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ORIGINAL RESEARCH ARTICLE

Continuous flow left ventricular assist devices do not worsen endothelial function in subjects with chronic heart failure: a pilot study

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Abstract

Aims To evaluate endothelial function in subjects with left ventricular assist devices (LVADs), comparing them with subjects with chronic heart failure with reduced ejection fraction on the list for heart transplant (HT) and with HT patients with a normal systolic cardiac function to identify any differences.

Methods We enrolled 28 subjects with LVAD, 55 subjects with HT, and 42 subjects with heart failure on the transplant list. The subjects underwent a general physical examination, assessment of laboratory blood parameters, and assessment of endothelial function through flow-mediated dilation (FMD) of brachial artery.

Results The three groups were homogeneous as regards age, gender, smoke abuse, C-reactive protein (CRP) and FMD parameters (P = ns). In LVAD group percentage of FMD change showed an inverse correlation with CRP (rho: −0.5, P: 0.003), a well-known marker of inflammation and tissue damage.

Conclusions Continuous flow related to LVAD seems to not worsen endothelial function. Endothelial function was not affected by cardiovascular risk factors (hypertension, hypercholesterolaemia, diabetes, obesity, and tobacco habit), by the functional status expressed by New York Heart Association class, by the left ventricular systolic function and by the presence or absence of ischaemic heart disease in all the populations analysed. CRP was the only factor able to influence percentage of FMD change in patient with LVAD, reinforcing the hypothesis that inflammation is the main determinant of endothelial function.

Keywords Continuous flow left ventricular assist device; Heart failure; Heart transplant; Endothelial function

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Introduction

Continuous flow left ventricular assist devices (LVADs) represent a valid therapeutic option in the treatment of patients with chronic refractory heart failure (HF).[1]

These devices can draw blood from the left ventricle and pump it directly into the aorta, supplanting the depressed function of the left heart.[2] In recent years, LVADs have mainly been used as a bridge to transplantation, but increasing long-term reliability is opening the door for use as a definitive solution, the so-called "destination therapy", for the treatment of terminal HF.[1,3–5]

Current guidelines suggest the implantation of these devices as destination therapy in subjects with chronic refractory HF despite medical therapy, ineligible to heart transplantation, Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) level ≥2.[1]

The latest generation devices consist of rotating continuous flow pumps, of limited size, able to generate a range of up to 10/12 L/min of flow. Given the continuous flow, they

do not contain valves.[6] These devices have been shown to improve morbidity and mortality in critically ill patients waiting for heart transplant (HT) and at the same time to reduce adverse events, they also can determine a reverse remodelling of the heart in patients with nonischaemic cardiomyopathy and in a smaller subset of patients with ischaemic cardiomyopathy.[7–9]

One potential adverse event of long-term continuous flow LVAD support is arterial endothelial cell dysfunction that could result in impaired vascular reactivity.

After the implementation of LVAD circulatory support, the pulsatile nature of the arterial flow pattern decreases dramatically. In addition to the longitudinal stretching forces, the so-called "shear stress", the cyclical deformation produced by the pulsatility of the flow represents an independent modulator of the endothelial function, able, in fact, to exert an impact on nitric oxide synthase, cell Ph and blood cell physical alignment.[10] Pulsatile shear stress and cyclic strain of an appropriate magnitude are requisite to maintain endothelial cell homeostasis.[11]

The inflammatory status with high levels of cytokines in subjects with LVAD could contribute to the worsening of endothelial function.[12] Most of the available studies in the literature focusing on endothelial function in LVADs subjects have used healthy subjects as controls, making the comparison unreliable due to the different characteristics of populations.

The purpose of our study was to evaluate endothelial function in subjects with LVADs, comparing them with subjects with chronic HF with reduced ejection fraction on the list for HT and with HT patients.

The categories of subjects analysed represent three different expressions of the same pathology, the heart failure, in different clinical scenarios: in the end stage of HF, after HT, and after ventricular assistance devices implantation in those ineligibles for transplantation. The aim of our study was to detect any determinant of endothelial function in these three groups of subjects to evaluate the specific effect of continuous flow.

Material and methods

We performed an observational two-centres study on 28 subjects with LVADs, 55 subjects with HT, and 42 subjects with HF on the transplant list. Subjects were evaluated at the HF Clinics of 'Cardiology Unit' of the University of Bari and of the 'Niguardia' Hospital of Milan during the period from January 2018 to June 2019.

