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VASCULAR INFLAMMATION AND ABNORMAL AORTIC HISTOMORPHOMETRY IN PATIENTS FOLLOWING PULSATILE AND CONTINUOUS FLOW LEFT VENTRICULAR ASSIST DEVICE PLACEMENT

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Abstract

Objective—Left ventricular assist devices are increasingly used in patients with advanced heart failure as both destination therapy and bridge-to-transplantation. We aimed to analyze histomorphometric, structural and inflammatory changes following pulsatile and continuous flow left ventricular assist device placement.

Method—Clinical and echocardiographic data were collected from medical records. Aortic wall diameter, cellularity and inflammation were assessed by immunohistochemistry on aortic tissue collected at left ventricular assist device placement and at explantation during heart transplantation. Expression of adhesion molecules was quantified by western blot.

Results—Decellularization of the aortic tunica media was observed in patients receiving continuous flow support. Both device types showed an increased inflammatory response following left ventricular assist device placement with variable T cell and macrophage accumulations and increased expression of vascular E-selectin, ICAM and VCAM in the aortic wall.

Conclusion—Left ventricular assist device implantation is associated with distinct vascular derangements with development of vascular inflammation. These changes are pronounced in patients on continuous flow left ventricular assist and associated with aortic media decellularization. These findings help to explain the progressive aortic root dilation and vascular dysfunction in patients following continuous flow device placement.

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Disclosures

The authors declare no conflict of interest related to the subject of this study.

Keywords

Heart Failure; Left Ventricular Assist Device; Aorta

Introduction

Left ventricular assist devices are increasingly used in end stage heart failure as a bridge-to-transplant as well as destination therapy. Currently, continuous flow LVADs (cfLVADs) are the preferred device type because of their smaller size, long-term durability, energy efficiency, decreased thrombogenicity, lower risk of infection and decreased surgical trauma compared to pulsatile flow LVADs (pLVADs).^{3,5} Furthermore, past studies have demonstrated that cfLVADs are associated with increased survival during LVAD support in patients awaiting heart transplantation.^{5,6} Nevertheless, use of the current generation of continuous flow devices is associated with significant bleeding rates, in particular gastrointestinal bleedings due to arteriovenous malformations⁷ and van Willebrand factor (vWF) deficiency,⁸ cerebrovascular events,⁹ drive line and pocket infections,¹⁰ development of aortic insufficiency^{11,12} and a substantial rate of device thrombosis.^{13,14}

Current evidence suggests that pulsatile flow is not needed for systemic end-organ perfusion.^{2,3,15,16} However, the long-term implications of non-pulsatile blood flow on the vasculature, particularly the aorta, remain unclear and it has been reported that vascular compliance and distensibility are altered during cfLVAD support.¹⁷ The aim of this study was to compare vascular histomorphometric, molecular and physiologic changes in patients supported by pulsatile compared to cfLVADs.

Materials and Methods

We retrospectively analyzed 27 patients undergoing LVAD implantation as bridge-to-transplantation followed by subsequent LVAD explantation for cardiac transplantation at Columbia University Medical Center between February 2005 and November 2010. This included 15 pLVAD and 12 cfLVAD patients. The pLVAD group received the Heart Mate XVE device (Thoratec Corp, Pleasanton, CA, USA) and the cfLVAD group received the Heartmate II device (Thoratec Corp). All patients in the study had New York Heart Association stage IV HF at the time of LVAD implantation. Aortic tissue was collected at the time of LVAD placement (at the site of the outflow graft-aorta anastomosis) and at the time of LVAD explantation (at the site of end-to-end aortic anastomosis) during cardiac transplantation. Samples were immediately snap-frozen, placed in liquid nitrogen for transport and stored at -80°C until final analysis. Clinical and laboratory characteristics were collected from electronic medical records. Of the cohort, only 2 of the LVAD implant and explant samples were paired.

The present study was approved by the Institutional Review Board of Columbia University Medical Center. All patients provided written informed consent before inclusion into the study.

Echocardiography

Echocardiography was used to determine the dimensions of the proximal aortic root and determine any degree of aortic insufficiency (Philips Healthcare Crop, Andover, MA, USA). A standard comprehensive M-mode, 2D-echocardiogram and Doppler studies were performed on each patient before surgery.

