Treatment of GI Bleed in Patients with LVAD

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Objectives

- To gain a better understanding of causes of gastrointestinal bleeding (GIB)in patients with left ventricular assist devices (LVAD)
- To gain a better understanding of treatments for GIB in patients with LVAD

LVADs

- LVADS are an adjunct to traditional medical treatment
- Destination or bridge to heart transplantation
- From 2006-2010 LVAD implantation has increased from 206 to 1451
- 2014: INTERMACS registry 3500 CF- LVAD

Marsano et al. Dig Dis Scie (2015) 60:1859-1867

LVADs

- Pulsatile LVADs
  - Thromboembolic events (CVA)
  - 10% GI Bleed
  - Driveline Infections
  - High rate of pump replacement for pump failure 12 to 18 months after implant

Holman et al. Jour Thoracic and Cardiovascular Surgery Vol 146 (2)

LVADs

- Continuous Flow (CF) LVADs
  - Post-operative bleeding
  - Infection
  - Non-surgical bleeding
  - GIB
  - Pump thrombosis

Holman et al. Jour Thoracic and Cardiovascular Surgery Vol 146 (2)

GIB

- Incidence: 18.9% to 22.3%
- Risk Factors:
  - Older age (20.5 times greater)
  - Kidney insufficiency

Draper et al. Gastrointestinal Endoscopy Vol 80 (30): 2014
Guha et al. houtonmethodist.org/debakey-journal. MCDVJ X1(1) 2015

Causes of GIB

- Chronic anti-coagulation and anti-platelet therapy
- CF physiology
- Acquired von-Willebrand disease
- AV malformations
- RV dysfunction

Draper et al. Gastrointestinal Endoscopy. Vol 80(3):2014
Guha et al. houtonmethodist.org/debakey-journal. MCDVJ X1(1) 2015

Chronic Anti-coagulation

- Warfarin and ASA
- Comparison to patients with mechanical valves
  - Both cohorts were on warfarin and ASA
  - 8% on triple therapy: warfarin, ASA and clopidogrel
  - 19% incidence GIB in LVAD patients compared to 1.5% (Dual) 8% (Triple) in patients with mechanical valves

Kushnir et al. Gastrointest Endosc 2012 May; 75(5)

Physiological Changes

- Pulsatility
  - Human cells detect and adapt to cyclic changes of pressure and flow
  - Creates shear and strain forces on the endothelium, smooth muscle and fibroblast cells in the macro and microciruclation
  - Results in endothelium regulation of vasodilation and vascular remodeling

Cheng et al. Ann Cardiothorac Surg 2014;3(6):573-581
Draper et al. Gastrointestinal Endoscopy Vol 80 (3): 2014

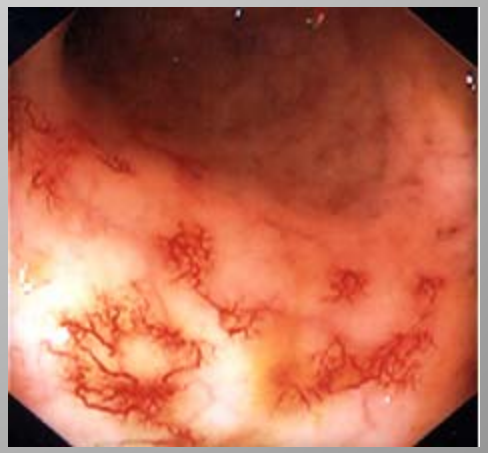
Physiological Changes cont.

- Without Pulsatility:
  - results in thinning of vasculature
  - decreased bradykinin-dependent vascular relaxation
  - increased vascular oxidative stress
  - degradation of vascular cell proliferation

Cheng et al. Ann Cardiothorac Surg 2014;3(6):573-581

Angiodysplasias

- Attribute to 55 - 60% of bleeding lesions in patients with LVADs
- Four times higher in CF-VAD
- Heyde Syndrome
  - aortic stenosis
  - reduced aortic pulse pressure
  - decreased pulsatility



Guha et al. houtonmethodist.org/debakey-journal. MCDVJ X1(1) 2015
Cheng et al. Ann Cardiothorac Surg 2014;3(6):573-581
Kushnir et al. Gastrointet Endosc. 2012 May; 75(5)

