von Willebrand Factor Degradation Fragments Are A Mechanistic Link Between Continuous-Flow LVAD Support And Gastrointestinal Angiodysplasia And Bleeding

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• No relevant disclosures
Gastrointestinal Bleeding During LVAD Support

- 25 – 40% of patients
- Most frequent cause of hospital readmission
- Gastrointestinal angiodysplasia is the most common source
- LVAD support causes a distinct form of intestinal angiodysplasia

Control Small Bowel

LVAD Small Bowel

What is the mechanism of angiodysplasia formation during LVAD support?

LVAD Support Causes von Willebrand Factor (vWF) Degradation

- vWF is an important regulator of angiogenesis
- LVAD support causes marked degradation of vWF into small vWF fragments

What is the relationship between vWF degradation and angiodysplasia?
Clinical Study

What is the profile of vWF in LVAD patients with gastrointestinal bleeding?

- Continuous-flow LVAD patients (n=35, 417±53 days support)
- Paired blood samples
- Quantified vWF
- Stratified patients as non-bleeders or gastrointestinal bleeders
- Confirmed angiodyplasia via endoscopy
In all patients, LVAD support caused significant degradation of vWF protein.
Clinical Results – Non-Bleeders vs. Angiodysplasia Bleeders

- 28 non-bleeders
- 7 bleeders from intestinal angiodysplasia

vWF Fragments

- vWF fragments were significantly higher in LVAD patients with gastrointestinal angiodysplasia and bleeding

What is the biological mechanism?
In Vitro Study

Do vWF fragments alter angiogenesis?

- Production of vWF pure fragments
- Endothelial cell culture with vWF fragments
- Quantification of angiogenesis

Bartoli et al. JTCVS. 2015.
In Vitro Study - Results

vWF fragments caused abnormal angiogenesis *in vitro*
Conclusions

1. LVAD patients with bleeding from angiodysplasia have higher levels of vWF fragments than non-bleeders

2. vWF fragments cause abnormal angiogenesis in vitro: (tubule formation, migration, proliferation, apoptosis)

3. Two-hit hypothesis for LVAD-associated gastrointestinal bleeding:
   A. vWF degradation alone
   B. vWF fragments alter angiogenesis and promote angiodysplasia
Proposed Mechanism Of LVAD-Associated Gastrointestinal Angiodysplasia And Bleeding

Inactive vWF → Shear Stress → Activated vWF → ADAMTS-13 Cleavage → vWF Fragments → Abnormal Angiogenesis → Gastrointestinal Angiodysplasia → Predisposition to Bleeding

Hit 1

Hit 2

vWF Metabolism May Be A Clinical Target To Reduce Gastrointestinal Bleeding In LVAD Patients