Histomorphometric analysis

Formalin-fixed aortic tissue samples were embedded in paraffin and cut into 5- μ m thick sections. Hematoxylin and eosin staining (H&E) (Sigma) was carried out to determine cellularity and wall thickness of the aorta. Image J software (NIH) was used to quantify the number of cells for the tunica intima, media and adventitia of the aortic wall (100 $\times$ magnification, # of cells per mm²). Additionally, Image J software was used to quantify aortic wall thickness (40 $\times$ magnification, average of 3 measurements).

To prepare the sections for immunohistochemistry, the slides were deparaffinized and rehydrated. Antigen retrieval was completed with 10 mM sodium citrate (heated), pH 6.0 for 30 minutes. Sections were blocked in 6% normal serum and incubated with primary antibodies for 1 hour. CD3 (AbD Serotec, MCA1477) and CD68 (Abcam, ab955) antibodies were used and to detect the presence of T-cells and macrophages respectively. Endogenous horseradish peroxidase (HRP) activity was reduced by incubating the sections in a 3% peroxidase solution for 10 minutes. Sections were then incubated with the appropriate biotinylated secondary antibody for 30 minutes. Secondary staining was carried out using the VECTA-STAIN ABC kit (Vector Laboratories, Inc., Burlingame, CA). Sections were then developed using immPACT NOVA-red chromogen substrate (Vector Laboratories). Sections were counterstained with hematoxylin and dehydrated before mounting the coverslip. Image J software was used to quantify the number of T-cells and macrophages (100 $\times$ magnification, # of cells per mm²).

Protein analysis

Tissue homogenates were processed in 200–300 μ L of precipitation assay buffer (Sigma) supplemented with phosphatase and protease inhibitors (Roche, Indianapolis, IN.) Protein extraction was performed with standard techniques. Protein extracts were resolved on 4–15 % SDS-PAGE reducing gels (Bio-Rad) transferred to polyvinylidene difluoride membranes (Bio-Rad) and probed with E-Selectin (Santa Cruz Biotechnology, 3631-100), ICAM (Cell Signaling, SC-1511), VCAM (Santa Cruz Biotechnology, AC-1504) and GAPDH (Cell Signaling Technologies Inc., 3683S) antibodies. Membranes were washed in TBS and incubated with the appropriate secondary antibody conjugated to HRP. Detection was carried out using the ECL Western Blotting System kit (Thermo Scientific). All western blots were analyzed with the Molecular Imager Gel Doc XR+ system with Image Lab software (Bio-Rad).

Statistical analysis

Graphpad Prism 5 was used for all statistical analyses. Results for unpaired data were analyzed using two-tailed unpaired Student's t-tests. Data are expressed as mean $\pm$ SD. Values of $p < 0.05$ were considered significant.

RESULTS

Baseline Characteristics

We retrospectively analyzed 27 patients undergoing LVAD implantation as bridge-to-transplantation followed by LVAD explantation for HTx. This included 15 pLVAD patients (9 patients at implantation and 6 patients at explantation) and 12 cfLVAD patients (7 patients at implantation and 5 patients at explantation). Descriptive characteristics are shown in Table 1, with no significant differences in age, gender or BMI within the groups. Average duration of LVAD support for the pulsatile and continuous group was 237 ± 164 and 216 ± 132 days, respectively. Laboratory examinations before LVAD implantation and at LVAD explantation are summarized in Table 1.

Echocardiographic Assessment

A comparison of the mean proximal aortic root diameter pre-LVAD and post-LVAD demonstrated a non-significant increase of 0.16 ± 0.20 cm ($p=0.187$) for the continuous group and a slight decrease of 0.10 ± 0.35 cm ($p=0.56$) in the pulsatile group. Change in aortic root diameter was defined as aortic diameter at time of implant minus the aortic diameter just before explant. Also, we did not observe differences in the degree of aortic insufficiency ($p=0.21$).