Angiodysplasias

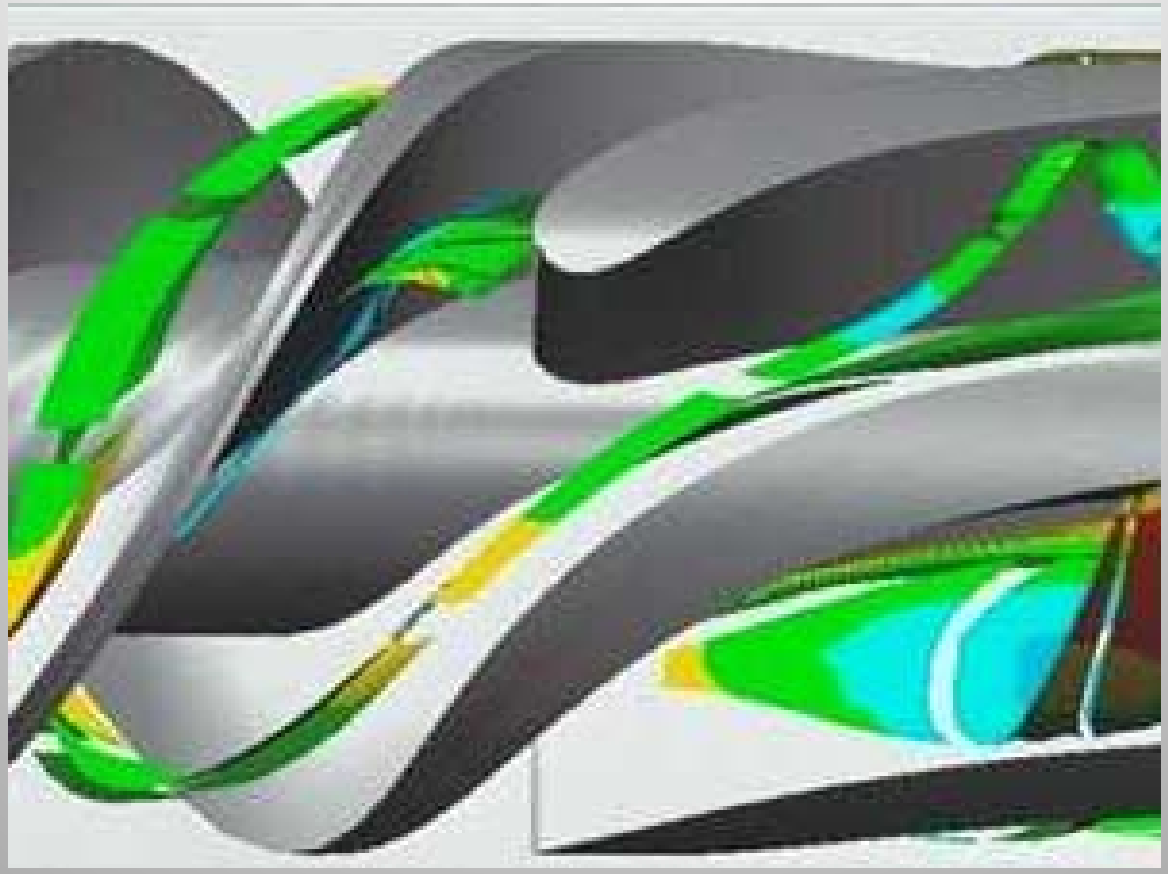
- LVADs
  - Blood directed out of the left ventricle directly into the aorta bypassing the aortic valve
  - Results in less frequent opening of the aortic valve causing a reduced aortic pulse pressure
  - Arteriole smooth muscle tone is reduced resulting in dilated mucosal veins and arterio-venous malformations (AVM's)
  - 91% are found in upper GI tract

Cheng et al. Ann Cardiothorac Surg 2014;3(6):573-581
Rennyson et al. DOI 10.1097/MAT.0b013e318295232d

