Association of Blood Group O with Gastrointestinal Bleeding in Continuous-Flow LVAD Patients

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Authors’ contributions
This work was carried out in collaboration between all authors. Authors NN and AS read and approved the final manuscript.

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ABSTRACT

Background: Increasing use of mechanical circulatory devices for advanced heart failure therapy has led to challenges in managing complications that arise from device implantation for long term support either as a bridge to transplant or as destination therapy. Patients with continuous flow left ventricular assist devices (CF-LVADS) show increasing incidence of gastrointestinal (GI) bleeds. Lack of pulsatility and narrow pulse pressure result in initiation and progression of arteriovenous malformations. High shear forces generated lead to destruction of von Willebrand factor (vWF) making it functionally inactive predisposing patients to increasing bleeding. Literature suggests that patients with blood type O have lower baseline levels of von Willebrand factor. It therefore seemed relevant to study the role of blood groups in this population.

Methodology: Retrospective data analysis of 119 CF-LVADS patients discharged between 01/2005 and 07/2014. This study was approved by the Institutional Review Board on 08/01/2014.

Results: Blood type (p=0.23), gender (p=0.16) and the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile (p=0.86) were not associated with significant incidence of GI bleeding. Blood group O was not associated with a higher incidence of GI bleeding (correlation coefficient =0.07) Patients supported on the HeartMate II (HMII) LVAD experienced
more GI bleeding than patients supported on the HeartWare LVAD (HVAD) (p=0.009). HMII LVAD patients who experienced GI bleeding had a mean age of 59.8 years vs. 55.7 years for HMII LVAD patients in the Non-GI bleed group. Age was a significant factor for GI bleeding (p=0.016).

Conclusion: Blood group and GI bleeding did not show any significant association in our study. Patients with blood group O did not show increased incidence of GI bleeding despite reported lower baseline levels of von Willebrand factor suggesting contribution of additional factors leading to this complication. The HVAD had a decreased incidence of GI bleeding as compared to Heartmate II. This study is limited by the fact that it was a retrospective analysis in a small population.

Keywords: Continuous-flow ventricular assist devices; blood groups: arterial-venous malformations: gastrointestinal bleeding; von willebrand factor.

1. INTRODUCTION

With increasing use of continuous flow left ventricular assist devices (CF-LVADS) patients are subjected to complications secondary to pump support. The presence of narrow pulse pressure and lack of pulsatility have been attributed to the increased gastrointestinal (GI) bleeds. Such effects lead to initiation and progression of arteriovenous malformations (AVMs). High shear forces lead to the destruction of high molecular weight von Willebrand factor (vWF) making it functionally inactive. Both of these problems have been implicated in the process. On a broad spectrum these complications are widely noted in patients with CF-LVADS. The incidence of GI bleeding associated with CF-LVADS is similar to that associated with other implantable LVADs which require anti-coagulation [1]. vWF - 250 kDa is a globular protein in circulation synthesized by endothelial cells and megakaryocytes. Blood flow through areas of high shear stress causes an unfolding of the vWF protein, exposing sites for proteolysis and cleavage by the enzyme ADAMTS13. ADAMTS 13 or von Willebrand factor-cleaving protease (VWFCP)-is a zinc metalloprotease that cleaves vWF. ADAMTS 13 cleavage divides the vWF protein into smaller segments or multimers. A shear force of at least 500pN is required to cause unfolding of the vWF high molecular weight form. Total amount of vWF in circulation remains unchanged but the number of high molecular weight multimers (HMWM) is decreased. Clinically, HMWM loss is associated with bleeding secondary to the decreased capacity of vWF to bind collagen and platelets to achieve hemostasis [2].

Prior literature suggests that patients with blood group O have decreased levels of vWF [2,3]. Alteration of vWF levels has been postulated to be associated with increased GI bleeding in CF-LVAD patients. The primary aim of this retrospective analysis was to determine if LVAD patients with blood group O experienced increased GI bleeding. The secondary objective was to determine if age, gender, INTERMACS profile, and continuous flow LVAD type are associated with increased GI bleeding.