Decellularization of the aortic media in cfLVAD patients

We next analyzed the cellularity of the aortic wall on H&E stained sections of the aorta (Figure 1). For the pulsatile group, we observed increased cellularity in the media and adventitia layers (34.4 ± 3.98 vs. 48 ± 3.59 cells per mm^2 in explants; $p=0.039$ and 32.5 ± 2.41 vs. 46.8 ± 5.06 cells per mm^2 in explants; $p=0.015$). In contrast, for the cfLVAD group, we observed decellularization of the media (32.0 ± 1.38 vs. 22.8 ± 2.51 cells per mm^2 at explantation; $p=0.006$).

T-cell and macrophage levels in post LVAD support patients

Sections of the aortic wall immunostained for T-cells (anti-CD3) and macrophage markers (anti-CD68) were used to determine the degree of inflammation in both pLVAD and cfLVAD patients (Figure 2A and 2B). There were no significant differences in T-cell (5.2 ± 3.2 in pLVAD vs. 8.2 ± 4.2 cells/ mm^2 in cfLVAD; $p=0.2255$) and macrophage counts (5.2 ± 2.6 in pLVAD vs. 6.86 ± 3.3 cells/ μm^2 in cfLVAD; $p=0.6549$).

Increased vascular expression of E-selectin, ICAM-1 and VCAM-1 in patients on cfLVAD support

Expression of adhesion molecules E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) in the aorta increased in patients following both pulsatile and continuous flow LVAD support (Figure 3A and 3B). All calculations achieved statistical significance except comparisons between ICAM-1 concentrations before and after cfLVAD treatment (E-selectin: 1.00 ± 0.14 vs. 2.21 ± 0.05 in pLVAD; $p=0.0002$, and 1.0 ± 0.38 vs 2.23 ± 0.31 in cfLVAD; $p=0.046$, ICAM-1: 1.00 ± 0.33 vs. 4.39 ± 0.82 in pLVAD; $p=0.008$, and 1.00 ± 0.42 vs 2.14 ± 0.47 in cfLVAD; $p=0.12$, VCAM-1:

1.00±0.32 vs 5.22±0.04 in pLVAD; $p=0.0001$ and 1.00±0.19 vs 1.81±0.14 in cLVAD; $p=0.014$).

Discussion

The advent of LVADs has dramatically changed the treatment options for patients with advanced HF. LVADs have been successfully implanted in both patients awaiting HTx as bridge-to-transplantation^{3,4} and in patients who are not candidates for HTx as destination therapy.² Nevertheless, associated morbidity remains high and vascular complications such as aortic insufficiency, thromboembolic events and bleeding remain frequent complications.^{6,8,10–12,14} The current study revealed distinct vascular rearrangements of the aorta following cLVAD implantation. This process is likely mediated, in part, by the clear inflammatory response of increased levels of several adhesion molecules reported after LVAD support.

Bioengineering has driven the development of smaller and technically more advanced ventricular assist devices and the switch from rather large pulsatile devices to smaller continuous flow devices. An important hemodynamic difference between cLVADs and pLVADs is that continuous-flow devices unload the failing left ventricle throughout the cardiac cycle, whereas pulsatile devices unload the LV only through a portion of the cardiac cycle triggered by either volume or the cardiac cycle. As a result, the effects of pre-load and after-load on output for the two device types are different. The pulsatile and non-pulsatile duality of these devices has a profound and different impact on the morphological and physiologic environment of the cardiovascular system, in particular, the aorta. While pulsatile devices pump blood in a pseudo-physiologic pulsatile pattern with changes in filling pressures of the aorta mimicking systole and diastole, continuous flow devices pump blood with nearly absent pulsatility to the aorta leading to continuous pressure patterns and relatively stable aortic wall tension and absent peripheral pulse. One might speculate that the observed progressive dilation seen in cLVADs results from the continuous pressure on the aortic wall and the inability of effective vascular relaxation due to the flow patterns of these devices.

