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FEATURED ARTICLES

Association between cell-derived microparticles and adverse events in patients with nonpulsatile left ventricular assist devices

Angelo Nascimbene, MD,[a] Ruben Hernandez, MD,[b] Joggy K. George, MD,[a] Anita Parker, RN,[b] Angela L. Bergeron, BS,[c] Subhashree Pradhan, PhD,[c] K. Vinod Vijayan, PhD,[c] Andrew Civitello, MD,[a] Leo Simpson, MD,[a] Maria Nawrot, PhD,[d] Vei-Vei Lee, MS,[e] Hari R. Mallidi, MD,[b] Reynolds M. Delgado, MD,[a] Jing Fei Dong, MD,[d,f] and O.H. Frazier, MD[b]

From the [a]Departments of Cardiology, Texas Heart Institute, Houston, Texas; and [b]Departments of Cardiovascular Surgery, Texas Heart Institute, Houston, Texas; the [c]Division of Thrombosis Research, Department of Medicine, Baylor College of Medicine, Houston, Texas; the [d]Puget Sound Blood Center, Seattle, Washington; the [e]Division of Biostatistics and Epidemiology, Texas Heart Institute, Houston, Texas; and the [f]Hematology Division, Department of Medicine, School of Medicine, University of Washington, Seattle, Washington.

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BACKGROUND: Continuous-flow left ventricular assist devices (LVADs) expose blood cells to high shear stress, potentially resulting in the production of microparticles that express phosphatidylserine (PS+) and promote coagulation and inflammation. In this prospective study, we attempted to determine whether PS+ microparticle levels correlate with clinical outcomes in LVAD-supported patients.

METHODS: We enrolled 20 patients undergoing implantation of the HeartMate II LVAD (Thoratec Corp, Pleasanton, CA) and 10 healthy controls who provided reference values for the microparticle assays. Plasma was collected before LVAD implantation, at discharge, at the 3-month follow-up, and when an adverse clinical event occurred. We quantified PS+ microparticles in the plasma using flow cytometry.

RESULTS: During the study period, 8 patients developed adverse clinical events: ventricular tachycardia storm in 1, non–ST-elevation myocardial infarction in 2, arterial thrombosis in 2, gastrointestinal bleeding in 2, and stroke in 3. Levels of PS+ microparticles were higher in patients at baseline than in healthy controls (2.11% ± 1.26% vs 0.69% ± 0.46%, $p = 0.007$). After LVAD implantation, patient PS+ microparticle levels increased to 2.39% ± 1.22% at discharge and then leveled to 1.97% ± 1.25% at the 3-month follow-up. Importantly, levels of PS+ microparticles were significantly higher in patients who developed an adverse event than in patients with no events (3.82% ± 1.17% vs 1.57% ± 0.59%, $p < 0.001$), even though the 2 patient groups did not markedly differ in other clinical and hematologic parameters.

Reprint requests: O.H. Frazier, MD, Texas Heart Institute, PO Box 20345, MC 3-147, Houston, TX 77225–0345. Telephone: 832-355-3000. Fax: 832-355-6798.

E-mail address: lschwenke@texasheart.org

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CONCLUSIONS: Our results suggest that an elevation of PS+ microparticle levels may be associated with adverse clinical events. Thus, measuring PS+ microparticle levels in LVAD-supported patients may help identify patients at increased risk for adverse events.
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Left ventricular assist devices (LVADs) have become a mainstream therapy for patients with end-stage heart failure who are considered ineligible for cardiac transplantation. LVADs are increasingly used as a bridge to transplant or as destination therapy because these devices are readily available and can be used in patients with a wide spectrum of heart failure symptoms. Compared with the first-generation pulsatile LVADs, the new continuous-flow LVADs have a lower rate of pump failure and have improved the overall patient survival rate.[1] However, device-related complications, especially those involving the extremes of the hemostasis spectrum (i.e., hemorrhage and thrombosis), may pose challenges to patient recovery after implantation and are a cause of morbidity in long-term support therapy.

