Published in final edited form as:

Artif Organs. 2014 June ; 38(6): 447–455. doi:10.1111/aor.12200.

Temporal Leukocyte Numbers and Granulocyte Activation in Pulsatile and Rotary Ventricular Assist Device Patients

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Introduction

Ventricular Assist Devices (VADs) have become an established treatment for advanced heart failure, prolonging the life of patients when used as a bridge to transplantation or as destination therapy. Despite technological advances and increased experience, VAD patients are still vulnerable to infection and hemostatic complications such as bleeding and thromboembolism. While the mortality from bleeding or thromboembolism has been shown to decrease substantially after the first 30 days of support, infection is an ongoing risk while on mechanical support [1–3]. The speculated causes for the occurrence of infection range from the existence of a percutaneous line providing a pathway for infectious agent migration [2], to impaired leukocyte function from interactions with the foreign surfaces of some VADs [4].

Most previous VAD immunological studies included patients with prior generations of pulsatile pumps, many of which are no longer available, rather than continuous flow pumps, which are currently the dominant technology. This is significant in that the design of contemporary rotary VADs is considerably different than pulsatile VADs and may lead to a different leukocyte response from that reported in previous studies [5, 6]. Additionally, few studies have presented temporal leukocyte counts [7], as most investigators report leukocyte counts at a specific post-operative time point where they are incorporated as risk factors in outcome scores [8]. The effects of VAD support on granulocytes have also been studied, but only one study followed granulocyte populations over time [7] and no studies have reported the degree of granulocyte activation through the expression of macrophage antigen-1 (MAC-1). The objective of this study was to investigate the influence of current VAD technology on patient granulocyte activation, leukocyte counts and infection.

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Contributions

Mr. Woolley and Drs. Wagner and Kormos contributed to the study design, data and statistical analysis and manuscript preparation and approval. Mrs. Lockard collected data and revised the manuscript. Drs. Teuteberg, Bermudez and Bhama aided in data collection and critically revised the article.

Patients and Methods

Patients and Devices

All study procedures and consent forms for data collection, blood collection and data analysis for this investigation were approved by the University of Pittsburgh's Institutional Review Board (IRB).

This study was a single-center investigation which consisted of patients who underwent placement of a long-term left ventricular assist device (LVAD) (intended length of support >14 d) at the University of Pittsburgh Medical Center (UPMC) Presbyterian Hospital between 1999 and 2011. Patients were excluded if they had a temporary LVAD, had a long-term right ventricular assist device implanted, or were supported < 30 d by the device. Three different devices were included in this study: the Thoratec® PVAD™ pneumatic device (PVAD; Thoratec Corp, Pleasanton, CA), and the Thoratec® HeartMate II® (HMII; Thoratec) and HeartWare® HVAD® (HW; HeartWare Inc, Framingham, MA) rotary blood pumps. All patients had traditional driveline tunneling with partial velour exposure. Patient medical history, infection events and hospital or outpatient laboratory test values were collected from the IRB-approved Transplant Patient Management System database at UPMC. A subset of these patients that were implanted between 2009 and 2011 were included in an investigation of granulocyte activation levels and consented to providing blood samples pre-operatively and throughout device support. Data from this subset is presented to POD 30 and POD 120 to present short- and long-term perspectives; whereas data were available for all patients in the subset to at least POD 30, some lab values were unavailable when followed to POD 120 and these patients were not included in the long-term analysis. The Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS) definition for an infection event was used to determine the occurrence of infections [9].