Aortic insufficiency (AI) is a common complication after LVAD placement and the risk increases proportionately with duration of support.^{11,12} Hemodynamic changes following LVAD placement is thought to be the primary etiology of AI development and progression.¹¹ At higher levels of unloading and ventricular support, LV pressure and volume decrease progressively and as a result, the aortic valve is consistently closed.^{6,11,12} This pattern is used in the RAMP studies analyzing the relationship between LVAD performance and ventricular unloading patterns.¹⁸ Chronic closure or only rare intermittent valve opening with concomitant valvular damage caused by high supralvalvular pressure and high velocity retrograde flow into the left ventricle can lead to progressive commissural fusion and reduced valve pliability.^{11,12} The malcoaptative valve in turn promotes the development of aortic insufficiency.^{6,11,12} Not surprising and in line with pathophysiologic changes seen in patients with progressive root dilation due to aortic media diseases such as Marfan's syndrome, aortic valve coaptation is sensitive to the diameter of the aortic annulus and subsequently aortic root dilation is a common hallmark of isolated AI.^{6,11,12} The

hemodynamic variations between cLVADs and pLVADs affect the vasculature differently and data on severe aortic dilation cases indicate that cLVAD flow dynamics may lead to an increased propensity for AI and related pathologies. We did not observe differences between the pulsatile and continuous groups regarding change in aortic diameter or degree of aortic insufficiency. Of note, it is possible that the size of each cohort limits this analysis.

Next, we attempted to investigate the possible differences in aorta histomorphometry due to LVAD flow modalities on a cellular and molecular level. The most powerful results indicated that dual LVAD hemodynamics alter the vasculature differently as there was a significant decrease in medial smooth muscle cell count post-cfLVAD support and overall increased cellularity post-pLVAD. Such a large disparity implies that the health and functionality of the aorta is altered depending on the lack of a pulse. This is similar to the findings of Segura et al. as they also observed morphologic changes in the aortic wall media post-cfLVAD support.¹⁹ Normal pulse and mean arterial pressure is required for ventricular-vascular coupling, the feedback process necessary for maintaining the appropriate vascular resistance and shear stress needed to optimize cardiac functionality. This is abnormal in advanced HF and partially restored following LVAD placement.²⁰ In cfLVAD patients, long-term support is typically characterized by diminished pulse pressure and hypotension. It is hypothesized that the hemodynamic characteristics associated with long-term use of cfLVADs might not allow the ventricular-vascular coupling to function properly. Therefore non-pulsatile hemodynamics is likely accompanied by stiffening of the vasculature which together further attenuates blood flow dynamics.^{19,21,22} After an extended period of non-pulsatile support, progressive vascular stiffening and arterial remodeling seem to develop that further impairs physiologic shear stress and wall tension.

To understand the mechanism mediating this phenomenon, we have demonstrated an increased vascular expression of the adhesion molecules VCAM-1, ICAM-1 and E-selectin during both pLVAD and cfLVAD support. These findings are significant, as increased vascular inflammation, at least in part, is regulated through expression of adhesion molecules and may play a pivotal role in the detrimental remodeling of the aorta seen following cfLVAD placement with progressive media decellularization. It has been well documented that increased expression of cell adhesion molecules is a pro-inflammatory marker and enhances the recruitment of monocytes to the vascular wall contributing to enhanced atherosclerosis.²³ Infiltrating macrophages and T-cells initiate remodeling through apoptotic pathways, growth factors, cytokines and matrix metalloproteinases.²³ However, we did not observe significant increases in concentrations of T-cell or macrophages in either cohort. As the process of T-cell and macrophage recruitment is well known, it is likely that the small sample size and lack of consistency in obtaining samples during the same timeframe of VAD support might have contributed to the lack of significant result. As our study is retrospective, the samples collected represent various different points in the pathology of the patients studied. Potentially, an analysis of a larger cohort would demonstrate the expected increase in macrophage and T-cell concentrations.

Our study has several limitations. Our present study is limited by its retrospective nature, single center design and small cohort size. Due to the different periods of clinical use of pLVADs versus cfLVADs, the patient population and clinical treatment algorithms (both

surgical and medical) are different. Differences in medical management could have an effect on our results. Medications common to HF therapies could exacerbate hypotension already seen during cfLVAD support. Further, only 2 of the samples analyzed in the current study were paired.

