Editorial

Stop the LVAD bleeding

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Among the therapeutic options available for patient with advanced heart failure, left ventricular assist devices (LVAD) are a safe and durable option as bridge to transplantation or as destination therapy. Despite improving survival and quality of life, nonsurgical bleeding—manifesting as epistaxis, gastrointestinal bleeding, and hemorrhagic strokes—contribute to plague this group of patients and is a major cause of both morbidity and mortality and contributes to a significant socioeconomic burden. While much has been made of shear forces, breakdown of von Willebrand polymers, and anticoagulation regimens, little has changed with respect to LVAD-related bleeding complications. As such, much interest exists to identify biomarkers that could not only predict these events but that could also inform potential therapeutic targets.

Most recently, Tabit and colleagues from the University of Chicago reported the result of their study investigating the relationship between markers of angiogenesis and nonsurgical bleeding in three groups of patients: those supported with an LVAD, those with chronic heart failure, and those who received heart transplantation (1). They hypothesized that LVAD-related nonsurgical bleeding results from arteriovenous malformations (AVM) that are mechanistically based on deregulation of angiopoietin-2. Angiopoietins are a family of vascular growth factor molecules that promote embryonic and postnatal angiogenesis. There are four identified angiopoietins. Angiopoietin-1 (Ang1) is critical for vessel maturation, adhesion, migration, and survival. Ang1 is expressed by pericytes and vascular smooth muscle cells and is a major agonist for the tyrosine kinase receptor, Tie-2. Binding of Ang1 to Tie-2 promotes vessel integrity, inhibits vascular leakage, and suppresses inflammatory gene expression. Angiopoietin-2 (Ang2), on the other hand, promotes cell death and disrupts vascularization. Yet, when it is in conjunction with vascular endothelial growth factors (VEGF), it can promote neo-vascularization. Ang-2 is produced and stored in Weibel-Palade bodies in endothelial cells and acts as an antagonist for Tie-2. As a result, endothelial activation, destabilization, and inflammation are promoted.

In the general population, high levels of circulating Ang2 and Tie-2 soluble receptor in serum are associated with a greater risk for all-cause and cardiovascular mortality suggesting that subtle increases in Ang2 levels might reflect processes including pathologic vascular remodeling (2). In patients who have suffered acute myocardial infarction, level of serum Ang1, Ang2 and Ang2/Ang1 ratio are elevated and correlate with the extent of myocardial damage (3). Angiopoietins have been implicated in heart failure patients as serum Ang2 levels and Ang2/Ang1 ratios are positively correlated with pro-BNP levels and negatively correlated with left ventricular ejection fraction (LVEF). Ang2 levels are progressively increased with hemodynamic and functional decline in these patients and is an independent risk factor for mortality in patients with acute decompensate heart failure (4).

In the Tabit study, the investigators performed an elegant translational study that correlated human patient phenotypes to *in vitro* mechanistic findings. They demonstrated that

LVAD patients have a shift in Tie2 regulation from Ang1 to Ang2 as well as over-expression of VEGF. This expression pattern favors abnormal angiogenesis, and, interestingly, was reversed in patients who had their LVADs removed with transplantation. They identified a potential source of elevated Ang2 in the of freshly-isolated vena cava endothelial cells. They were able to clinically correlate over-expression of Ang2 with increased risk of nonsurgical bleeding events within the first three months post LVAD implantation. They further observed that LVAD patients have a persistently elevated activated contact coagulation system, with increased factor XII and XIa, that ultimately leads to excess thrombin activation. Thrombin activation is then tied to induction of Ang2 secretion.

The authors can lean on a strong history suggesting that dysregulation of angiogenetic factors like Ang1, Ang2 and VEGF, are responsible for angiodysplasia and bleeding complications in different human organs. Cerebral arteriovenous malformations, small bowel angiodysplasia and inflammatory bowel disease, soft tissue vascular malformations, as well as tumor angiogenesis and progression have a shared denominator of angiogenetic factors imbalanced expression. Intracranial vessels are exposed to abnormal high blood flow and shear forces that activate molecular pathways in smooth muscle cells and brain endothelial cells leading to proliferation and vascular remodelling. In sporadic or genetic mutation related cerebral AVMs, Ang-2 has a role in deconstructive signalling, promoting remodelling, and vessel destabilization (5). Mechanistically, vascular instability has been correlated with increased Ang2 mRNA and protein levels, decreased Ang1 protein levels, and markedly decreased Tie2 protein and Tie2 mRNA levels (6).

