spent in systole and to augmentation of telediastolic left ventricular pressure [3,5]. Our data fit well with this picture, showing an average increase of PBF equal to 1.2 l/min and 1.6 l/min in fixed- and increasing-speed tests, respectively (Fig. 1 and Table 2), consistent with that reported by Jacquet et al. [3]. Peak PBF did not differ between $\Delta peak\%VO_2 \geq 3$ and $\Delta peak\%VO_2 < 3$ and the PBF increase vs. rest was quite modest both in fixed- and increasing-speed tests (Table 2), an expected finding based on the reduced LVAD preload sensitivity [19].

Table 3
Gas exchange and ergometric parameters.

	Total group ($n = 22$)		$\Delta peak\%VO_2 \geq 3$ ($n = 13$)		$\Delta peak\%VO_2 < 3$ ($n = 9$)	
	Fixed pump speed	Increasing pump speed	Fixed pump speed	Increasing pump speed	Fixed pump speed	Increasing pump speed
Resting VO_2 (ml/kg/min)	3.7 ± 0.5	3.7 ± 0.6	3.7 ± 0.5	3.8 ± 0.5	3.7 ± 0.5	3.6 ± 0.7
Peak VO_2 (ml/kg/min)	12.8 ± 2.2	13.7 ± 2.6[a]	12.8 ± 2.5	14.4 ± 2.8[a]	12.7 ± 1.9	12.5 ± 1.8
Peak %pred·VO_{2max}	44 ± 8	47 ± 9[a]	43 ± 8	49 ± 9[a]	45 ± 9	44 ± 9
Peak RER	1.16 ± 0.11	1.17 ± 0.12	1.14 ± 0.10	1.13 ± 0.10	1.20 ± 0.12	1.22 ± 0.13
VE/VCO_2 slope	40.9 ± 6.1	39.9 ± 6.5	41.7 ± 6.8	40.7 ± 7.4	39.8 ± 5.3	38.9 ± 5.0
Peak HR (bpm)	114 ± 20	115 ± 20	117 ± 21	118 ± 18	109 ± 19	110 ± 22

Values are mean ± standard deviation.
$\Delta peak\%VO_2 \geq 3$ = increase of peak % predicted VO_{2max} between fixed and increasing pump speed tests ≥3; $\Delta peak\%VO_2 < 3$ = increase of peak % predicted VO_{2max} between fixed and increasing pump speed tests <3; RER = respiratory exchange ratio; VE = ventilation; HR = heart rate.
[a] $P < 0.05$ vs. fixed pump speed.

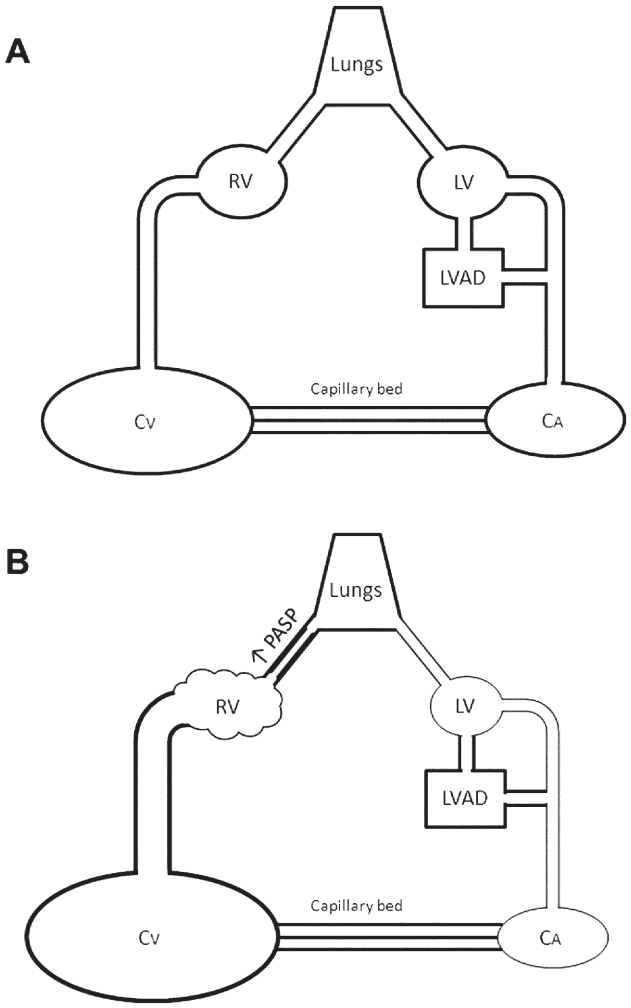

Fig. 2. Models of cardio-circulatory system dynamics during incremental exercise in left ventricular assist device recipients. Panel A shows a right ventricle still able to cope with the systemic venous return, with no significant shift of blood volume between the arterial and venous compartments. Panel B shows 'discordant' failure of the right ventricle vs. the left ventricle/LVAD system, in the presence of significant right ventricular systolic dysfunction and high systolic pulmonary artery pressure. The net effect is a shift of volume from the arterial to the venous compartment, with a resultant lower systemic perfusion than in panel A. See text for further details. RV = right ventricle; LV = left ventricle; PASP = pulmonary arterial systolic pressure; CV = venous capacitance; CA = arterial capacitance.