In conclusion, our study represents the first detailed analysis of histomorphometric, structural and molecular vascular changes in patients undergoing LVAD placement with different flow modalities. Decellularization and increased expression of pro-inflammatory adhesion molecules seem likely indicators of and contributors to vascular remodeling leading to progressive remodeling and dilation of the aorta. Further studies will analyze the impact of medical and pharmacologic treatments as well as the distinct flow and pulsatility patterns in newer assist devices on vascular remodeling and function in patients with advanced HF following LVAD support.

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Figure 1.

(A) H&E stained sections of human aortic tissue from pLVAD And cfLVAD patients at the time of implant and explant (100× magnification). (B) Cell counts (cells per mm²) for tunica intima, media and adventitia layers of the aorta pre-vs post cfLVAD and pre-vs. post pLVAD (C). *=p<0.05; **=p<0.01; ***=p<0.001

Figure 2.

(A) Immunohistological sections of aortic tissue for T-cells from pLVAD and cfLVAD Patients at the time of implant and explant (200× magnification). (B) Immunohistological Sections of aortic tissue for macrophages from pLVAD and cfLVAD patients at the time of I mplant and explant (200× magnification)

Figure 3.

Western Blot analyses for E-selectin, ICAM and VCAM in pLVAD and cfLVAD patients at implant and explant and Quantitative analyses for E-selectin, ICAM and VCAM. *= $p < 0.05$; **= $p < 0.01$; ***= $p < 0.001$

Table 1

Baseline characteristics and laboratory values.

	Pulsatile Flow			Continuous Flow		
	Pre-LVAD (n=9)	Post-LVAD (n=6)	p-value	Pre-LVAD (n=7)	Post-LVAD (n=5)	p-value
Male (n(%))	7 (78)	5 (83)	0.476	5 (71)	4 (80)	0.188
Age (yrs)	52 ± 15	61 ± 8	0.209	60 ± 10	63 ± 9	0.576
Race/ethnicity			<0.0001			0.002
Caucasian	5 (56)	5 (83)		3 (43)	3 (60)	
African American	2 (22)	1 (17)		1 (14)	1 (20)	
Other	2 (22)	0 (0)		3 (43)	1 (20)	
BMI (kg/m²)	29 ± 4	31 ± 11	0.731	24 ± 4 *	25 ± 6	0.763
BSA (m²)	2.06 ± 0.15	1.99 ± 0.18	0.465	1.87 ± 0.31	1.89 ± 0.35	0.902
Heart Rate	88 ± 17	86 ± 18	0.523	80 ± 13	75 ± 13	0.572
Systolic BP (mmHg)	99 ± 20	128 ± 23	<0.0001	98 ± 10	–	–
Diastolic BP (mmHg)	70 ± 13	69 ± 10	0.892	64 ± 13	–	–
Mean Arterial BP (mmHg)	80 ± 19	89 ± 10	0.280	76 ± 11	85 ± 13 #	0.058
Etiology of HF (n(%))			0.002			0.774
Ischemic Cardiomyopathy	4 (44)	4 (67)		4 (57)	3 (60)	
Dilated Cardiomyopathy	5 (56)	2 (33)		3 (43)	2 (40)	
Ejection Fraction (%)	20 ± 7	18 ± 5	0.694	16 ± 4	18 ± 5	0.419
LVAD support (days)	–	237 ± 164		–	216 ± 132	
Medications (n(%))			<0.0001			<0.0001
Diuretics	6 (67)	4 (67)		7 (100)	4 (80)	
β-blocker	6 (67)	3 (50)		7 (100)	3 (60)	
ACE/ARBs	5 (56)	2 (33)		2 (29)	1 (20)	
Aspirin	4 (44)	3 (50)		2 (29)	3 (60)	
Coumadin	4 (44)	1 (17)		2 (29)	2 (40)	
Statins	4 (44)	2 (33)		5 (71)	2 (40)	
Insulin	3 (33)	0 (0)		1 (14)	1 (20)	
Anti-arrhythmic	3 (33)	1 (17)		2 (29)	2 (40)	