In patients with inflammatory bowel disease, both Ang2 and Tie-2 levels are elevated (7). Sporadic small bowel angiodysplasia account for 50% of obscure gastrointestinal bleeding and is thought to occur due to a dysregulation in the angiogenic pathways. Indeed, elevated serum levels of Ang2 and decreased levels of Ang1 were found in patients with small bowel angiodysplasia and anemia. Furthermore there is significant difference in gene expression levels of Ang1, Ang2 and the Tie2 receptor in affected angiodysplasia tissue areas compared with controls, further strengthening the likely role of this factor in the pathogenesis of intestinal AVM formation (8). Herein lies the rationale for the use of thalidomide in this patient population as it can inhibit Ang2 even a low concentrations (9).

Obviously, angiogenesis plays an important role in oncologic science. Indeed unbalanced expression of angiopoietins promotes tumorigenesis and a high Ang2/Ang1 ratio correlates with poor prognosis in many solid tumours. As such, therapeutic approaches targeting the angiopoietin-Tie system are being investigated. In studies of AMG-386 (a peptide trapping both Ang1 and Ang2) and CVX-060 (selective antibody against Ang2), a significant reduction in tumor blood flow was observed (10). Similarly, other targeted inhibitors of Ang2 have shown some pre-clinical efficacy in decreasing blood flow and growth of tumors (11,12).

Taken together, the Tabit study offers much food for thought with regards to a major adverse event in LVAD patients. Nonsurgical bleeding in LVAD patients is more than a menace for these patients. Significant resources associated with rehospitalization and diagnostic and therapeutic procedures (endoscopy, angiography, etc.) compound the effect on the patients. For example, many of these patients have to stop their anticoagulation, thereby putting them at risk for thrombotic events. Having a biomarker, such as Ang2, to predict those at higher risk for angiodysplastic bleeding might inform clinicians as to selective management of anticoagulation. Outside of anecdotal reports with various medicines (mesalamine, thalidomide), few novel approaches have been identified for this problem. Targeted therapies aimed at the Ang2 axis, supported by well-performed, mechanistic studies such at offered by Tabit and colleagues, give hope to these patients and will be welcomed by the advanced heart failure community.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. 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;134:141-52.
2. Lorbeer R, Baumeister SE, Dörr M, et al. Circulating

angiopoietin-2, its soluble receptor Tie-2, and mortality in the general population. Eur J Heart Fail 2013;15:1327-34.
3. Chen S, Guo L, Cui M, et al. Dynamic changes in serum angiopoietin-1, angiopoietin-2, and angiopoietin-2/angiopoietin-1 ratio in acute myocardial infarction patients treated with primary percutaneous coronary intervention. Biomarkers 2012;17:441-6.
4. Eleuteri E, Di Stefano A, Giordano A, et al. Prognostic value of angiopoietin-2 in patients with chronic heart failure. Int J Cardiol 2016;212:364-8.
5. Hashimoto T, Wu Y, Lawton MT, et al. Coexpression of angiogenic factors in brain arteriovenous malformations. Neurosurgery 2005;56:1058-65;discussion 1058-65.
6. Young IR, Loose JM, Kleftogiannis F, et al. Prostaglandin E2 acts via the hypothalamus to stimulate ACTH secretion in the fetal sheep. J Neuroendocrinol 1996;8:713-20.
7. Koutroubakis IE, Xidakis C, Karmiris K, et al. Potential role of soluble angiopoietin-2 and Tie-2 in patients with inflammatory bowel disease. Eur J Clin Invest 2006;36:127-32.
8. Holleran G, Hall B, O'Regan M, et al. Expression of Angiogenic Factors in Patients With Sporadic Small Bowel Angiodysplasia. J Clin Gastroenterol 2015;49:831-6.
9. Feng Q, Tan HH, Ge ZZ, et al. Thalidomide-induced angiopoietin 2, Notch1 and Dll4 downregulation under hypoxic condition in tissues with gastrointestinal vascular malformation and human umbilical vein endothelial cells. J Dig Dis 2014;15:85-95.
10. Huang H, Lai JY, Do J, et al. Specifically targeting angiopoietin-2 inhibits angiogenesis, Tie2-expressing monocyte infiltration, and tumor growth. Clin Cancer Res 2011;17:1001-11.
11. Thomas M, Kienast Y, Scheuer W, et al. A novel angiopoietin-2 selective fully human antibody with potent anti-tumoral and anti-angiogenic efficacy and superior side effect profile compared to Pan-Angiopoietin-1/-2 inhibitors. PLoS One 2013;8:e54923.
12. Zhang ZL, Zhang JF, Yuan YF, et al. Suppression of angiogenesis and tumor growth in vitro and in vivo using an anti-angiopoietin-2 single-chain antibody. Exp Ther Med 2014;7:543-52.

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