2. METHODS AND PROCEDURES

Retrospective data analyses were performed on 119 discharged CF-LVAD patients between 01/2005 and 07/2014. This project IRB #1950 was approved by the Institutional Review Board (IRB), at Providence Sacred Heart Medical Center, Spokane, WA on 08/01/2014 prior to commencement of the study. Data was collected retrospectively from patient charts and decoded by the study investigators. All data was placed in Microsoft Excel spreadsheets in a password protected database. Only the study investigators have access to the password protected database. Strict patient confidentiality was maintained in accordance with institutional and federal government regulations. Primary objective of the study was to assess the impact of blood groups on GI bleeding in patients supported on CF-LVADS and to determine any dependence on blood group O. Bleeding was defined as any event requiring transfusion of 2 or more units of packed red blood cells in a time span of 24 hours. Confirmation of diagnosis of GI bleeding was done by endoscopy performed by the gastroenterology service.

Descriptive statistics were used to characterize the patient population, including baseline characteristics and outcomes. The chi-square test was performed to test for statistical independence (p<0.05) between the Non-GI bleed group, GI bleed group and categorical variables (e.g. blood group, gender, INTERMACS profile, device type). The t-test was
performed to test for significance (p<0.05) between groups for age.

3. RESULTS

Table 1A shows the baseline characteristics of the study patients. Females constituted 23% overall. Ischemic and non-ischemic cardiomyopathy patients were roughly equal in number. A one sample binomial test showed p=0.271, confirming that results are not significant for prior history of type of cardiomyopathy. Hypertensive and diabetic subjects constituted 39.5% and 32.8% respectively. Peripheral vascular disease was present in 9% of the study subjects approximately. Tobacco use was estimated as 52.9%. Only 15% of the CF-LVADs implanted were HVADS. Length of pump support varied from approximately 28 to 2115 days. Majority of patients were of blood group O in this study population. As shown in Table 1B about 80% of the patients were in INTERMACS classes 2, 3 and 4. Most patients were bridge to transplant (BTT) (73.1%) versus (26.9 %) as destination therapy (DT).

Blood group (p=0.23), gender (p=0.16) and INTERMACS profile (p=0.86) were not associated with significant incidence of GI bleeding. Blood group and GI bleeding did not show any significant association in our study (correlation coefficient =0.07). Patients on the HeartMate II (HMII) LVAD experienced more GI bleeds than patients on the HVAD (p=0.009). Age was a significant factor for GI bleeding (p=0.016). HMII LVAD patients who experienced GI bleeding had a mean age of 59.8 years vs. 55.7 years for HMII LVAD patients in the Non-GI bleed group (Table 2). Blood group O was not associated with increased incidence of GI bleeding (Table 2). Table 2 shows a summary of factors influencing GI bleeding. No comparison was done between GI bleeders and non - GI bleeders within any particular blood group. Overall 30% of the CF-LVAD patients experienced GI bleeds and 10% had repeated episodes of bleeding. 0% mortality was noted secondary to GI bleeding in this study population.

4. DISCUSSION

It has been shown by several investigators that a decrease in vWF is noted in patients with continuous-flow LVADs [4-6]. Hence this study was undertaken to investigate if a lower baseline level of vWF in blood group O patients would exacerbate this abnormality. Blood group O in particular and GI bleeding in LVAD patients had no association either (correlation coefficient = 0.19, p = 0.23). This is interesting from the point of view that despite reported lower levels of vWF in patients with blood group O, the GI bleeding episodes are not increased in this population. It also highlights another noteworthy point that though von Willebrand syndrome type 2 is seen in all patients after LVAD implantation not all patients have extensive bleeding events suggesting a multifactorial etiology. Other factors such as altered coagulation patterns and anticoagulation regimens could also play a role in the bleeding complications noted. Reversibility of increased bleeding episodes has been noted after removal of the device [7]. Crow et al. [8] noted in their small study that although 37 patients had reduced high molecular weight vWF within 30 days post CF- LVAD implantation only 10 of these patients actually had bleeding episodes again emphasizing the impact of multiple factors in this phenomenon. Crow et al. [9] also noted that the decrease in functional high molecular weight vWF is not seen in the pulsatile VADs though this was a small study. Study presented in this paper shows no significant changes in bleeding events in patients with blood group O. Absolute determinations of vWF levels were not done in the study population reported here.