	Pulsatile Flow			Continuous Flow		
	Pre-LVAD (n=9)	Post-LVAD (n=6)	p-value	Pre-LVAD (n=7)	Post-LVAD (n=5)	p-value
Digoxin	3 (33)	3 (50)		3 (43)	2 (40)	
Vasodilators	2 (22)	0 (0)		0 (0)	0 (0)	
Laboratory Values						
WBC ($\times 10^9/L$)	10.9 $\pm$ 3.7	7.2 $\pm$ 2.1	0.049	9.4 $\pm$ 4.6	7.4 $\pm$ 0.7	0.352
Hematocrit (%)	34 $\pm$ 8	33 $\pm$ 5	0.649	33 $\pm$ 4	35 $\pm$ 7	0.705
Platelets ($\times 10^9/L$)	163 $\pm$ 88	200 $\pm$ 49	0.362	231 $\pm$ 91	193 $\pm$ 81	0.479
Glucose (mg/dL)	126 $\pm$ 57	132 $\pm$ 45	0.814	138 $\pm$ 69	130 $\pm$ 54	0.837
Sodium (mEq/L)	135 $\pm$ 4	139 $\pm$ 1	0.029	132 $\pm$ 3	138 $\pm$ 2	0.003
Potassium (mEq/L)	4.0 $\pm$ 0.5	4.2 $\pm$ 0.2	0.456	4.2 $\pm$ 0.4	4.0 $\pm$ 0.1	0.286
BUN (mg/dL)	27 $\pm$ 12	28 $\pm$ 10	0.842	39 $\pm$ 21	26 $\pm$ 10	0.222
Creatinine (mg/dL)	1.3 $\pm$ 0.4	1.5 $\pm$ 0.4	0.337	1.6 $\pm$ 0.6	1.3 $\pm$ 0.5	0.39
Albumin (g/dL)	3.5 $\pm$ 0.9	3.7 $\pm$ 0.7	0.738	3.7 $\pm$ 0.2	3.6 $\pm$ 0.7	0.95
Total bilirubin (mg/dL)	1.7 $\pm$ 1.0	0.7 $\pm$ 0.2	0.038	1.1 $\pm$ 0.5	0.9 $\pm$ 0.3	0.299
Direct bilirubin (mg/dL)	0.5 $\pm$ 0.4	0.1 $\pm$ 0.1	0.055	0.4 $\pm$ 0.2	0.3 $\pm$ 0.2	0.454
AST (U/L)	85 $\pm$ 188	31 $\pm$ 25	0.502	28 $\pm$ 12	22 $\pm$ 8	0.346
ALT (U/L)	41 $\pm$ 59	26 $\pm$ 8	0.57	64 $\pm$ 82	40 $\pm$ 47	0.567
APT (U/L)	79 $\pm$ 25	88 $\pm$ 41	0.62	93 $\pm$ 37	120 $\pm$ 45	0.27
Cholesterol (mg/dL)	139 $\pm$ 45	156 $\pm$ 51	0.515	112 $\pm$ 24	159 $\pm$ 50	0.053
HDL (mg/dL)	31 $\pm$ 14	41 $\pm$ 14	0.209	28 $\pm$ 9	47 $\pm$ 19	0.043
LDL (mg/dL)	77 $\pm$ 31	90 $\pm$ 44	0.527	61 $\pm$ 17	92 $\pm$ 36	0.068
Triglycerides (mg/dL)	122 $\pm$ 45	127 $\pm$ 46	0.845	117 $\pm$ 128	100 $\pm$ 25	0.785

LVAD -left ventricular assist device, BMI-body mass index, BSA-body surface area, BP-blood pressure, ACE/ARBs-Angiotensin-converting enzyme/Angiotensin II receptor blocker, WBC-white blood count, BUN-blood urea nitrogen, AST-aspartate aminotransferase, ALT-alanine aminotransferase, APT-alkaline phosphatase, BNP-b-type natriuretic peptide, HbA1c-hemoglobin A1c, HDL-high density lipoprotein, LDL-low density lipoprotein, TNF α -tumor necrosis factor alpha. Continuous variables are expressed as mean $\pm$ standard deviation.

* p<0.001 for pre-pLVAD versus pre-cfLVAD.

Doppler occlusion pressure.