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FEATURED PAPERS

Evaluation of von Willebrand factor with a fully magnetically levitated centrifugal continuous-flow left ventricular assist device in advanced heart failure

Ivan Netuka, MD, PhD,[a,b] Tomáš Kvasnička, MD, PhD,[c] Jan Kvasnička, MD, PhD,[c] Ingrid Hrachovinová, MD,[d] Peter Ivák, MD,[a,e] František Mareček, MD,[d] Jana Bílková,[c] Ivana Malíková,[c] Michaela Jančová,[f] Jiří Malý, MD, PhD,[a] Poornima Sood, MD,[g] Kartik S. Sundareswaran, PhD,[g] Jean M. Connors, MD,[h] and Mandeep R. Mehra, MD[i]

From the [a]Department of Cardiac Surgery, Institute for Clinical and Experimental Medicine, Prague, Czech Republic; [b]Second Department of Surgery, First Faculty of Medicine, Charles University of Prague, Prague, Czech Republic; [c]Thrombotic Centre and Central Hematology Laboratory, Institute of Medical Biochemistry and Laboratory Diagnostics of the General University Hospital and First Faculty of Medicine of Charles University of Prague, Prague, Czech Republic; [d]NRL for Hemostasis, Institute of Hematology and Blood Transfusion, Prague, Czech Republic; [e]Third Faculty of Medicine, Charles University of Prague,Prague, Czech Republic; [f]Laboratory Methods, Institute for Clinical and Experimental Medicine, Prague, Czech Republic; [g]St. Jude Medical, Minneapolis, Minnesota, USA; [h]Department of Hematology, Brigham and Women's Hospital, Boston, Massachusetts, USA; and the [i]Heart and Vascular Center, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA.

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BACKGROUND: Contemporary continuous-flow left ventricular assist devices (CF-LVADs) are associated with degradation of von Willebrand factor (vWF) high-molecular-weight multimers (HMWMs), a critical factor supporting platelet function. We hypothesized that the HeartMate 3 fully magnetically levitated LVAD, designed to reduce circulatory shear stress, favorably influences these hemostatic parameters.

METHODS: Fifteen consecutive HeartMate 3 LVAD patients were compared with 11 consecutive HeartMate II controls. Serial plasma samples were collected pre-implant and on Days 2, 7, 30 and 45 post-operatively. Changes in vWF HMWMs were evaluated by 2 independent, study-blind hematologists and confirmed using densitometry-based computerized software. Ristocetin cofactor (RiCO) and vWF antigen (vWF Ag) were measured using standard protocols with enzyme-linked immunosorbent assay.

RESULTS: HeartMate 3 patients and HeartMate II controls had a mean age of 67.3 ± 1.4 and 52.8 ± 2.5 years, respectively (INTERMACS Profiles 2 to 4 in 93.3% and 91%, respectively). HeartMate 3 group demonstrated a significantly greater preservation of HMWMs compared with the HeartMate II group, with the most prominent decrease occurring by Day 2 post-operatively and sustained through 45 days (71.94% vs 31.16%, $p = 0.001$). Laboratory values (normalized to baseline) for RiCO activity, vWF Ag and RiCO: vWF Ag ratio remained in the functional range with no statistically significant differences observed between groups.

Reprint requests: Ivan Netuka, MD, PhD, Department of Cardiac Surgery, Institute for Clinical and Experimental Medicine, Vídeňská 1958/9, 140 21 Prague, Czech Republic. Telephone: +420-26-136-5017. Fax: +420-24-172-1362.

E-mail address: ivan.netuka@ikem.cz

See Related Editorial, page 857

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CONCLUSION: The HeartMate 3 LVAD is associated with enhanced hemocompatibility compared with the HeartMate II LVAD, as demonstrated by the improved preservation of vWF HMWMs, In contrast, effects on HMWM degradation appeared to be dissociated from functional attributes. Further confirmation of these findings in randomized clinical trials is warranted.
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Contemporaneous continuous-flow left ventricular assist devices (CF-LVADs) are a mainstay in the therapeutic armamentarium in selected patients with advanced heart failure. Although favorable 1- and 2-year survival rates of 80% and 70% have been reported,[1–3] significant morbidity related to major bleeding, neurologic complications and device thrombosis limits broader clinical acceptance of this therapy.[1,4,5]

Continuous flow, and consequent low pulsatility, can disrupt the normal circulation by increasing circulatory shear stress. In such settings, unique rheologic changes are noted, manifested as hemolysis due to deformation of circulating red blood cells[6,7] and, within plasma, as the development of an acquired von Willebrand syndrome (avWS).[8,9] Furthermore, these physiologic changes are associated with thrombosis and bleeding complications, which are reversed once heart transplantation restores a more normal pulsatile circulatory state.