Flow Cytometric Determination of MAC-1 Expression on Circulating Granulocytes

Flow cytometry was performed by a modified method from *Donnenberg et al* [10]. Within 4 hr of collection 100 mL citrated (Vacutainer, BD, Pleasanton CA) whole blood was placed in polystyrene tubes and lysed by the addition of 2 mL ammonium chloride lysis buffer. The lysed solution was centrifuged at 400×g for 10 min and, following removal of supernatant, the cells were washed with 1 mL Dulbecco's Phosphate-Buffered Saline without Ca++ or Mg++ with 4% calf bovine serum (Staining Buffer; MP Biomedicals LLC, Solon, OH) and centrifuged again at 400×g for 10 min. The leukocyte pellets were decanted dry and then stained with 2 µL fluorescein isothiocyanate isomer 1-conjugated mouse anti-human CD15 (clone MEM-158) and 2 µL either R. Phycoerythrin-conjugated mouse anti-human MAC-1 (CD11b, clone ICRF44) or a R. Phycoerythrin-conjugated mouse IgG1 isotype control (all from AbD Serotec, Raleigh, NC), incubated for 20 min in the dark and washed with 1 mL Staining Buffer. Following centrifugation at 400×g for 10 min, the cells were resuspended in 500 µL 1% paraformaldehyde (Sigma, St. Louis, MO) and stored at 4°C (<36 hr) until analyzed. At least 4000 CD15+ events were collected on a 3-color FACScan (BD) and analyzed with WINList flow cytometry software (Verity Software House, Topsham, ME). Granulocytes expressing MAC-1 were defined as CD15+ cells, exhibiting the characteristic

granulocyte forward- and side-scatter values, that had displayed MAC-1 binding higher than 98% of the isotype control as measured through fluorescence intensity.

Infection Events and Peak Granulocyte MAC-1 Expression

The influence of infections as a confounding factor on peak granulocyte MAC-1 expression in HMII patients was investigated by comparing the average pre-operative MAC-1 expression levels to average values during an infection and average peak levels which were not during an infection. The 3 groups in this comparison are “Pre-operative Values”, “During Infection Event” and “Highest Value Not During Infection Event”. “Pre-operative Values” are defined as blood samples that were collected and analyzed within 5 days prior to implantation. No patients exhibited signs of infection prior to device placement. “During Infection Event” values were from blood samples withdrawn an average of 3.9 days after a confirmed infection event and before the apparent resolution of the event. Blood samples for the “Highest Value Not During Infection Event” values were collected during periods when the patient was not actively infected (at least 14 days before a confirmed event).

Statistical Analyses

All continuous data is mean $\pm$ standard error of the mean. All continuous data were analyzed by ANOVA with Bonferroni *post hoc* tests or Kruskal-Wallis test with Mann-Whitney *U post hoc* analysis (and Bonferroni correction). Categorical data was tested with Chi-square (using the Likelihood Ratio statistic). Temporal studies were analyzed by repeated measures ANOVA with Bonferroni *post hoc* testing. The analysis of infection events on granulocyte MAC-1 expression in HMII patients contained 5 patients that experienced at least one infection during implantation; however, 3 of the 5 patients experienced two infections. In instances of two infection events, the second infection event was used in the comparison to allow for repeated measures ANOVA tests without affecting the average for the group. Statistical significance was assumed at $P < 0.05$. All statistical tests were performed with SPSS v16.0 (IBM Corp, Armonk, NY).

Results

Patient Demographics, Bypass Time, Chest Tube Output and Blood Product Exposure

A total of 56 patients were followed for this study, with a subset of 20 patients that had additional blood collected for granulocyte activation determination. Most patients were male (77%) with a mean age of 55 and a pre-operative diagnosis of ischemic cardiomyopathy (46%). The only significant pre-operative differences between the patients implanted with each device were implant age, pre-operative diabetes, and mean blood pressure (Table 1). The operation rates for all pumps were within each manufacturer’s suggested range, and did not vary greatly over the course of the study. For the HMII cohort, the median rotations per minute (RPM) was 9400 at POD 14 and POD 120, with a maximum of 10,200 and a minimum of 8800. HW patients had median RPMs of 2800 at POD 14 and 2880 at POD 120, with a maximum of 3160 and a minimum of 2500. PVAD patients had a median beats per minute rate of 82 at POD 14 and POD 120, with a maximum of 99 and minimum of 64. No differences were found between any group for cardiopulmonary bypass (CPB) time,

chest tube output during the first 24 h post-implant, or blood product exposure during the first 48 h post-operation (Table 2).