We enrolled only subject with LVAD and HT after at least 1 year from the intervention, all the subjects were evaluated in optimal medical therapy and after at least 1 month of clinical stability. We excluded subjects with important non-cardiological comorbidities: that is, symptomatic cerebrovascular diseases and relevant kidney diseases requiring dialysis.

The subjects underwent a general physical examination, assessment of laboratory blood parameters, and the assessment of endothelial function through flow-mediated dilation (FMD) of brachial artery. Patients were informed about the aim of the study and signed consent forms. The study was approved by the Institutional Review Board of the two hospitals and carried out in accordance with the principles of the Declaration of Helsinki.

Clinical and laboratory evaluation

The demographic and clinical characteristics are shown in *Table 1*. Height (cm), weight (kg), arterial blood pressure, and heart rate were measured, and body mass index (BMI) (kg/m^2) was calculated. Functional status was evaluated using the New York Heart Association (NYHA) functional classification.[13]

Mean arterial pressure was determined in LVAD subjects using Omron HBP-1300 oscillometric device at the level of brachial artery,[14] while in subjects with HF and HT using the standard method.[15]

Subjects were classified as hypertensive, if they had systolic/diastolic blood pressure values >140/90 mmHg, or if they assumed anti-hypertensive medication,[16] dyslipidaemic in presence of serum total cholesterol >200 mg/dL, low-density lipoprotein cholesterol >115 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, triglycerides >150 mg/dL, or if they used lipid-lowering agents,[16] are diabetic in presence of fasting glucose level >126 mg/dL, or when they assumed antidiabetic drugs[16]; overweight and obese if their BMI was ranging from 25 kg/m^2 to 29.9 kg/m^2 or >30 kg/m^2, respectively.[16] Finally, each participant was considered a "current daily smoker" in presence of a daily consumption of at least five cigarettes a day in the previous 3 months or if they had stopped smoking for less than one year from admission.[16]

C-reactive protein (CRP) and N terminal pro brain natriuretic peptide (NT-proBNP) values, using immunoenzymatic assay, were also obtained.

Endothelial function was evaluated by using FMD of brachial artery, according to the standard protocol.[17] The occlusion cuff was placed around the forearm, distal to the ultrasound probe.[16] To avoid confounding factors, the data collected underwent to an off-line analysis by a blinded observer with the determination of the following data: baseline diameter of brachial artery, peak diameter of the brachial artery, absolute FMD change, and percentage FMD change.[17]

Left ventricular ejection fraction was also assessed in all subjects using the echocardiographic evaluation through the Simpson method.[18]

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Table 1 Population characteristics

	LVAD population	HT population	HF population
Number	28	55	42
Age[a]	56.6 ± 8.2	52.2 ± 14.4	58.5 ± 6.5
Male gender *n* (%)	23	39 (70.9)	38 (90.5)
Tobacco abuse *n* (%)	3 (10.7)	3 (5.4)	5 (11.9)
BMI[a]	27.3 ± 3.5	24.4 ± 4.5	25.8 ± 4
Heart rate[a]	80.4 ± 12.9	90.5 ± 13	70.8 ± 11
Mean arterial blood pressure[a]	84.3 ± 9.2		
SBP[a]		127. 6 ± 16.7	107.9 ± 15.6
DBP[a]		81 ± 10	72 ± 10.7
NT-proBNP[b]	2202 (546.2–2748.25)	1430 (555–1898.5)	3482 (1532–5240.7)
CRP[b]	2.43 (0.45–2.87)	3.5 (0.3–3.7)	3.63 (0.2–3.8)
Baseline diameter (mm)[b]	3.9 (3.5–4.2)	3.8 (3.4–4.5)	3.9 (3.5–4.3)
Peak diameter (mm)[b]	4.2 (3.8–4.6)	4.2 (3.7–4.6)	4.2 (3.9–4.6)
Absolute FMD change (mm)[b]	0.3 (0.2–0.4)	0.3 (0.2–0.4)	0.3 (0.2–0.5)
Percentage FMD change (%)[b]	7.06 (4.6–11.7)	7.1 (5.8–10.8)	7.2 (5.9–11.6)
LVEF (%)[a]	22.8 ± 4	57.7 ± 6.6	24.5 ± 6.5
NYHA class[b]	2 (1–2)	1 (1–2)	3 (3–3)
Hypercholesterolaemia *n* (%)	8 (28.6)	16 (29.1)	13 (31)
Hypertension *N* (%)	3 (10.7)	17 (30.9)	13 (31)
Diabetes *N* (%)	8 (28.6)	15 (27.3)	14 (33.3)
Obesity (%)	7 (25)	5 (9.1)	5 (11.9)
Ischaemic aetiology *N* (%)	16 (57)	22 (40)	14 (33.3)
Non ischaemic aetiology *N* (%)	12 (43)	33 (60)	28 (66.7)
Beta blocker *N* (%)	18 (64.3)	17 (30.9)	38 (90.5)
Diuretics *N* (%)	22 (78.6)	32 (58.2)	41 (97.6)
Digoxin *N* (%)	0	1 (1.8)	10 (23.8)
Amiodarone *N* (%)	9 (32.1)	5 (9.1)	21 (50)
Oral anticoagulant *N* (%)	26 (92.9)	5 (9.1)	20 (47.6)
Aspirin *N* (%)	22 (78.6)	39 (70.9)	16 (38.1)
Angiotensin receptor blockers *N* (%)	5 (17.9)	8 (14.5)	12 (28.6)
Calcium antagonist *N* (%)	8 (28.6)	10 (18.2)	2 (4.8)
Statins *N* (%)	3 (10.7)	19 (34.5)	21 (50)