Acquired von Willebrand Syndrome

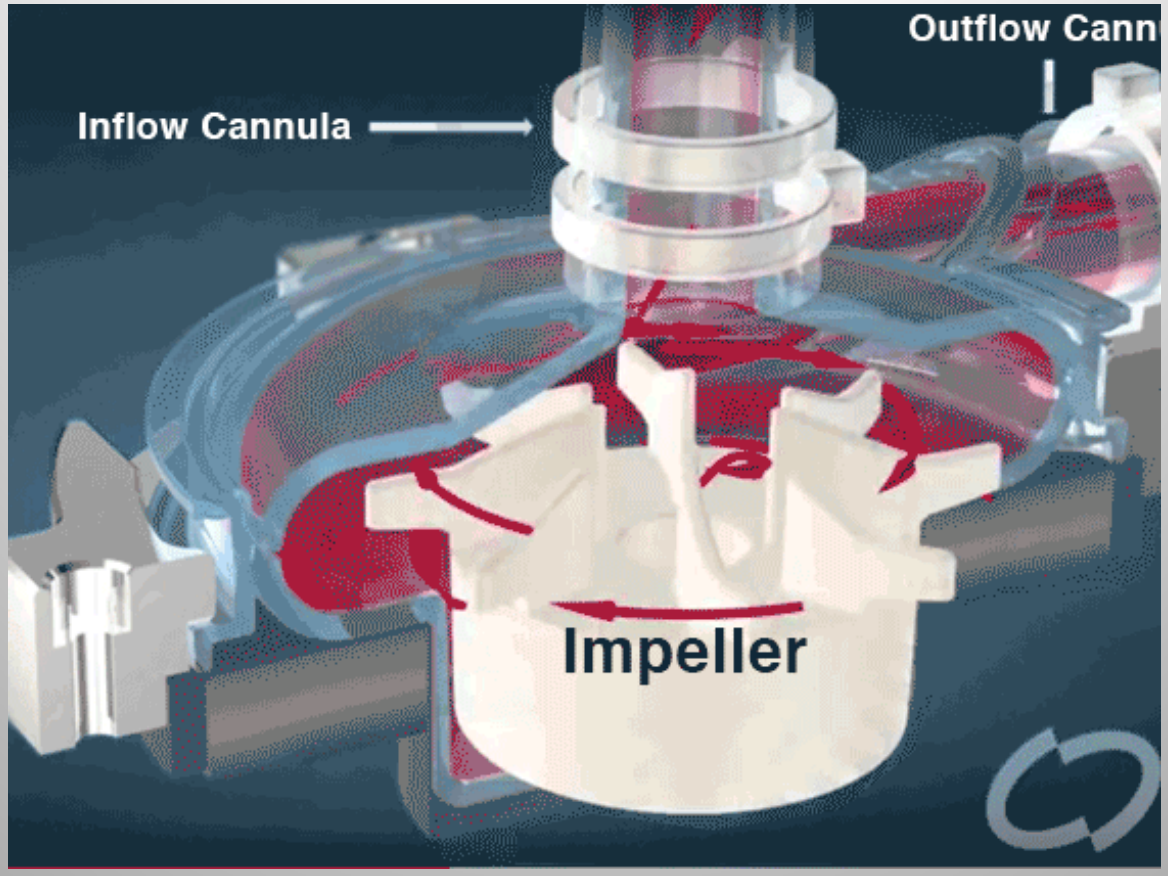
- von Willebrand factor is necessary for platelet aggregation
- travels in multimer with factor VIII which are disrupted by shear stress of the LVAD impellar
  - Results in decreased platelet functionality
  - Von Willebrand factor is found in all LVAD patients
  - Corrected in all patients that have LVAD explant for transplant or recovery

Guha et al. houtonmethodist.org/debakey-journal. MCDVJ X1(1) 2015
Rennyson et al. DOI 10.1097/MAT.0b013e318295232d



HeartMate II

Guha et al. houtonmethodist.org/debakey-journal. MCDVJ X1(1) 2015



HeartWare

Guha et al. houtonmethodist.org/debakey-journal. MCDVJ X1(1) 2015

RV Dysfunction

- Associated with malnutrition
- Abnormal liver function and hepatic congestion
- Increases bleeding and coagulopathy

Miller et al. Journal of Amer Coll Card Vol 61(12), 2013
Petrovic et al. VAD Journal: DOI:10.13023/VAD.2016.22

Diagnosing

- History and physical exam
- Medications
- Procedures:
  - Upper GI Bleed (melena, hematemesis): Endoscopy
  - Lower GI Bleed (hematochezia): Colonoscopy

Additional Testing

- Video Capsule Endoscopy (56%)
- Push Enteroscopy (26%)
- Small bowel follow-through (6%)
- CT with Tagged Red blood cell scan
- Standard Angiography

Guha et al. houtonmethodist.org/debakey-journal. MCDVJ X1(1) 2015

Management

- Octreotide
- Thalidomide
- Danazol
- Factor VIII
- Pulsatility

Octreotide

- Somatostatin analog
  - Splanchnic vasoconstrictor
  - Improves platelet aggregation
- Dosing
  - Octreotide gtt at 50 mcg/hr
  - Octreotide 100 to 500 mcg SQ BID for initial therapy
  - Octreotide 20 mg IM

Loyaga-Rendon et al. DOI: 10.1097/MAT.0000000000000143
Reynnyson et al. DOI: 10.1097/MAT.0b013e318295232d

