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Macrovascular and microvascular function after implantation of left ventricular assist devices in end-stage heart failure: Role of microparticles

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KEYWORDS:
left ventricular assist device;
endothelial function;
microvascular perfusion;
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BACKGROUND: The hemodynamic vascular consequences of implanting left ventricular assist devices (LVADs) have not been studied in detail. We investigated the effect of LVAD implantation compared with heart transplant (HTx) on microvascular and macrovascular function in patients with end-stage heart failure and evaluated whether microparticles may play a role in LVAD-related endothelial dysfunction.

METHODS: Vascular function was assessed in patients with end-stage heart failure awaiting HTx, patients who had undergone implantation of a continuous-flow centrifugal LVAD, and patients who had already received a HTx. Macrovascular function was measured by flow-mediated vasodilation (FMD) using high-resolution ultrasound of the brachial artery. Microvascular function was assessed in the forearm during reactive hyperemia using laser Doppler perfusion imaging and pulsed wave Doppler. Age-matched patients without heart failure and without coronary artery disease (CAD) (healthy control subjects) and patients with stable CAD served as control subjects. Circulating red blood cell ($CD253^+$), leukocyte ($CD45^+$), platelet ($CD31^+/CD41^+$), and endothelial cell ($CD31^+/CD41^-$, $CD62e^+$, $CD144^+$) microparticles were determined by flow cytometry and free hemoglobin by enzyme-linked immunosorbent assay.

RESULTS: FMD and microvascular function were significantly impaired in patients with end-stage heart failure compared with healthy control subjects and patients with stable CAD. LVAD implantation led to recovery of microvascular function, but not FMD. In parallel, increased free hemoglobin was observed along with red and white cell microparticles and endothelial and platelet microparticles. This finding indicates destruction of blood cells with release of hemoglobin and activation of endothelial cells. HTx and LVAD implantation led to similar improvements in microvascular function. FMD increased and microparticle levels decreased in patients with HTx, whereas shear stress during reactive hyperemia was similar in patients with LVADs and patients with HTx.

CONCLUSIONS: Our data suggest that LVAD support leads to significant improvements in microvascular perfusion and hemodynamics. However, destruction of blood cells may

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contribute to residual endothelial dysfunction potentially by increasing nitric oxide scavenging capacity.
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Left ventricular assist devices (LVADs) are considered a vital therapeutic option to assist temporarily or permanently the failing circulation in patients with end-stage heart failure as a bridge to heart transplant (HTx) or in elderly patients as destination treatment.[1] Several studies demonstrated that continuous flow LVADs improve morbidity and mortality in critically ill patients awaiting HTx, while reducing adverse events.[2,3] Most patients with a continuous flow system exhibited significantly increased daily functional capabilities compared with before implantation.[4] Nevertheless, cardiovascular mortality and morbidity are still greater than after HTx. In this context, the impact of LVADs on arterial endothelial function has not been studied in detail.

Heart failure is associated with endothelial dysfunction.[5] Structural maintenance of arteries is coupled to blood flow to a significant degree by shear stress-dependent endothelial nitric oxide (NO) production. In the absence of endothelial nitric oxide synthase (eNOS), arteries lose their ability to couple blood flow demands to vascular structural remodeling.[6] Decreased eNOS-dependent vasodilation, as measured by flow-mediated vasodilation (FMD), has been linked to increased progression of early atherosclerosis and poor cardiovascular outcome.[7] Several mechanisms lead to impaired NO bioavailability. Free NO is scavenged rapidly by cell-free hemoglobin.[8] Hemolysis is a relevant sequela of several LVAD types, especially axial LVADs.[9] Destruction of red blood cells (RBCs) is the result of wall shear stress, flow acceleration, and interaction with artificial surfaces[10] and leads to release of free hemoglobin and RBC microparticles, which are defined by the expression of CD235 antigen. Increased levels of RBC microparticles have been found in patients with sickle cell disease[11] and β-thalassemia major,[12] which are also characterized by hemolysis. However, the role of RBC microparticles in patients with LVADs is unknown.

Microparticles are membrane particles with a diameter <1 μm that are thought to be shed from endothelial cells and various blood cells, including platelets, leukocytes, and erythrocytes, and released in the circulation.[13–15] The microparticles in the circulation constitute a heterogeneous population of different cellular origins, numbers, size, and antigenic composition. Proposed mechanisms of microparticle generation include apoptosis and cellular activation by cytokine.[13–16] NO synthesis and shear stress are key inhibitors of microparticle generation in endothelial cells.[16] RBC microparticles may be released during hemolysis.[17] Although microparticles circulate in blood from healthy individuals, their numbers are increased in blood samples from patients several cardiovascular diseases and conditions that predispose to cardiovascular disease,[13–15] and they are associated with adverse outcomes in patients with ischemic chronic heart failure[18] and in patients after LVAD implantation.[19] The literature suggests that the number of circulating microparticles may be a marker of endothelial activation or damage and platelet activation.[13,15] In addition, it was appreciated that microparticles harbor numerous membrane and cytoplasmic proteins from the cells from which they originate[20–22] and may play a role as a disseminated storage pool of bioactive effectors in intercellular communication mediating effects in cardiovascular physiology and pathophysiology.[13–15,23,24] Endothelium-derived microparticles of healthy subjects may carry a functional eNOS that is associated with better endothelium-dependent vasodilation,[25] whereas RBC microparticles appear to be potent NO scavengers owing to their hemoglobin content and parallel release of free hemoglobin during hemolysis.[26] It is unknown whether microparticle generation, potentially through hemolysis,[27] after LVAD implantation may affect vascular function. We investigated the effect of LVAD implantation compared with HTx on microvascular and macrovascular function in patients with end-stage heart failure and evaluated whether microparticles may play a role in LVAD-related endothelial dysfunction.

Methods

Study subjects and protocol

The study protocol was approved by the institutional review board of Heinrich-Heine University, and all subjects gave written informed consent (ClinicalTrials.gov Identifier: NCT02174133). Patients included in the study were screened and recruited from the patients routinely presenting in the specialized clinic within the Düsseldorf Heart Failure Program and were awaiting HTx (end-stage heart failure; status highly urgent was excluded from the study), had already received a Htx transplant, or were provided with a LVAD as a bridge to transplantation according to the definitions in the current guidelines.[28] Clinical data measurements were taken at 3 months after HTx or LVAD implantation. Patients with pump thrombosis were routinely excluded clinically and according to data retrieval from LVAD. Subjects for the 2 control groups were recruited from the general cardiology outpatient clinic. We included patients with stable coronary artery disease (CAD) and normal systolic left ventricular function (left ventricular ejection fraction $>60\%$) and healthy male subjects without signs or symptoms of cardiovascular disease who presented for a routine checkup. During the screening interview, control subjects were excluded if a physician had ever told them that they had cardiovascular disease, including coronary, lower limb, or carotid artery disease; they had experienced a myocardial infarction; they were taking any medication indicative of cardiovascular disease, including statins, daily aspirin, anti-diabetic medication (insulin, metformin), or blood pressure–lowering medication (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, beta blocker, diuretic, calcium channel blocker); or had symptoms