

Gastrointestinal bleeding in recipients of left ventricular assist devices

Abstract

Background: Acute gastrointestinal bleeding has an annual incidence of about 150 episodes per 100,000. The mortality rate is 5 to 10 percent, and increases in those with heart failure and other comorbidities. Arteriovenous malformations (AVMs) are abnormal blood vessels in the gastrointestinal (GI) tract that are a common source of bleeding. They develop through venous obstruction or hypoperfusion, and may be associated with aortic stenosis or renal insufficiency. It has been suggested that nonpulsatile left ventricular assist devices (LVADs) may contribute to AVM formation due to the lower pulse pressure generated by these devices, similar to aortic stenosis.

Methods: We performed a retrospective analysis of 52 consecutive LVAD recipients. Nonpulsatile devices included VentrAssist, HeartMate II, and Jarvik 2000. Pulsatile devices included Novacor and HeartMate XVE. The primary endpoint was GI bleeding that was clinically evident by hematemesis, melena, guaiac positive stool, or iron deficiency anemia, and confirmed by endoscopy. Data were analyzed by odds ratio, logistic regression, and the t test.

Results: There were 25 (48%) patients with nonpulsatile ventricular assist devices and 27 (52%) patients with pulsatile devices. When considering gastrointestinal bleeding from arteriovenous malformations, there was 1 (4%) event in the nonpulsatile group and 2 (7%) in the pulsatile group ($p = 0.607$). For gastrointestinal bleeding from all sources, there were 2 (8%) in the nonpulsatile group and 6 (22%) in the pulsatile group ($p = 0.162$). Of the 10 subjects who received pre-implant colonoscopies, 7 had pathologic findings (4 polyps, 2 diverticulosis, 1 colitis), and 3 went on to develop post-implant GI bleeding ($p = 1.000$). On multivariate analysis, only age was found to be an independent predictor of gastrointestinal bleeding ($p = 0.001$).

Conclusions: Nonpulsatile LVADs were not associated with an increase in AVMs or GI bleeding. The limited number of pre-implant colonoscopies was not predictive of post-implant GI bleeding.

Introduction

Heart failure affects more than 5 million people in the United States. For those greater than 65 years old, heart failure has an incidence of about 10 per 10,000 and is the primary reason for 20% of hospital admissions [1]. In people who no longer respond to medical management, a ventricular assist device can provide circulatory support [2]. These devices are mechanical pumps that can be used either as a bridge to heart transplant or as destination therapy.

Ventricular assist devices create forward flow through two different mechanisms [3]. The first is a displacement mechanism, which pumps a discrete volume of blood at regular intervals, and results in pulsatile flow. Newer pump designs use a rotor or axial mechanism to provide a continuous or nonpulsatile flow.

It has been suggested that nonpulsatile ventricular assist devices may contribute to gastrointestinal bleeding from arteriovenous malformations [4]. To further evaluate this theory,

we compared the rates of gastrointestinal bleeding in recipients of these devices. The objective was to provide insight into which heart failure patients would benefit from nonpulsatile devices, identify correlations with gastrointestinal bleeding, and evaluate the effectiveness of current endoscopic screening guidelines.

Background

Arteriovenous malformations are abnormal blood vessels frequently found in the gastrointestinal tract, but which may appear elsewhere. They are known synonymously as angiodysplasias and vascular ectasias. They can be congenital or acquired. Among the general population, they have an estimated prevalence of about 1% and are the most common gastrointestinal vascular malformation. Their clinical course is variable, with most lesions remaining clinically silent, and a small number causing occult or overt bleeding.

These vascular malformations are composed of dilated, tortuous, thin-walled vessels in the mucosa and submucosa. They are lined by endothelium with little or no smooth muscle. They are not associated with inflammation, fibrosis, or atherosclerosis. During endoscopy, they characteristically appear as cherry red lesions, 5 to 10 mm, in a fern-like pattern. They tend to be clustered together, but 20% of the time they are associated with synchronous lesions elsewhere in the gastrointestinal tract. The colon is the most common site in the gastrointestinal tract, but they can be found anywhere from the stomach to the rectum.

