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Dysregulation of the Angiopoietin-2/Tie-2 Axis is Associated with Reduced Pulsatility and Increased Arteriovenous Malformation Related Gastrointestinal Bleeding Following Left Ventricular Assist Device Implantation

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Disclosures

- I will not discuss off label use and/or investigational use of drugs/devices
- The following relevant financial relationships exist related to this presentation: None

Background

- Left ventricular assist devices (LVADs) decrease mortality and improve quality of life among patients with advanced heart failure (HF)
- Gastrointestinal bleeding (GIB) is a common complication of LVAD support, occurring in 18-40% of patients
  - 30-50% of GIB episodes are attributable to arteriovenous malformations (AVMs)
- Associated with reduced quality of life

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Aggarwal A, Pant R, Kumar S, et al.: Incidence and management of gastrointestinal bleeding with continuous flow assist devices *Ann Thorac Surg* 93: 1534–1540, 2012
Kushnir VM, Sharma S, Ewald GA, et al.: Evaluation of GI bleeding after implantation of left ventricular assist device *Gastrointest Endosc* 75: 973–979, 2012
Morgan JA, Paone G, Nemeh HW, et al.: Gastrointestinal bleeding with the HeartMate II left ventricular assist device *J Hear Lung Transplant* 31: 715–718, 2012
Demirozu ZT, Radovancevic R, Hochman LF, et al.: Arteriovenous malformation and gastrointestinal bleeding in patients with the HeartMate II left ventricular assist device. *J Heart Lung Transplant* 30: 849–53, 2011

Background: Why do LVAD patients develop GIB?

- Clinical associates
  - Age
  - RV failure
  - Reduction/loss of pulsatile blood flow with continuous flow devices

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Tomizawa Y, Tanaka A, Kitahara H, et al.: Preoperative Right-Sided Cardiac Congestion Is Associated with Gastrointestinal Bleeding in Patients with Continuous-Flow Left Ventricular Assist Devices *Dig Dis Sci*, 2018
Sparrow CT, Nassif ME, Raymer DS, Novak E, LaRue SJ, Schilling JD: Pre-Operative Right Ventricular Dysfunction Is Associated With Gastrointestinal Bleeding in Patients Supported With Continuous-Flow Left Ventricular Assist Devices *JACC Hear Fail* 3: 956–964, 2015
Jabbar HR, Abbas A, Ahmed M, et al.: The Incidence, Predictors and Outcomes of Gastrointestinal Bleeding in Patients with Left Ventricular Assist Device (LVAD) *Dig Dis Sci* 60: 3697–3706, 2015

Background: Why do LVAD patients develop GIB?

- Laboratory associates
  - Acquired von-Willebrand deficiency due to shearing and destruction of the vWF multimers
  - Elevated Angiopoietin-2

Uriel N, Pak SW, Jorde UP, et al.: Acquired von Willebrand syndrome after continuous-flow mechanical device support contributes to a high prevalence of bleeding during long-term support and at the time of transplantation *J Am Coll Cardiol* 56: 1207–1213, 2010
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* 134: 141–52, 2016

Background: Blood vessel homeostasis

- Angiogenesis in adults is tightly regulated through activating and inhibitory signals, including the angiopoietins (Ang-1, Ang-2) and their receptor, Tie-2

Fagiani E, Christofori G: Angiopoietins in angiogenesis *Cancer Lett* 328: 18–26, 2013

Background: Blood vessel homeostasis

- Ang-1
  - Expressed by pericytes, vascular smooth muscle cells, and fibroblasts
  - Binding to Tie-2 receptor stimulates intracellular pathways which *promote endothelial cell survival, maintenance of an endothelial barrier, and vascular stability*
- Ang-2
  - Transcription induced by VEGF, tissue hypoxia
  - Production is low at baseline and upregulated upon angiogenic activation
  - Binds to Tie-2 receptor, however it is a weaker agonist than Ang-1 and therefore acts as an antagonist by displacing Ang-1 from the receptor
  - *Allows endothelium to respond to destabilizing and angiogenic signals; promotes blood vessel sprouting*

