LVAD-Associated von Willebrand Factor Degradation Alters Angiogenesis: A Mechanistic Link Between LVAD Support, Gastrointestinal Angiodysplasia, and Bleeding


Purpose: Gastrointestinal (GI) bleeding occurs frequently in patients with a left ventricular assist device (LVAD). Evidence suggests a major role for von Willebrand Factor (vWF). However, a mechanistic link between vWF degradation and GI angiodysplasia has not been explored. We investigated whether LVAD-associated vWF degradation fragments generated by shear stress and ADAMTS-13 (the vWF protease) affected angiogenesis in vitro.

Methods: Purified human vWF protein and/or recombinant human ADAMTS-13 protein was exposed to LVAD-like shear stress (4 hours, ~175 dyne/cm²). Human umbilical vein endothelial cells (15,000 cells, n=8/condition) were cultured with: 1. vWF, 2. Small vWF multimers generated from shear stress, 3. vWF + ADAMTS-13, 4. vWF fragments from ADAMTS-13 cleavage during shear stress. Small vWF multimers and vWF fragments were characterized by gel electrophoresis and immunoblotting. Endothelial angiogenesis was quantified with a Matrigel assay (vasculogenic tube formation), a scratch assay (migration), 5-ethyl-2'-deoxyuridine uptake (proliferation), and terminal transferase dUTP nick-end labeling (apoptosis). For the first time, these data suggest that LVAD-associated vWF degradation fragments alter angiogenesis. These data support our novel hypothesis for LVAD-associated GI angiodysplasia. Abnormal angiogenesis in bowel mucosa, which proliferates continuously, may promote GI angiodysplasia and predispose LVAD patients to bleeding events.

Results: All indices of angiogenesis were abnormal when endothelial cells were grown with LVAD-associated vWF degradation fragments. Endothelial migration (450±49 vs. 277±53 μm, p = 0.01), vascular tube formation (36.8±4.0 vs. 19.7±3.6 mm, p < 0.001), and proliferation (12±3 vs. 6±1%, p = 0.08) decreased with vWF degradation fragments. Similarly, endothelial proliferation decreased with small vWF multimers (10±2 vs. 1±1%, p = 0.002). Endothelial apoptosis increased with small vWF multimers (12±2 vs. 36±2%, p < 0.001) and with vWF fragments (15±2 vs. 23±2%, p = 0.03).

Conclusion: For the first time, these data suggest that LVAD-associated vWF degradation fragments alter angiogenesis. These data support our novel hypothesis for LVAD-associated GI angiodysplasia. Abnormal angiogenesis in bowel mucosa, which proliferates continuously, may promote GI angiodysplasia and predispose LVAD patients to bleeding events.

Thrombophilias Prospective Detection Tailored Anticoagulation Protocol Without Antiplatelet Therapy in Patients With Axial-Flow Ventricular Assist Device

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Purpose: Current recommendations for antithrombotic therapy for patients with the HeartMate II (HMII) left ventricular assist device (LVAD) include the use of both an anticoagulant (Warfarin) and an antiplatelet agent. In order to reduce the risk of bleeding, device induced abnormalities such as acquired von Willebrand syndrome have been reflected in recent trials using protocols without anti-platelet therapy in HMII patients. On the other hand, an impact of patient related factors as thrombophilias mutations to the bleeding and thrombotic complications still remain chronically overlooked.

Methods: 119 HMII consecutive patients have been prospectively screened for major thrombophilias mutations (Factor II Prothrombin, Factor V Leiden and homozygote MTHFR). Subsequently, consistently anti-platelet free protocol with individualized Warfarin anticoagulation with target INR of 2.5-3.0 in thrombophilia positive and INR of 1.8-2.2 in negative patients have been conducted.

Results: Mean age was 51±12 years, 83% were male and total follow-up on LVAD reached 111±5 years. Mean HMII support duration was 342±301 days. At 1 year post implant in major thrombophilias positive cohort, freedom from bleeding, hemorrhagic stroke, ischemic stroke and pump thrombosis were 97±3%, 100%, 84±9% and 94±4% respectively. Whereas, at 1 year endpoint in thrombophilias negative group, freedom from bleeding, hemorrhagic stroke, ischemic stroke and pump thrombosis were 91±3%, 94±3%, 93±4% and 94±3% respectively. Statistical analysis did not identify any significant differences between corresponding groups.

Conclusion: To the best of our knowledge this is a first reported consecutive cohort of this individualized approach. Data suggest that managing HMII patients without aspirin may help to reduce the incidence of major bleeding without increasing the risk of thromboembolic events including ischemic stroke and device thrombosis as compared to recent clinical series. Importantly, individualized thrombophilias based antithrombotic protocol may lead to a safe incremental decrease of target INR level to 1.8-2.2 in negative population while keeping a risk of bleeding events in thrombophilic group with more aggressive anticoagulation regimen in impeccably low rates. Further, prospective randomized studies are needed.