Abbreviations: BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; FMD, flow-mediated dilation; HF, heart failure; HT, heart transplant; LVAD, left ventricular assist device; NT-proBNP, N terminal pro brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure.
[a]Mean ± standard deviation.
[b]Median (interquartile range).

LVADs, all at continuous flow, were thus distributed in our population: 10 subjects had Heartwave devices (Medtronic), 6 Heart Mate II (Abbot), 8 Heart Mate III (Abbott), and 4 subject reliant devices (HeartAssist5).

Statistical analysis

The data were analysed using the Kolmogorov–Smirnov test to determine their distribution. Statistical significance between the groups was calculated on data with normal distribution using the Student *t* test for independent samples and for non-normal distributed data using the Kruskal–Wallis test and Mann–Whitney's *U* tests. The correction analysis with Bonferroni test was used to compare quantitative variables between the groups. Correlation analysis was performed with the Spearman rank correlation test. Statistical significance was considered for $P < 0.05$. All statistical analyses were performed with the SPSS Statistics 20 software.

Results

Demographic characteristics of the population are shown in *Table 1*.

The three groups were homogeneous as regards age, gender, smoke abuse, CRP, and FMD parameters, *Table 2*.

LVADs subjects had higher BMI values than those with HT and those with chronic HF. Average heart rate was lower compared with subjects with HT and higher compared with subjects with HF.

NT-proBNP values of subjects with HT were significantly lower compared to subjects with LVADs and with HF.

Finally, HF subjects had a significantly lower heart rate compared to the other two groups, higher values of NT-pro BNP, and a lower prevalence of ischaemic heart disease compared with LVADs subjects.

Because no significant differences were found among the groups about the several parameters obtained by using

Table 2 Comparison among the main characteristics of the three populations

	LVAD vs. HT		HT vs. HF		HF vs. LVAD	
Age	*z*: −0.8	*P*: 0.38	*z*: −1.7	*P*: 0.09	*z*: −0.7	*P*: 0.47
Male gender	0.06	*P*: 0.9	*z*: −1.09,	*P*: 0.27	: −1.07	*P*: 0.3
Smoke	*z*: −0.9	*P*:0.3	*z*: −1.14	*P*:0.25	*z*: −0.04	*P*:0.9
BMI	*t*: 3.1	*P*: 0.003	*t*: −1.6	*P*: 0.12	*t*: 1.6	*P*: 0.12
Heart rate	*t*: −3.1	*P*: 0.003	*t*: 7.9	*P*: 0.0001	*t*: 3.2	*P*: 0.02
NT-pro BNP	*z*: −1.3	*P*: 0.2	*z*: −4.7	*P*: 0.000	*z*: −2.8	*P*: 0.005
CRP	*z*: −0.1	*P*: 0.9	*z*: −0.5	*P*: 0.6	*z*: −0.8	*P*: 0.4
Baseline diameter[a]	*z*: −0.3	*P*:0.7	*z*: −0.6	*P*: 0.5	*z*: −0.8	*P*: 0.4
Peak diameter[a]	*z*: −0.4	*P*:0.7	*z*: −0.5	*P*:0.6	*z*: −0.9	*P*: 0.4
Absolute FMD change	*z*: −0.3	*P*: 0.8	*z*: −0.09	*P*: 0.9	*z*: −0.2	*P*:0.8
Percentage FMD change	*z*: −0.05	*P*: 0.9	*z*: −0.2	*P*: 0.8	*z*: −0.04	*P*: 0.9
LVEF (%)	*z*: −7.1	*P*: 0.000	*z*: −8.4	*P*: 0.0001	*z*: −1.2	*P*:0.2
Ischaemic aetiology	*z*: −1.6	*P*: 0.1	*z*: −1.8	*P*: 0.1	*z*: −2.8	*P*: 0.005