Thalidomide

- Immunomodulatory drug
- Decreases formation of AVMs due to antivascular proliferative effects
- Antiangiogenic agent that inhibits vascular endothelial growth factor
- Increase risk of pump thrombosis

Botero et al. Blood Coagulation and Fibrinolysis 2013, 24: 884-886

Danazol

- Weak androgen
- Effects endothelial permeability by decreasing permeability and leakage in AVMs due to increasing cortical actin ring and stress fibers
- Also shown to increase factor VIII levels, shortens activated partial thromboplastin time
- Dosing:
  - 100 mg BID

Longacre et al. American Journal of Gastroenterology. Vol 98 (1) 2003
Botero et al. Blood Coagulation and Fibrinolysis 2013, 24: 884-886
Schettle et al. Heart and Lung Transplantation.
http://dx.doi.org/10.1016/j.healun.2014.01.922

Factor VIII

- vWF concentrate or desmopressin
- Treats von Willebrand disease phenotype 2a
- FVIII transfusion in patients with LVAD resulted in controlled GI bleeding but also associated with repeated LVAD thrombotic events
- Attributed to antiangiogenic affect reducing AVM's

Cushing et al. Transfusion 2012:52:1535-41

Pulsatility

- Multiple studies have looked at changing LVAD settings to enhance pulsatility
- Decrease pump speed to provide better pulsatility
- Can exacerbate heart failure
- Data suggest no benefit to changing LVAD speed to enhance pulsatility in the prevention or treatment of GI bleed

Draper et al. Gastrointestinal Endoscopy. Vol 80(3): 2014
Petrovic et al. VAD Journal. DOI. 10.13023/VAD.2016.22

Danazol as a treatment to reduce reoccurrence of hospitalization for GIB in patient with CF LVAD

Candice Falls, MSN, ACNP-BC, Maya Guglin, MD, PhD

Purpose

Gastrointestinal bleeding is one of the most common adverse events and causes and re-hospitalization in patient with LVAD. Medical management of these patients continues to be challenging given the need for continuous anticoagulation. In some case reports, Danazol, a weak androgen, was suggested for prevention of recurrent GIB. The purpose of this study was to determine the reoccurrence of gastrointestinal bleeding (GIB) after implantation of Left Ventricular Assist Device (LVAD) before and after the treatment with Danazol.

Presented at ISHLT 2016

Methods

Data were collected by retrospective analysis of adult patients (>18 years) who underwent continuous flow LVAD implantation at University of Kentucky Hospital between 2012 and 2015. Electronic medical records were reviewed for presenting symptoms, average days to initial and repeat GI bleed and treatment of GI bleed.

Presented at ISHLT 2016

Results

In the studied period of time, 93 patients received a continuous flow LVAD. Six patients with LVAD implantation who presented with Gastrointestinal bleeding (GIB) were placed on Danazol. One patient discontinued the drug because of side effects. In the remaining five patients, mean time to initial GIB after LVAD implant was 9.6 months. Only one patient was started on Danazol after the first episode of GIB, while the rest of them had recurrent events.

Presented at ISHLT 2016

Results Cont.

The average number of episodes of GIB was 3.4. Before Danazol, mean time in between hospital readmissions related to recurrent GIB was 1.5 months. After the patients were initiated on Danazol for treatment of GIB, mean time in between hospital readmissions related to recurrent GIB after initiation of Danazol increased to 4.4 months. Only one patient experienced another episode of GIB on Danazol. The four that did not remained free of GIB for an average of 2.9 months. After that, two were transplanted and the other two continue to be on LVAD support.

Presented at ISHLT 2016

Conclusions

Danazol may increase the intervals between the episodes of GIB and prevent the recurrent episode in some patient with LVADS. Danazol should be considered as a treatment in patients with LVAD and GIB.

Presented at ISHLT 2016

Future Research

- HM III: currently in clinical trials

- The design of the HeartMate 3 includes large, consistent blood flow gaps - 10 to 20 times greater than other LVADs - designed to reduce blood cell trauma.
- Full MagLev™ (magnetically-levitated) technology allows the device's rotor to be "suspended" by magnetic forces. Since the parts "float," there is no friction and therefore less wear and tear on the rotor. This contact-free environment is designed to reduce blood trauma through gentle blood handling.
- Full range of operation. Provides flow from 2.5 to 10 L/min to accommodate a broad range of clinical needs

https://www.thoratec.com/medical-professionals/vad-product-information/heartmate3/HeartMate3_PressKit-UK.pdf