A significant effect of age on bleeding events was noted in our study (Table 2). This is consistent with an earlier report [9]. In our analysis prior history of GI bleeding, elevated international normalized ratio (INR), and low platelet count showed a combined odds ratio shown in parenthesis (OR, -0.98; CI, 0.98 -0.99; p=0.001) were independent predictors of GI bleeding (Table 2). Our antiplatelet and anticoagulation regimen involved maintaining the patient on aspirin and coumadin. The target INR was 1.8-2.3 for HMII and 2-3 for the HVAD. The anticoagulation and antiplatelet parameters were also assessed using thromboelastograms. Only 5.9% of the GI bleeders had an elevated INR and a low platelet count at the time of the bleeding event. Recurrent bleeding was more common in older patients with a mean age of 70±7.45 in the study by Aggarwal et al. [10] Table 2 shows p values determined only between the blood group types and not GI bleeders and non-bleeders as depicted in the footnotes of the table.
Table 1A. Baseline characteristics of patients

|                          | All study subjects (n=119) | Non-GI bleeders (n=81) | GI bleeders (n=38) |
|--------------------------|----------------------------|------------------------|-------------------|
| Age (in years at implant)| 55.8                       | 54.1                   | 59.3              |
| Gender                   | **28 (23.5%)** F,          | **16 (19.8%)** F,      | **12 (31.6%)** F, |
|                          | **91 (76.5%)** M           | **65 (80.2%)** M       | **26 (68.4%)** M  |
| Ischemic CM              | 66 (55.5%)                 | 45 (55.6%)             | 21 (55.3%)        |
| Non ischemic CM          | 53 (44.5%)                 | 36 (44.4%)             | 17 (44.7%)        |
| HTN                      | 47 (39.5%)                 | 34 (42.0%)             | 13 (34.2%)        |
| DM                       | 39 (32.8%)                 | 27 (33.3%)             | 12 (31.6%)        |
| Peripheral vascular disease | 11 (9.2%)             | 6 (7.4%)               | 5 (13.2%)        |
| History of tobacco use   | 63 (52.9%)                 | 37 (45.7%)             | 26 (68.4%)        |
| CF HMII                  | 101 (84.9%)                | 64 (79.0%)             | 37 (97.4%)        |
| CF HVAD                  | 18 (15.1%)                 | 17 (21.0%)             | 1 (2.6%)          |
| Length of pump support (days) | 539                | 489 (28 to 2115)       | 644 (62 to 1854)  |
| BTT                      | 87 (73.1%)                 | 65 (80.2%)             | 22 (57.9%)        |
| DT                       | 32 (26.9%)                 | 16 (19.8%)             | 16 (42.1%)        |
| Pump exchange            | 7 (5.9%)                   | 6 (7.4%)               | 1 (2.6%)          |
| Blood group O            | 61 (51.3%)                 | 43 (53.1%)             | 18 (47.4%)        |
| Blood group B            | 12 (10.1%)                 | 6 (7.4%)               | 6 (15.8%)         |
| Blood group A            | 45 (37.8%)                 | 32 (39.5%)             | 13 (34.2%)        |
| Blood group AB           | 1 (0.8%)                   | 0 (0%)                 | 1 (2.6%)          |

Table 1B. INTERMACS classification *

|                          | n=114 | n=79 | n=35 |
|--------------------------|-------|------|------|
| INTERMACS Profile 1      | 9 (7.9%) | 6 (7.6%) | 3 (8.6%) |
| INTERMACS Profile 2      | 31 (27.2%) | 19 (24.1%) | 12 (34.3%) |
| INTERMACS Profile 3      | 38 (33.3%) | 27 (24.2%) | 11 (31.4%) |
| INTERMACS Profile 4      | 23 (20.2%) | 16 (20.3%) | 7 (20.0%) |
| INTERMACS Profile 5      | 7 (6.1%) | 6 (7.6%) | 1 (2.9%) |
| INTERMACS Profile 6      | 5 (4.4%) | 4 (5.1%) | 1 (2.9%) |
| INTERMACS Profile 7      | 1 (7.1%) | 1 (1.3%) | 0 (0%) |

* The INTERMACS classification for 5 patients were missing during retrospective analyses