Abbreviations: BMI, body mass index; CRP, C-reactive protein; FMD, flow-mediated dilation; HF, heart failure; HT, heart transplantation; LVAD, left ventricular assist device; LVEF, left ventricle ejection fraction.
Statistical significance was considered for $P < 0.05$.
[a]Of brachial artery.

FMD (*Table 2*), we performed the correlation analyses with the main characteristics of the population using only the percentage of FMD change, the most widely used index of endothelial function, *Table 3*.[19]

This analysis showed only a significant negative correlation between FMD and CRP values among subjects with LVAD. No other significant correlations were found between population's characteristics and percentage difference of FMD.

Moreover, no other significant correlations were found among CPR and the other parameters of endothelial function (baseline and peak diameter of brachial artery and absolute FMD change), *Table 4*.

Discussion

The objective of our study was to investigate whether the use of continuous flow LVADs could exert negative effects on endothelial function compared to subjects with homogeneous anthropometric characteristics with chronic HF and HT. At this purpose, we compared three populations, expression of different stages of the same pathology, that is chronic HF.

Our analysis showed no significance differences as regards the several FMD parameters among subjects with LVAD, HF, and HT.

Moreover, endothelial function, expressed as percentage difference of FMD, was not affected by cardiovascular risk

Table 3 Correlation analysis between percentage FMD change and the main characteristics of the population

	FMD					
	LVAD		HT		HF	
	rho	*P*	rho	*P*	rho	*P*
Age	0.15	0.45	−0.07	0.6	−0.1	0.4
Male gender	0.15	0.46	−0.2	0.13	−0.05	0.7
Smoke	0.03	0.7	0.04	0.8	−0.2	0.2
BMI	0.2	0.26	−0.3	0.014	−0.2	0.16
Heart rate	−0.2	0.26	0.02	0.84	0.2	0.1
Mean arterial pressure	−0.11	0.57				
SBP			−0.2	0.09	−0.05	0.7
DBP			−0.19	0.16	−0.05	0.7
NT-pro BNP	−0.2	0.3	0.1	0.42	0.1	0.4
CRP	−0.4	0.02	−0.2	0.1	−0.02	0.8
LVEF (%)	0.01	0.9	0.09	0.5	0.18	0.3
NYHA class	0.2	0.27	−0.01	0.39	−0.1	0.6
Hypercholesterolaemia	0.2	0.18	0.05	0.7	0.03	0.8
Hypertension	0.2	0.2	−0.1	0.3	−0.1	0.47
Diabetes *N* (%)	−0.09	0.6	−0.2	0.2	−0.1	0.46
Obesity (%)	0.07	0.69	0.01	0.9	−0.2	0.1
Ischaemic aetiology	0.25	0.18	−0.2	0.06	0.002	0.9

Abbreviations: BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; FMD, flow-mediated dilation; HF, heart failure; HT, heart transplantation; LVAD, left ventricular assist device; LVEF, left ventricle ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure.
Statistical significance was considered for $P < 0.05$.

Table 4 Correlation analysis between the other FMD parameters and CRP

	LVAD		HT		HF	
	rho	*P*	rho	*P*	rho	*P*
	Baseline diameter[a]					
CRP	0.3	0.13	0.2	0.16	0.09	0.5
	Peak diameter[a]					
CRP	0.17	0.4	0.14	0.3	−0.07	0.7
	Absolute FMD change[a]					
CRP	−0.3	0.1	−0.1	0.4	−0.03	0.8

Abbreviations: CRP, C-reactive protein; FMD, flow-mediated dilation; HF, heart failure; HT, heart transplantation; LVAD, left ventricular assist device.
Statistical significance was considered for $P < 0.05$.
[a]Of brachial artery.

factors (hypertension, hypercholesterolaemia, diabetes, obesity, and tobacco habit), by the functional status expressed by NYHA class, by the left ventricular systolic function, and by the presence or absence of ischaemic heart disease in all the populations analysed (*Table 3*).