On the other hand, in the whole study population peak systemic perfusion values were significantly higher than those of peak PBF in both fixed- and increasing-speed tests (Table 2), approaching cardiac output values reported in CHF patients for similar peak work rates [17]. This testifies to a significant LVBF contribution to systemic perfusion increase during incremental exercise in LVAD patients. However, a markedly different pattern of LVBF/PBF interaction between $\Delta peak\%VO_2 \geq 3$ and $\Delta peak\%VO_2 < 3$ was evident. Namely, at peak fixed-speed exercise, LVBF contribution to systemic perfusion increase was significantly larger than that of PBF in $\Delta peak\%VO_2 \geq 3$, which did not happen in $\Delta peak\%VO_2 < 3$ (Fig. 1). This pattern was even amplified in the increasing-speed tests, with peak LVBF further increasing in $\Delta peak\%VO_2 \geq 3$ but significantly decreasing in $\Delta peak\%VO_2 < 3$ (Fig. 1), with PBF providing almost the whole peak systemic perfusion in the latter group (Table 2). Importantly, $\Delta peak\%VO_2 \geq 3$ had a better right ventricular systolic function and lower pulmonary pressures and NT-proBNP levels than $\Delta peak\%VO_2 < 3$, i.e. a less compromised hemodynamic and neurohormonal picture. These findings highlight a possible role played by the right ventricle in determining the hemodynamic response to exercise in LVAD patients. This would especially be true when the right ventricle is or starts functioning on the flat portion of the cardiac function curve [20]. In such a situation (panel B of Fig. 2), a severely dysfunctioning right heart could not keep pace with the systemic venous return rate, and some dynamic shift of blood volume from the arterial to the venous compartment would occur [21,22], so reducing the blood content of the arterial compartment, i.e. systemic perfusion. This hypothesis is indirectly supported by data from Hayward et al. [16], who found suction episodes and/or ventricular arrhythmias occurring during pump speed increase at rest only in patients with moderate-to-severe right ventricular dysfunction. Protocols evaluating exercise-induced changes in both central venous pressure and telediastolic left ventricular pressure in an experimental setting similar to that of the present study may help to further clarify this issue.

4.2. Peak VO_2 at fixed vs. increasing pump speed

In a group of 8 LVAD patients with preserved exercise capacity, Brassard et al. [9] evaluated the effects of a pump speed increase algorithm similar to that used in the present study on peak work rate, finding no changes; however, no information about peak VO_2 was provided by these authors. On the other hand, Salamonsen et al. [10] measured peak VO_2 in 10 LVAD patients with severely reduced exercise capacity exercising at 80%, 100% and 130% of baseline pump speed, finding a statistically significant 9% peak VO_2 increase between exercise tests conducted at the lowest and highest pump speed. Finally, Jung et al. [11] recently found a significant 9% increase of peak VO_2 after a pump speed increase of 16% during incremental exercise in a group of 14 LVAD patients. Our data demonstrate a peak VO_2 increase (7%) in the whole study population quite similar to that reported by Salamonsen and Jung, however occurring after a much lower percent pump speed increase. Interestingly, according to our data a TAPSE $\leq$13 mm was the only independent predictor of a peak%VO_2 change $<$3 among several clinical–instrumental parameters (Table 4). This finding is not unexpected, as right ventricular function is known to be related to functional capacity much more than the left ventricular one in a wide range of pathophysiological pictures, i.e. chronic heart failure [23], repaired tetralogy of Fallot [24], chronic obstructive pulmonary disease [25] and pulmonary hypertension [26]. As a whole, these findings lend support to the pathophysiological picture proposed in Fig. 2. Of note, starling-like controllers designed to provide automatic PBF adaptations to exercise are usually tested assuming both no/minimal left ventricular contribution to systemic perfusion and a venous return to the left heart not significantly limited by the right ventricle [11,27]. The results of the present study suggest that such assumptions may not always prove to be true in the real world of LVAD recipients.

4.3. Study limitations

We acknowledge that measuring systemic perfusion invasively during the exercise tests would have provided more reliable information; conversely, right-heart catheterization may have resulted in less flexible experimental conditions and less certain attainment of maximal or near-maximal effort. In any case, as far as systemic perfusion calculation is concerned, the only estimated parameter was peak peripheral O_2 extraction, which is known to be far more predictable than peak VO_2 during incremental exercise in both normal subjects and patients with CHF [13,28]. In this regard, the estimated increase of hemoglobin level equal to 0.5 g/l at peak exercise with respect to baseline (11.8 $\pm$ 1.2 g/l) used in the present study corresponds to the 4% average hemoconcentration observed in our laboratory when performing arterial blood gases analysis during exercise in CHF patients. In addition, the assumption of a normal resting hemoglobin oxygen saturation with no significant changes at peak incremental exercise is expected in stable LVAD patients with no associated lung disease. Also PBF was an estimated value, based on speed settings and power consumption, and must be interpreted with some caution. We evaluated patients implanted with 3 different LVAD

models. This may have affected the pump hemodynamic response during exercise, in the light of possible differences in pump preload sensitivity [19] and different baseline pump speeds. However, study data did not differ in patients with different LVAD types, nor was LVAD type retained in the $\Delta peak\%VO_2$ logistic regression predictive model, which seems to rule out possible significant effects of LVAD type on exercise hemodynamics. Finally, the sample size of the present study was conditioned by the scarcity of LVAD patients; however, our preliminary data will enable the design of adequately powered future protocols.

5. Conclusions

A significant native left ventricle contribution to peak exercise systemic perfusion is detectable in LVAD recipients. Patients with quite a preserved right ventricular systolic function and stable hemodynamic picture, demonstrate to be able to increase their native left ventricle blood flow and peak VO_2 in response to pump speed increase to a larger extent than those more hemodynamically compromised. These findings let hypothesize a better management of systemic venous return during incremental exercise in patients still provided with some amount of right ventricular preload reserve, in a context of hemodynamic stability. These results should be taken into consideration when conceiving and designing LVAD controllers able to increase pump speed in response to increasing exercise demands.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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