Studies of LVAD-induced hemostatic defects have predominantly focused on the loss of high-molecular-weight von Willebrand factor (VWF) multimers,[2] which is believed to be caused by persistently high shear stress generated by the LVAD pump.[3] In addition, de novo arteriovenous malformations that are prone to bleeding can occur after LVAD implantation and spontaneously resolve after LVAD explantation.[4,5] These arteriovenous malformations occur primarily in the gastrointestinal tract,[6] but the underlying pathogenesis is poorly understood.[7] Patients also have an increased incidence of ischemic and hemorrhagic stroke.[8–10]

The clinical and pathologic effects of high shear stress generated by the LVAD pump on red blood cells, platelets, leukocytes, and endothelial cells are poorly understood. Blood cells and endothelial cells that have been activated or have undergone apoptosis produce membrane fragments known as microparticles, which are less than 1 μm in diameter.[11–15] Microparticles from apoptotic and mechanically disrupted cells express anionic phospholipids, especially phosphatidylserine (PS). Phosphatidylserine is essential for initiating and propagating the coagulation cascade at sites of vascular injury,[16,17] but PS can also induce endothelial damage in inflammatory conditions[11,16,18,19] and stimulate neoangiogenesis.[20] A persistent and systemic generation of microparticles can, therefore, lead to a sustained pro-inflammatory and pro-coagulant state and can cause activation of the endothelium, which responds to microparticle-bound tissue factor.[21–23] Significantly higher levels of microparticles from platelets, leukocytes, and endothelial cells have been reported in patients with LVADs than in healthy controls.[24] However, whether the elevated level of circulating microparticles found in these patients contributes to the development of adverse events, such as thrombosis and bleeding diathesis, is unclear.

In this pilot, prospective study, we assessed the levels of PS+ microparticles in patients before and after LVAD implantation to determine whether longitudinal changes in circulating PS+ microparticles are associated with the development of adverse events in LVAD-supported patients. Our findings suggest that PS+ microparticle levels may have prognostic value in predicting future clinical events.

Methods

The Texas Heart Institute Institutional Review Board approved this study. Informed consent was obtained from participants before enrollment.

Patients and study design

This prospective, observational study enrolled 20 patients who were eligible for LVAD implantation at the Texas Heart Institute and 10 healthy volunteers to provide normal reference values for microparticle assays. All patients received a HeartMate II (Thoratec, Pleasanton, CA) LVAD, which was implanted according to standard surgical procedure as destination therapy or as a bridge-to-heart transplant to treat New York Heart Association (NYHA) class IV symptoms. Patients on LVAD support received standard anti-thrombotic therapy with aspirin (81 mg/day), warfarin with a targeted international normalized ratio (INR) of 2 to 3, and dipyridamole, (75 mg 3 times daily).

Blood samples (30 to 40 ml) were collected by peripheral venipuncture at admission (baseline), at discharge after LVAD implantation (on average 28 days after implantation), and at 3 months after implantation. At each time point, we analyzed basic hematology and biochemistry variables (i.e., blood cell count, platelet count, renal function, and liver function), platelet consumption, coagulation profile, and hemolysis markers (i.e., lactate dehydrogenase [LDH], hemoglobin, hematocrit, bilirubinemia, and free plasma hemoglobin). LVAD function (i.e., power output, power index, and impeller speed) and mean arterial pressure on support were assessed during each follow-up visit. All tests were repeated when a patient was readmitted for an adverse clinical event (as defined below). Clinical events were recorded at each outpatient visit and in the event of readmission.

Inclusion and exclusion criteria

All patients who were eligible for LVAD implantation at the end of an institutional evaluation at the Texas Heart Institute, according to current consensus and guidelines,[25] were considered for inclusion in this study.

Patients with known malignancy, autoimmune disease, or hypercoagulable conditions were excluded, regardless of their eligibility for LVAD implantation. These exclusion criteria were instated to minimize confounding factors known to be associated with thrombotic risk independent of LVAD implantation.

Clinical adverse events

Adverse events were defined according to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) adverse event definitions. Major bleeding was defined as an episode