Table 2. Factors influencing GI bleeding^^

|                          | GI bleeders | Non GI bleeders | p- value  |
|--------------------------|-------------|----------------|-----------|
| Age (years)              | 59.3        | 54.1           | 0.016     |
| Gender                   | 12 (31.6%)  | 16 (19.8%)     | 0.156     |
| INTERMACS                | 1-7 tested  | 1-7 tested     | 0.855     |
| HMII                     | 37          | 64             |           |
| HVAD                     | 1           | 17             | **0.009   |
| Blood Group O            | 47.40%      | 53.10%         | ^         |
| Blood Group A            | 34.2%       | 39.50%         | 0.94*     |
| Blood Group B            | 15.50%      | 7.40%          | 0.17***   |
| Blood Group AB           | 2.60%       | 0.00%          | ***       |
| Blood group O vs all other blood groups | 0.232 | | |
| Combined odds ratio for GI bleeding, elevated INR, low platelet count, | -0.98 | | p=0.001 |

* p value denotes GI bleeding in blood group O versus A
++ p value denotes GI bleeding in blood group O versus B
*** p value denoting HMII vs HVAD  ** p value denotes GI bleeding in blood group O versus AB was not determined due to small numbers
^ No comparison was done between GI bleeders and non - GI bleeders within blood group O patients
^ No comparison was done between GI bleeders and non - GI bleeders within any particular blood group
In the current study the HVAD patients had a decreased incidence of GI bleeding as compared to those on Heartmate II with a p value of 0.009 (Table 2). This is in contrast to the report by Lalonde et al. [11] where HVAD had higher number of bleeding episodes. Survival and the incidence of perioperative bleeding, renal dysfunction, liver dysfunction, and infection were similar between the groups in the study by Lalonde et al. [11]. In the study by Lalonde [11] HVAD had a significantly higher incidence of gastrointestinal (GI) bleeding (31% vs. 0% in HMII patients, p<0.01) and stroke (44% vs. 10% in HMII patients, at one year p=0.04). There was a higher incidence of hemorrhagic strokes in HVAD patients but this observation was not significant [11]. The fact that HMII LVAD patients had significantly higher incidence of GI bleeding can probably be explained by the high shear stress secondary to high speed and small gap distance between the impeller and pump housing [12,13].

This study is limited by the fact that it was a retrospective analysis in a small population. Besides, actual quantitation of vWF was not done in patients with different blood groups but was assumed to be different in these patients as defined in the literature. This makes it difficult to strongly argue against influence of blood groups on GI bleeding because levels of vWF were not estimated in the study patients. The impact of length of pump support in influencing GI bleeds was not systematically studied because the patients had a high variability in the length of support in a small population. The length of pump support may influence the GI bleeding but this effect is counteracted by maintenance of appropriate levels of anticoagulation and platelet inhibition. The combination of high INR and low platelet count was noted only in 5.9% of the total population suggesting that this has no substantial effect on the results obtained. Besides 85% of the subjects in the GI bleeder group had low INR or were therapeutic.

Though differences in bleeding complications between the axial versus centrifugal pumps were incidentally noted during data analysis and are not the primary theme of this paper; further investigations will be needed to address this observation. The study discussed here shows that the bleeding complications are lower with the centrifugal continuous flow pumps which are in contrast to that shown in an earlier report [11]. Larger studies will be needed to better define bleeding with respect to pump design and physiological changes instituted status post implantation of these devices.

5. CONCLUSION

Blood type and GI bleeding did not show any significant association in our study. Patients with blood group O did not show increased incidence of GI bleeding. Age was a significant factor that influenced GI bleeding. The HVAD (centrifugal CF- LVAD) showed a lower incidence of GI bleeding as compared to Heartmate II (axial CF-LVAD). This observation was incidental during data analysis and not part of the main hypothesis of this paper. This study was limited by the fact that it was a retrospective analysis in a small population and absolute determinations of vWF levels were not carried out in the study population reported here.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

DISCLOSURE STATEMENT

The authors have no conflicts of interests to disclose with respect to this study. Dr. A. Schmitt works as a consultant engineer for Thoratec Corporation. Dr. N. Nair has served once in 2014 as a member of the scientific advisory committee for Heartware.

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