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Hemolysis: A harbinger of adverse outcome after left ventricular assist device implant

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BACKGROUND: The clinical relevance of elevated serum markers of hemolysis during left ventricular assist device (LVAD) support has not been fully ascertained.

METHODS: Lactate dehydrogenase (LDH) and serum free hemoglobin (sfHg) values were tallied monthly in 182 patients on HeartMate II (Thoratec, Pleasanton, CA) LVAD support. Peak values for each marker were identified, and 2 hemolysis definitions were applied to the cohort: Hemolysis according to Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) criteria (sfHg $>$ 40 mg/dl with signs/symptoms) and/or hemolysis defined by an LDH $\geq$ 600 IU/liter (2.5-times the upper limit of laboratory normal). Kaplan-Meier survival free from death, urgent United Network of Organ Sharing 1A transplant for thrombosis, device exchange for thrombosis, and stroke/peripheral embolism was estimated, and Cox hazard ratios (HR) with the 95% confidence interval (95% CI) were calculated. Areas under the receiver-operating characteristic curves (AUCs) for predicting 1-year event-free survival were calculated.

RESULTS: Hemolysis occurred in 32 patients (18%) by INTERMACS criteria and in 68 (37%) patients by LDH criteria. Over a median (25^{th}, 75^{th}) support of 427 days (245, 793 days), there were 78 events. One year event-free survival after the onset of INTERMACS-defined hemolysis was 16% $\pm$ 8.3% compared with 85% $\pm$ 3.2% in non-hemolyzers (HR, 14.7; 95% CI, 7.9–27; AUC 0.70 $\pm$ 0.05; $p < 0.001$;). One year event-free survival after the onset of LDH-defined hemolysis was 32% $\pm$ 7.2% compared with 89% $\pm$ 3.2% in those with persistent LDH values $<$ 600 IU/liter (HR, 8.0; 95% CI, 4.4–14; AUC 0.87 $\pm$ 0.04; $p < 0.001$). Patients who met the LDH hemolysis definition had longer times from hemolysis onset to clinical events and larger magnitudes of risk for embolism and device exchange for thrombosis than those with INTERMACS hemolysis.

CONCLUSIONS: Serum hemolysis marker elevations are associated with increased events in LVAD patients. LDH monitoring provides an earlier diagnosis of adverse events than sfHg, supporting need for a new INTERMACS definition of VAD-associated hemolysis.

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Device thrombosis and hemolysis have gained recent attention in the field of mechanical circulatory support (MCS). In major trials of continuous-flow (CF) pumps with axial-flow (AF) design (CFAF), rates of confirmed device thrombosis were low (2 events in the HeartMate II Destination Therapy trial and 4 in the Bridge to Transplant

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Pivotal trial), but overall study follow-up was short (155 days–1.5 years).[1,2] In the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) 2012 third quarter report of 6,033 patients with continuous-flow LVAD implants, 448 hemolysis episodes were reported in 363 patients.[3] To date, only 8 deaths in the INTERMACS Registry have been directly attributed to hemolysis.[3]

Although device thrombosis is not common and reported deaths from thrombosis are low, its occurrence subjects patients to great risks, including organ failure, heart failure, embolic events, and need for reoperation. Hemolysis, evidenced by an elevation in serum markers representing red blood cell disintegrity, (eg lactate dehydrogenase [LDH] and serum free hemoglobin [sfHg]) or by the presence of clinical signs such as hemoglobinuria and jaundice, has not been well studied, and the accuracy of the current INTERMACS definition of hemolysis (sfHg $>$ 40 mg/dl with clinical signs and symptoms) is not known.[4] The aims of this analysis were to (1) assess the frequency of index hemolysis episodes during CFAF-LVAD support, (2) assess the associated morbidity and mortality of hemolysis episodes, and (3) compare the magnitudes of risk associated with the presently accepted INTERMACS definition of hemolysis vs one based soled on elevations in serum LDH.

Methods

This was a single-center cohort study of consecutive patients who underwent implant of CFAF-LVAD support (HeartMate II devices, Thoratec Corp, Pleasanton, CA) at the University of Michigan (UM) Cardiovascular Center between January 2006 and December 2012. Excluded were 11 patients who survived $<$ 30 days after implant and 3 actively on long-term ($>$30 days) biventricular support. All patients were enrolled in the UM Mechanical Circulatory Support Database, a prospective registry of patients undergoing implantation of a MCS device. Patients provided written informed consent before study inclusion.

Serum markers of hemolysis were obtained prospectively beginning 30 days after LVAD implant and included sfHg and LDH. Samples for laboratory analysis were obtained daily after device implant until hospital discharge and then monthly thereafter as part of the UM outpatient device management protocol. In the setting of device exchange for non-thrombotic indications, tallying of hemolysis markers was resumed 30 days after pump exchange.