The pathogenesis of arteriovenous malformations is not well understood, although several mechanisms have been proposed [5,6]. One theory is that they develop in response to chronic low grade venous obstruction due to muscular contractions or increased intraluminal pressure. A neurovascular mechanism has also been proposed, where sympathetic nerves stimulate vascular smooth muscle relaxation in response to low-grade local hypoperfusion secondary to cardiac, vascular, or pulmonary disease. With both mechanisms, these changes result in venous dilation, which propagates proximally until the precapillary sphincter becomes incompetent and results in a small arteriovenous communication.

The prevalence of arteriovenous malformations may increase with age and in those with certain predisposing conditions. This includes chronic renal failure [7,8,9], von Willebrand disease [10,11,12], aortic stenosis [13,14,15,16,17], scleroderma [18], portal hypertension [19], and Turner syndrome [20]. Some of these findings have been inconsistent, and there is little evidence to support an association with portal hypertension or Turner syndrome. The proposed mechanisms for chronic renal insufficiency include uremia-induced platelet dysfunction causing arteriovenous malformations to become clinically evident, intermittent vascular overload resulting in retrograde capillary dilation, hypertension, and vascular disease. The likely mechanism for von Willebrand disease is similar to platelet dysfunction from chronic renal insufficiency. With aortic stenosis, the proposed mechanisms include mucosal ischemia from lower pulse pressures causing existing angiodysplasias to bleed, and increased sympathetic tone in response to low-grade local hypoperfusion resulting in dilated vessels. A stronger association exists with aortic stenosis and von Willebrand disease, where it is proposed that sheer stress around the stenotic aortic valve leads to increased breakdown of the very large von Willebrand molecule. In scleroderma, the occurrence of telangiectasias (which are histologically the same as gastrointestinal arteriovenous malformations) make an association between the two conditions credible.

Methods

This study was conducted at the University of Maryland Medical Center, a 665-bed academic and tertiary care facility that performs over 800 cardiac surgeries and 40 ventricular assist device implantations annually. The study received IRB approval from the University of Maryland Medical Center.

The eligible sample included all 53 consecutive recipients of intracorporeal left ventricular assist devices between May 7, 2002 and October 20, 2006. All study data were obtained from the hospital's information system. For each patient, demographic data, past medical history, device history, gastrointestinal studies, and bleeding events were recorded. The principal outcome variables were gastrointestinal bleeding from documented arteriovenous malformations, other gastrointestinal bleeding, and non-gastrointestinal bleeding.

The primary analysis compared bleeding events with nonpulsatile ventricular assist devices to those with pulsatile devices. Categorical variables were analyzed using the Fisher's exact test and odds ratio. Logistic regression was used for multivariate analysis. Continuous variables were analyzed using the t test. A significance level of 5% with two tails was used.

Results

One participant died on the day of implantation and was excluded from the analysis. Of the 52 remaining participants, 25 received a nonpulsatile ventricular assist device and 27 received a pulsatile device. The patients in each group were nearly identical with respect to age, sex, race, and history, except for the indication and the average days on device. In addition, 10 (19%) patients received screening colonoscopies. See Table 1.

	Nonpulsatile (n=25)	Pulsatile (n=27)	p
Implant age in years	52 ±15	54 ±16	0.495
Male	16 (64%)	19 (70%)	0.633
Caucasian	16 (64%)	17 (63%)	0.843
Pre-implant screening colonoscopy	6 (24%)	4 (15%)	0.411
Days on device	112 ±119	254 ±251	0.013
Ischemic cardiomyopathy	9 (36%)	13 (48%)	0.386
Aortic stenosis (AV \leq 1.5 cm ²)	1 (4%)	1 (4%)	0.957
Chronic kidney disease (Cr \geq 1.5 mg/dl)	9 (36%)	6 (22%)	0.248

Table 1: Baseline Characteristics

In the nonpulsatile group, 2 (8%) people had gastrointestinal bleeding after device implantation, including 1 (4%) from an arteriovenous malformation. In the pulsatile group, 6 (22%) people had gastrointestinal bleeding, including 1 (4%) from an arteriovenous malformation. The difference between the two groups was not significant for arteriovenous malformations ($p = 0.607$) or for gastrointestinal bleeding in general ($p = 0.162$). See Table 2.