No further damage at the endothelial level is therefore associated with the use of these devices, as already demonstrated.[20,21]

In LVAD, cohort percentage of FMD change showed an inverse correlation with CRP (*Table 3*), a well-known marker of inflammation and tissue damage, associated with atherothrombotic events both in patients with known cardiovascular disease and in healthy individuals.[22]

The results show us how the mechanisms for regulating endothelial function are complex and not easily classified into specific categories, but inflammation plays the main role.[22]

Although the favourable effects on the endothelial function of the first generation of pulsatile flow LVADs have been widely demonstrated,[23,24] the increasingly widespread use of continuous flow LVADs makes open the discussion of the long-term effects of continuous flow on the cardiovascular system.

In addition to longitudinal stretching forces, the so-called "shear stress", the cyclical deformation produced by the pulsatility of the flow, represents an independent modulator of the endothelial function,[25] able, in fact, to exert an impact on nitric oxide synthase, cellular Ph, and physical alignment of blood cells, with effects also at the genic level.[10] The loss of pulse pressure could significantly endothelial function.

While the autoptic study of Potapov's group found no histological differences in the vascular beds between subjects with HF and subjects with continuous LVADs,[26] Segura's group highlighted the presence of changes in aortic tunica media related to continuous LVADs.[27] In addition, reduced pulsatility and cyclical deformation cause atrophy of vascular walls and reduction of vascular calibre.[28]

On the other hand, studies on humans are limited and show a deterioration or no improvement in endothelial function in subjects with LVADs.

In the study of Amir *et al*., subjects with continuous-flow LVADs had significantly lower FMD values than patients with pulse-flow LVAD, the latter associated with better vascular reactivity.[29]

In 2012, the study of Lou X *et al*.[20] evaluated endothelial function, through changes in the plethysmographic signal at the level of the finger artery for 5 min after reactive hyperaemia, in a group of seven patients in NYHA IV class before the LVAD implant, in a second group of six patients 1–4 months after the LVAD implant and in a third group of seven healthy subjects of the same age was used as a control group.

The results of the study showed significantly higher values of the reactive hyperaemia index (endothelial function measure) in the control group than in patients with HF and LVAD, while no difference between subjects with HF and LVAD, showing that the presence of LVAD had no effects on endothelial function in patients with HF.

On the other hand, Hasin *et al*.[30] evaluated the reactive hyperaemia index in eight subjects with HF before and after (5–14 days, 1–2 months, and 3–6 months) the LVAD implantation. The study showed a progressive decline in the hyperaemia index and therefore a worsening of endothelial function related to the LVAD.

In 2013, Morgan *et al*.[31] showed no significant differences as regards FMD among 20 patients with LVAD, 19 patients with HF, and 19 patients with HT.

Later, in 2015, the study of Hasin *et al*.[32] showed a persistent decline of endothelial function, evaluated through the reactive hyperaemia index, up to 5 months later LVAD implantation in 18 subjects with a parallel increase of adverse cardiovascular events.

Recently, the study of Symons *et al*. showed no effect of durable continuous flow LVAD support on coronary artery endothelial function and even an improvement in subjects with non-ischaemic dilated cardiomyopathy, using ex vivo isometric tension procedures among 16 patients with ischaemic cardiomyopathy, 22 patients with non-ischaemic-cardiomyopathy, and in 7 donor controls.[21]

Limitations

The study has some limitations: first, the small dimension of the samples analysed; second, we did not evaluate endothelium-independent dilation through the sublingual glyceryl trinitrate administration for the high risk of side effects in these populations of subjects already under hypotensive drugs; third, shear rate stimulus was not assessed.[17]

Conclusions

Our study demonstrated no significant effect of continuous flow LVAD on endothelial function compared with two homogeneous groups by age and gender of subjects with HF and HT. Endothelial function was not affected by cardiovascular risk factors (hypertension, hypercholesterolaemia, diabetes, obesity, and tobacco habit), by the functional status expressed by NYHA class, by the left ventricular systolic function, and by the presence or absence of ischaemic heart disease in all the populations analysed. CRP was the only factor able to influence percentage FMD change in LVAD subjects, reinforcing the hypothesis that inflammation is the main determinant of endothelial function.

In conclusion, continuous flow related to LVAD seems to not worsen endothelial function. Larger studies are needed to confirm this concept.

Conflict of interest

The authors have nothing to disclose.

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