Patients were then classified as INTERMACS hemolyzers, LDH hemolyzers ($\geq$ 600 IU/L), dual hemolyzers (LDH $\geq$ 600 IU and sfHg $>$ 40 mg/dl), and non-hemolyzers (for each definition). The index hemolysis episode date and numeric value for the measured marker in each hemolysis category was recorded such that a patient could be an LDH hemolyzer and (simultaneously or on separate occasion) an index INTERMACS hemolyzer. According to the INTERMACS definition, the INTERMACS hemolyzers were required to have a sfHg $>$ 40 mg/dl with clinical signs or symptoms.[4] The signs and/or symptoms used for defining INTERMACS hemolysis were an elevated serum bilirubin, drop in Hg $>$ 1 g/dl, sustained power spikes on VAD interrogation 2W over baseline, hemoglobinuria, or heart failure symptoms.

The LDH threshold for LDH hemolysis criterion (an LDH $\geq$ 600 IU/L at any time during LVAD support) was obtained from UM LVAD sample data and was ~3 standard deviations from the sample mean (361 $\pm$ 76 mg/dl) and represents 2.5-times the upper limit of the UM laboratory normal. As demonstrated by Shah et al,[5] LDH values $>$ 600 IU/L are associated with increased risk of pump thrombosis in CFAF pumps.[5] Patients were classified as LDH or dual-hemolyzers solely by elevations of LDH and sfHg; these definitions did not require clinical signs or symptoms of hemolysis or thrombosis. For patients without sfHg and/or LDH values above threshold, the peak value obtained during the period of LVAD support was tallied.

Outcomes

The primary outcome of interest was survival free of death, pump exchange for suspected thrombosis, urgent United Network of Organ Sharing (UNOS) 1A transplant for device thrombosis, or peripheral embolic event (including ischemic stroke) from the onset of hemolysis or from device implant in those without hemolysis. Patients undergoing transplant for indications unrelated to device thrombosis or hemolysis were censored at the time of transplant. Secondary outcomes included (individually) death, freedom from device exchange for thrombosis, and freedom from combined peripheral embolism (e.g., limb ischemia, organ infarction) and ischemic stroke. Primary and secondary outcomes of interest were compared for INTERMACS hemolyzers (sfHg $>$ 40 mg/dl with signs/symptoms) vs all others (sfHg $\leq$ 40 mg/dl and/or no signs or symptoms), LDH hemolyzers (LDH $\geq$ 600 IU/L) vs all others (LDH $<$ 600 IU/L), and dual hemolyzers (LDH $\geq$ 600 IU/L with concomitant sfHg $>$ 40 mg/dl) vs all others (sfHg $\leq$ 40 mg/dl and LDH $<$ 600 IU/L).

Measurement of hemolysis markers

SfHg was measured using spectrophotometry (reference range values, 1.0–8.0 mg/dl). Enzymatic methods and a Siemens ADVIA 1800 machine (Siemens Inc, Erlangen, Germany) were used to quantify LDH activity (reference range, 120–240 IU/L).

Institutional device management algorithms

The UM preoperative protocol is as follows: Patients with international normalized ratios (INRs) $>$ 1.2 are normalized with vitamin K at the discretion of the implanting surgeon. Oral glycoprotein IIb/IIIa antagonists and direct thrombin inhibitors are stopped $>$ 10 days before surgery. Aspirin therapy is maintained. Administration of intraoperative blood products is at the discretion of the surgeon. Aprotinin use was discontinued after March 2008, and factor VII is not used.

Intravenous heparin is initiated post-operatively to maintain a partial thromboplastin time of 40 to 50 seconds. Warfarin is initiated when chest tubes are removed to achieve a goal INR of 2 to 3. On Post-operative Day 1, anti-platelet therapy with aspirin (81–325 mg daily) and dipyridamole (150–300 mg daily) is initiated. Aspirin and warfarin are continued in the outpatient setting, and INR monitoring is performed every 7 to 14 days through our anti-coagulation service. Since 2010, we have instituted the use of sub-cutaneous low molecular weight heparin (1 mg/kg twice daily) if INRs drop $<$ 1.8, and aspirin dosing has been increased from 81 to 325 mg in those without peptic ulcer disease or other contraindications.

Patients with concern for LVAD-induced hemolysis were admitted and administered intravenous heparin (regardless of INR) and intravenous fluids. Use of eptifibatide and/or tissue plasminogen activator was at the discretion of the surgeon. Device exchange was not performed solely because of elevated serum

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