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Review:

Bleeding continues to be a major adverse event in LVAD implants that impacts patient's functionality and increases morbidity and mortality. This adverse event has been associated with degradation of the von Willebrand Factor (VWF) multimer due to blood flow pathways of high shear stress. This phenomenon has been replicated in mock loops and proven in other types of mechanical circulatory support. Moreover, dysfunctional or deficiency of the vWF multimer has been associated with angiodysplasia formation and dysregulated angiogenesis causing increase bleeding of the gastrointestinal tract. In this month "what's new in MCS" we comment on 2 articles focusing on the issue of bleeding and angiogenesis in LVAD patients.

1. Journal of Heart and Lung Transplantation

Netuka I, Kvasnička T, Kvasnička J, et al. Evaluation of von Willebrand factor with a fully magnetically levitated centrifugal continuous-flow left ventricular assist device in advanced heart failure. *J Heart Lung Transplant*. 2016 Jul;35(7):860-867

The objective of the current study was to evaluate the effect of the HeartMate 3 (HM3) on clinical measures of shear stress by serial assessment of the vWF high molecular weight multimer (HMWM) compared to HeartMate II as control. The hypothesis was that the HM3 due to its magnetic fully levitated centrifugal rotor and wide blood flow paths would reduce shear stress. Fifteen HM3 and 11 HM II controls were analyzed. The HM3 group was older (mean age 67), of ischemic etiology and implanted as destination therapy. The HMII were younger (mean age 53), of non-ischemic etiology and bridge to transplant. Most were INTERMACS 2-4. On the patient-device interaction, no significant differences were noted for LDH values at baseline or follow up and the average speed for HMII was 8800 rpm vs. 5200 rpm for HM3. At 45 ± 15 days, more patients in the HM3 group had opened aortic valves during the cardiac cycle compared to HMII group (40% vs. 18.1%) with 33.3% of HM3 cohort having their aortic valve opening every beat compared to 18% of the HMII. A higher preservation of the vWF HMWM was noted in those with an aortic valve opening, but no statistical analysis was done due to small numbers. The HMWM primary analysis showed that HM3 patients had larger presence vWF multimers present compared to HMII with the most prominent presence of the multimer at postoperative day 2. A triple comparative analysis with the primary analysis supported the divergent pattern of HMWM degradation with preservation of the multimer in the HM3 cohort vs. HMII cohort. No statistical differences were noted among other functional indices of vWF activity including ristocetin cofactor activity, plasma vWF antigen concentration and vWF ristocetin activity/antigen ratio. Regarding clinical outcomes, all patients were followed by 180 days with no episodes of right heart failure, clinical hemolysis or pump thrombosis noted. The authors did however reported a similar instance of bleeding between both cohorts based on INTERMACS bleeding definition (63% for HMII and 60% for HM3).

Commentary: This study highlights the importance of developing hemocompatible devices to diminish adverse events. The advances in flow technology proposed by the new HeartMate 3 may allow to make this possible. Although the present study sheds light in the interaction between blood contact surfaces and rheological properties of these devices, it does not show a difference in bleeding events at 180 days. Perhaps longer follow up, avoidance of aspirin may reduce this significant event. More so, the fact that reduced or absent vWF-HMWM leads to bleeding has been inconclusive and no causal mechanisms explaining bleeding due to acquired vWF syndrome have been described. This unanswered question still looms with new evidence pointing towards endothelial factors that may be involved in the bleeding regulation process.

2. Circulation

Tabit CE, Chen P, Kim GH, et al. Elevated Angiopoietin-2 Level in Patients With Continuous-Flow Left Ventricular Assist Devices Leads to Altered Angiogenesis and Is Associated With Higher Nonsurgical Bleeding. *Circulation*. 2016 Jul 12;134(2):141-52.