	Nonpulsatile	Pulsatile	p
GI bleeding from AVM	1 (4%)	2 (7%)	0.607
All GI bleeding	2 (8%)	6 (22%)	0.162

Table 2: Post-LVAD Incidence of GI Bleeding

On univariate analysis, most covariates were not significant. Only age was found to be an independent predictor of gastrointestinal bleeding ($p = 0.001$). On multivariate analysis, there were no confounding effects from gender, race, number of days on device, etiology of cardiomyopathy, or aortic stenosis.

Discussion

Nonpulsatile ventricular assist devices have several advantages over their pulsatile counterparts. Their compact size allows for use in children and small adults. They have greater reliability due to mechanical simplicity. The safety of pulseless circulation has been studied elsewhere [21,22,23].

Letsou et al. has suggested that nonpulsatile devices may cause increased gastrointestinal arteriovenous malformations based on the so-called Heyde syndrome [24]. The proposed mechanism was the narrow pulse pressure of nonpulsatile devices, which was similar to that of aortic stenosis. This was based on a case report where 3 of 21 recipients of nonpulsatile devices developed gastrointestinal bleeding from arteriovenous malformations [4].

In our research, we found no difference in the rate of gastrointestinal bleeding from arteriovenous malformations when comparing nonpulsatile to pulsatile intracorporeal left ventricular assist devices. Ironically, there was a higher rate in the pulsatile group, but this was not statistically significant and was possibly biased by the longer time on device. With respect to the potential for gastrointestinal bleeding, there seems to be no reason to limit the use of nonpulsatile devices.

There are several possible explanations for the discrepancy between Letsou et al. and our results. First, note that recipients of these devices may still have pulsatile aortic pressures if their ventricles remain ejecting. Additional studies, which correlate actual pulse pressures to gastrointestinal bleeding, would help to clarify this issue. In addition, these studies searched for arteriovenous malformations only after signs of overt or occult bleeding (hematemesis, hematochezia, melena, guaiac positive stools, or iron deficiency anemia). The formation of clinically silent lesions is an open issue that merits further investigation. Finally, several other diseases have been associated with gastrointestinal arteriovenous malformations, and may be confounding factors. In our study, there were no confounding effects among those diseases associated with arteriovenous malformations, although most conditions were underrepresented.

When interpreting our results it is important to consider certain limitations. The study was small in size, retrospective, and restricted to a single academic medical center. In addition, a higher percentage of nonpulsatile devices were used as bridge to transplant leading to less time on device, as dictated by the Jarvik 2000 trial the University of Maryland was participating in.

Concern for colorectal disease in transplant recipients has been documented elsewhere [25]. Important issues include anticoagulation and immunosuppression contributing to gastrointestinal malignancy, infection, and bleeding. Routine pre-implantation gastrointestinal screening has traditionally been limited to colonoscopic screening for malignancy. In our population, 10 (19%) patients received screening colonoscopies. The findings from screening colonoscopies did not help predict those who would develop post-implant gastrointestinal bleeding. It therefore may be prudent to broaden the criteria for endoscopic screening to those with a history of prior bleeding events, unexplained anemia, aortic stenosis, renal insufficiency, gastrointestinal disease, liver disease, coagulopathy, or connective disease. The screening studies could include upper endoscopy, colonoscopy, and capsule endoscopy. Of note, capsule

endoscopy does not require holding anticoagulation, entails only minimal bowel preparation, has been shown to be safe when used with ventricular assist devices [26].

In conclusion, we found no difference in the rate of gastrointestinal bleeding from arteriovenous malformations when comparing nonpulsatile to pulsatile ventricular assist devices. This was done by comparing 53 consecutive recipients of intracorporeal left ventricular assist devices at the University of Maryland Medical Center. With respect to the potential for gastrointestinal bleeding, there seems to be no reason to limit the use of nonpulsatile devices. In addition, given that the limited number of pre-implant colonoscopies was not predictive of post-implant gastrointestinal bleeding, the criteria for pre-implantation endoscopic screening may need to be broadened.

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