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 angiodyplasia 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 dynes/cm²). Human umbilical vein endothelial cells (15,000 cells, n=6/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 (vacular tube formation), a scratch assay (migration), 5-ethyl-2'-deoxyuridine uptake (proliferation), and terminal transferase dUTP nick-end labeling (apoptosis).

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. 8±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.

Association of Warfarin Genotype With Thrombosis and Bleeding Events in Continuous-Flow Left Ventricular Assist Device (CF-LVAD) Patients


Purpose: Previous studies have suggested an association between rare variants in Warfarin metabolism genes with over-anticoagulation and an increased risk of bleeding events. The effect of rare variants on frequency of bleeding and thrombosis events in CF-LVAD patients remains unknown.

Methods: Patients who underwent CF-LVAD implantation at our center and had Warfarin genotype data were included in this analysis. DNA was extracted from peripheral blood. Genotypes tested were rs1799853 (c430C>A) in VKORC1, rs1057910 (c1075A>C) in CYP2C9 genes and rs9923231 (-1639G>A) in VKORC1 gene. Patients were categorized based on presence or absence of any rare variants in CYP2C9 and VKORC1 genes. Groups were then comparatively analyzed for LVAD-related complications.

Results: 77 patients with Warfarin genotype data were identified. 19 patients (24.6%) carried at least one rare variant in CYP2C9 gene whereas 22 patients (28.6%) carried at least one rare variant in VKORC1 gene. INR variability was increased in patients carrying the rare VKORC1 genotype (0.692 vs. 0.557 < p=0.0001) or the rare CYP2C9 genotype (0.709 vs. 0.58, p<0.0001). Carrying a rare genetic variant in CYP2C9 (OR 0.69, p=0.568) or VKORC1 (OR 0.62, p=0.462) genes did not alter the risk of GI Bleeding Events. Rare variants in CYP2C9 gene also did not have an effect on risk of device thrombosis (OR 1.27, p=0.717). However, patients carrying a rare variant in VKORC1 gene which increases sensitivity to Warfarin had significantly higher risk of device thrombosis compared to patients with wild-type only alleles (27.0% vs. 7.7% at 1 year, respectively, OR 4.76, p=0.030, Figure).

Conclusion: Our findings suggest an association between rare VKORC1 variants that increase sensitivity to Warfarin, increased INR variability, and risk of device thrombosis. Genotype specific warfarin dosing algorithms to reduce INR variability should be explored.

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 anti-platelet 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 thrombophila 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 p/t/years. Mean HMII support duration was 342±301 days. At 1 year post implant in major thrombophilias positive 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 impecabbly low rates.

Conclusion: To the best of our knowledge this 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 impecabbly low rates. Further, prospective randomized studies are needed.
Blood Product Utilization With Left Ventricular Assist Device Implantation: A Decade of Statewide Data

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Purpose: Blood transfusion (BTx) with cardiac surgery is associated with inferior outcomes. Although studies have shown a decrease in BTx rates with cardiac surgery over time, this trend has not been examined for patients undergoing left ventricular assist device (LVAD) implantation. We examined the BTx trends with LVAD implantation in a statewide database.

Methods: We analyzed STS data on all primary LVAD implants for long-term circulatory support.

Results: Between July 2004 to June 2014, 666 LVADs were implanted (age 54.5±12.6 yrs. 77% men); as bridge to transplantation 74.2%, destination therapy 23.5% and 2.3% as bridge to recovery. Preoperative variables included- DM 43%, HTN 65%. Hct 34.7±6 gr/dl, plt count 203 K±87 K/ml, BMI 28.5±6, ECMO support 1.8% and IABP use 21%. Re-op for bleeding was required in 22%. Post-op mortality was 13.2%. Over the decade, use of any blood products with LVAD surgery ranged from 83% to 100% (92±5.3%) (Fig). Intra-op and post-op blood products use was 71.8% and 73% respectively. Only 7.4% of patients did not receive any blood products. BTx during surgery consisted of plasma (60%), platelets (42%), RBCs (44.3%) and cryoprecipitate (32%), whereas after surgery RBC blood products was more frequent 68%, followed by plasma 42%, platelets 36% and cryoprecipitate 16%. Mean units of individual component BTx per LV AD use was 68%, followed by plasma 42%, platelets 36% and cryoprecipitate 16%. Mean units of individual component BTx per LVAD implantation were- RBC 8±11, plasma 6.2±7.8, platelets 2.6±3.8 and cryoprecipitate 1±1.9. Compared to the initial 5 years (2005 - 2009), the cryoprecipitate 16%. Compared to the initial 5 years (2005 - 2009), the cryoprecipitate 16%.

Conclusion: BTx with LVAD implantation remain very high. While the frequency of BTx remains same over the decade of study, the amount of blood product usage has decreased in the last five years. Efforts to further reduce the BTx with LVAD implantation need to be implemented.

Impact of Diastolic Dysfunction on Primary Graft Dysfunction (PGD) After Lung Transplantation

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Purpose: PGD is a significant cause of early morbidity and mortality after lung transplantation and is characterized by severe hypoxemia and infiltrates in the allograft. The pathogenesis of PGD is unclear, however subclinical increases in pulmonary venous pressure from left ventricular (LV) diastolic dysfunction may contribute by increasing capillary leak. We hypothesized that a higher ratio of early mitral inflow velocity (E) to early diastolic mitral annular velocity (e′), indicative of worse diastolic function, would be associated with a higher risk of PGD.