Angiopoietin-2 (Ang-2) is part of a group of angiopoietins that promote angiogenesis. It is synthesized by endothelial cells and stored with von Willebrand factor. It does however promote abnormal growth of vessels causing destabilization and inflammation. Mice overexpressing Ang-2 develop dilated, redundant capillaries in the GI tract. The objective of this study was to evaluate the expression of Ang-2 in LVAD patients and to assess its correlation with neovascularization and nonsurgical bleeding (NSB). A total of 32 heart failure (HF), 44 LVAD and 25 orthotopic heart transplant (OHT) patients were analyzed. Similar age, gender, race and renal function were noted. For the LVAD cohort, 32 were axial flow (AX) and 12 were centrifugal flow (CF). Pulse pressure was higher in the HF and OHT groups compared to LVAD groups and higher for the CF vs. AX VADs. The LVAD cohort showed elevated Ang-2 circulating levels compared to HF and OHT groups. Among LVADs, patients with CF had significantly higher Ang-2 levels compared to AX. Fresh isolated endothelial cells from the vena cava were obtained on all cohorts. Elevated Ang-2 expression was higher in LVAD patients compared to HF or OHT patients suggesting that overexpression of this protein in the endothelium may be responsible for the elevated circulating levels seen in LVAD patients. When serum of LVAD patients was taken to incubate human endothelial cells in vitro, an increase in tubule formation and angiogenesis was noted compared to plasma from HF or OHT patients. Furthermore, thrombin levels in LVAD patients were higher which is stimulated Ang-2 overexpression. Electronic medical records of all patients with LVAD were reviewed for instances of GI bleeding, intracranial hemorrhage or epistaxis. Among LVAD patients with serum Ang-2 level above the mean 12.32 ng/mL more non-surgical bleeding was noted compared to those with below the mean values. No relationship between Ang-2 and NSB was noted at 6 months. Ang-2 levels were significantly high in bleeders vs. no bleeders (27.69 ± 9.74 ng/mL vs. 9.99 ± 7.18 ng/mL; $P < 0.001$). no significant association was found between aortic valve opening or pulse pressure and NSB events or Ang-2 expression.

Commentary: The results of this study provide novel findings in the disruptive angiogenesis molecules seen in LVAD patients and may explain the increase risk of bleeding in some LVAD patients based on Ang-2 levels. However no relationship between AVM and Ang-2 was direct addressed. The authors did however noted that all patients with NSB had AVMs on endoscopy. Ang-2 levels in those LVAD patients with constant aortic valve opening were lower compared to intermittent or never opening but this was not statistically significant nor the association with pulse pressure, aortic valve opening and Ang-2 levels. However, none of the HF or OHT patients experienced NSB whose pulse pressure was higher than LVAD patients. Also, the fact 6 months after LVAD implant no bleeding was associated with Ang-2 levels, may show that other factors contribute to AVM and bleeding. Thus, pulsatile flow and finding more hemocompatible surfaces may still play a role in reducing risk of GI bleed. The findings of the study using this novel biomarker, Ang-2 may allow to further risk stratify those LVAD patients who will be at risk of bleeding postoperatively.

Journal of Heart and Lung Transplantation

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- Wever-Pinzon O, Naka Y, Garan AR, et al. National trends and outcomes in device-related thromboembolic complications and malfunction among heart transplant candidates supported with continuous-flow left ventricular assist devices in the United States. *J Heart Lung Transplant*. 2016 Jul;35(7):884-92
- Yu Xia, David Stern, Patricia Friedmann, Daniel Goldstein. Preoperative atrial fibrillation may not increase thromboembolic events in left ventricular assist device recipients on midterm follow-up. *J Heart Lung Transplant* 2016;35:906–912
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JACC Heart Failure

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- Koudoumas D, Malliaras K, Theodoropoulos S, et al. Long-Term Intra-Aortic Balloon Pump Support as Bridge to Left Ventricular Assist Device Implantation. *J Card Surg*. 2016 Jul;31(7):467-71

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- Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* (2016) 37 (27): 2129-2200