The HeartMate 3 LVAD (St. Jude Medical, Minneapolis, MN) is engineered to enhance hemocompatibility by reducing shear stress on circulating blood elements. The centrifugal device rotor is fully magnetically levitated, allowing for consistently wide blood flow paths, and also features an intrinsic pulse intended to enhance washout.[10,11]Early data from the Conformité Européene (CE) Mark Trial[12] suggest that these design features are associated with absence of clinically relevant hemolysis and lower levels of lactate dehydrogenase (LDH) and plasma free hemoglobin (PHGB). However, the impact of these device characteristics on von Willebrand factor (vWF) remain unknown.

The primary purpose of our prospective investigation was to assess the effect of the HeartMate 3 on clinical measures of shear stress by serial evaluation of vWF high-molecular-weight multimers (HMWMs), and functional activity. Furthermore, we sought to compare and contrast these effects of the HeartMate 3 by using the HeartMate II (St. Jude Medical) axial-flow assist device as a control.

Methods

Patients

The study was approved by the institutional ethics committee and informed consent was obtained from all patients before LVAD implantation.

Patients were enrolled at a single center within the HeartMate 3 CE Mark Trial and sequentially within the HeartMate 3 LIS (less invasive study) along with a consecutive control cohort of HeartMate II patients (Figure 1). The procedure was performed either via median sternotomy or as a less invasive implant via left lateral mini-thoracotomy combined with upper partial hemi-sternotomy, both on cardiopulmonary bypass. The inflow cannula was placed into the LV apex and the outflow graft anastomosed to ascending aorta. Unfractionated heparin was used in all procedures until target anti-coagulation with warfarin was reached. Based on our institutional standard-of-care anti-thrombotic regimen, all patients were maintained on warfarin therapy with a target international normalized ratio (INR) of 2.0 to 3.0. HeartMate 3 recipients were also prescribed an anti-platelet agent (acetylsalicylic acid 100 mg) as required by the study protocol, whereas HeartMate II patients were not treated with anti-platelet therapy in accordance with our institutional practice standard. If INR dropped below the therapeutic range, low-molecular-weight heparin was used for bridging.

Sample collection and laboratory assessment

Patients' characteristics, medical history, laboratory assessments, anti-coagulation, anti-platelet medications, device programming, echocardiographic aortic valve opening parameters and clinical outcomes were assessed over the course of LVAD support. Serial hematologic indices and blood plasma sample collection were conducted pre-implant and on Days 2, 7, 30 and 45 post-operatively in all patients (Figure 1). All enrolled patients completed the follow-up.

HMWM analysis

Multimeric structure was determined by separation of plasma vWF multimers with 1.6% sodium dodecylsulfate (SDS) agarose gel electrophoresis,[13] with minor modifications. Samples were diluted between 1:20 and 1:60, based on vWF antigen concentration to obtain commensurate samples for vWF multimer analysis (buffer of 10 mmol/liter Tris-HCl, 1 mmol/liter ethylene-diamine tetra-acetic acid, 2% SDS [pH 8.0]) and subjected to overnight electrophoresis. Separated multimers were then transferred onto nitrocellulose by electroblotting with 50 mmol/L phosphate buffer (pH 7.4), containing 0.04% SDS, and incubated sequentially with a

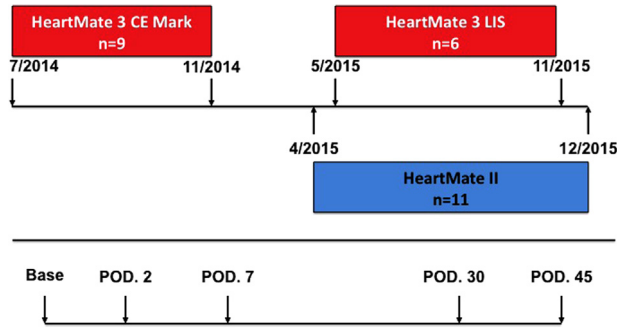

Figure 1 Study enrollment and sample collection timeline.