Fagiani E, Christofori G: Angiopoietins in angiogenesis *Cancer Lett* 328: 18–26, 2013

Purpose

- To evaluate the association between Ang-2, Tie-2, and VEGF with AVM-GIB and its clinical associates

Methods

- We evaluated 65 patients who underwent LVAD implantation at Loyola University Medical Center with Heartmate II (n=52) or HeartWare (n=13) devices
- Blood samples were obtained at routine outpatient visits a median of 13 (IQR 1.7-31.5) months following LVAD implantation
  - Samples were collected as part of a biobank repository independent of the present study
  - Samples were analyzed for levels of Ang-2, Tie-2, and VEGF using commercially available ELISAs

Methods

- Charts were reviewed to identify incidence of GIB due to AVMs
  - GIB was defined as an admission with clinical evidence of bleeding accompanied by a decrease in hemoglobin of at least 1 g/dL
  - AVM related GIB was defined by visualization of an AVM on endoscopy
- Patients were divided into two groups: Those that developed GIB due to AVMs, and those that did not
- Demographic, clinical, laboratory, imaging, and hemodynamic data were collected by chart review

Results

- Baseline characteristics
  - Patients that developed AVM-GIB were older at the time of LVAD implantation (63±10 vs. 53±15 years; p=0.048)
  - All other baseline characteristics were similar between groups
  - Most patients were male (71.8%) and Caucasian (58.5%). The majority of patients had non-ischemic cardiomyopathy (56.9%)
  - Atrial fibrillation was present in 43.1% of patients

Results

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Biomarkers in patients with AVM related GIB vs those without AVM related GIB

	AVM-GIB (n=19)	No-AVM-GIB (n=38)	P
Ang-2 (pg/mL)	8169 ± 4471	6560 ± 3978	0.02
Tie-2 (ng/mL)	20.0 ± 3.3	17.3 ± 4.0	0.07
VEGF (pg/mL)	200.5 ± 183.3	216.6 ± 220.9	0.70

Results

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Biomarkers in patients with frequent aortic valve opening vs those with less frequent aortic valve opening

	Aortic valve opens ≥ 80% of cardiac cycles (n=29)	Aortic valve opens <80% of cardiac cycles (n=36)	P
Ang-2 (pg/mL)	5566 ± 3691	7948 ± 4226	0.02
Tie-2 (ng/mL)	16.3 ± 3.2	19.6 ± 4.5	0.001
VEGF (pg/mL)	142.4 ± 121.3	253.4 ± 233.2	0.016

Results

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Biomarkers in patients with and without significant right ventricular dysfunction

	No or mild tricuspid regurgitation (n=32)	Moderate or severe tricuspid regurgitation (n=33)	P
Ang-2 (pg/mL)	7009 ± 3921	6765 ± 4404	0.81
Tie-2 (ng/mL)	18.9 ± 4.1	17.4 ± 0.79	0.17
VEGF (pg/mL)	215.2 ± 223.5	193.4 ± 173.1	0.66
	Pulmonary artery pulsatility index ≥ 2.6 (n=32)	Pulmonary artery pulsatility index < 2.6 (n=29)	P
Ang-2 (pg/mL)	6692 ± 4110	6995 ± 4109	0.77
Tie-2 (ng/mL)	17.7 ± 4.0	18.6 ± 5.1	0.44
VEGF (pg/mL)	223.4 ± 191.2	171.6 ± 127.1	0.21

Results summary

- Elevated levels of Ang-2 and Tie-2 were associated with AVM related GIB in patients supported by LVADs
- Ang-2, Tie-2, and VEGF were higher among patients whose aortic valve opened less frequently
- There was no correlation between these biomarkers and invasive or non-invasive indicators of right ventricular dysfunction

Conclusions

- Dysregulation of the Ang-2/Tie-2 axis among LVAD patients may be associated with AVM specific GIB
- Reduced pulsatility may be associated with elevations of these markers, providing a possible mechanistic link between reduced pulsatility and GIB in LVAD patients

Thank you

- Questions?
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