Temporal Leukocyte Numbers and Infection Events

PVAD patients had significantly different temporal trend of white blood cell counts than HW patients ($P=0.036$) (Figure 1A). Each group of patients significantly peaked on POD 14 above all other timepoints ($P<0.001$) and above the intra-hospital normal range. By POD 60, white blood cell counts in patients from each group had decreased significantly below the pre-operative counts. The percentage of leukocytes consisting of granulocytes in each group exhibited a slight peak at POD 14 but remained relatively flat for the study period (Figure 1B). Hematocrit significantly dropped below all other timepoints at POD 14 ($P<0.006$) and remained lower than pre-operative levels to 60 ($P<0.012$) (Figure 1C).

Infection events per patient-day were concentrated in the first 30 days of device support, though the PVAD patients exhibited a biphasic trend (Figure 1D). The HW group experienced a significantly lower number of infection events per patient during the study period than the HMII and PVAD groups (Table 3). The HMII and HW VAD patients were then combined to form a continuous flow VAD group, and infection events for this group were compared to the pulsatile flow PVAD patients. The continuous flow VAD patients ($N=44$) did not experience a different number of infections per patient during the study versus the pulsatile PVAD patients ($N=12$) (0.98 ± 0.25 versus 1.42 ± 0.36 , $P=0.099$). The continuous flow patients also did not experience a different number of sepsis events or localized non-device infections than the pulsatile group (respectively: 0.27 ± 0.09 versus 0.17 ± 0.11 , $P>0.999$; 0.64 ± 0.18 versus 0.75 ± 0.28 , $P=0.770$). However, the number of driveline infections per patient were significantly lower for continuous flow patients than for pulsatile patients (0.05 ± 0.03 versus 0.42 ± 0.23 , $P=0.007$).

Granulocyte MAC-1 Expression and Infection Events in a Subset of Patients

MAC-1 expression on circulating granulocytes had significantly different trend in HMII patients than HW or PVAD patients when evaluated to POD 30 ($P<0.035$) and HW patients to POD 120 ($P=0.014$) (Figure 2A, B). The HMII patients exhibited a 2.3 fold increase in MAC-1 expression on POD 14 over pre-operative levels and stayed elevated to POD 30 (Figure 2A). When followed to POD 120, the HMII patients had a 2.5 fold increase (from pre-operative levels) in MAC-1 expression on POD 14 and remained elevated to POD 60 (Figure 2B).

HMII patients that experienced an infection over the course of study enrollment were examined to determine the effect of infection events on granulocyte MAC-1 expression (Figure 3). MAC-1 expression during an infection event exhibited almost no increase over pre-operative values (9.6% to 9.0%, respectively); however, these same patients had peak granulocyte MAC-1 expression at levels >2.5 fold higher than those pre-operatively or during an infection (24.2%; $P<0.015$). The average POD of infection for these patients was 54 ± 22 d.

Comment

This study presents a window into the leukocyte and infection profiles of pulsatile and rotary VAD patients out to 120 days post-implantation, providing a few notable findings. First, white blood cell counts increased significantly in the early post-operative period, despite a simultaneous decrease in hematocrit (Figure 1A, C). While other authors have found similar trends with patients having undergone coronary artery bypass graft or heart valve surgeries [11, 12], both the white blood cell and hematocrit effects described in these studies returned to normal or pre-operative values by POD 5 and were not as pronounced as was found for patients in this report. This suggests that the surgery- and device- induced systemic response may be substantial, as post-operative bleeding and reduction of the inflammatory response would be expected to reduce circulating leukocytes by this timepoint. Second, HMII patients experienced a similar rate of infection to the Thoratec PVAD to POD 120, despite a greatly reduced percutaneous driveline exit area (and significantly less driveline infections) (Table 3). In contrast, HW patients had significantly fewer infection events than either the HMII or the PVAD patients, and the post-operative increase in white blood cell counts was lower than the PVAD group. In the PVAD and HMII patients, most infections occurred during the first 30 days of support, but they continued to be susceptible throughout the study (Figure 1D). The peak rates of infection for all VAD patients coincided with significant increases in white blood cell counts (above the normal range) and an upward trend in relative granulocyte concentration (Figure 1A, B). This result is in line with the observation that leukocyte proliferation is a hallmark of infection. In this setting, infectious agents are presented with increased opportunities to find safe harbor and flourish on devitalized tissues and along the synthetic surfaces of the percutaneous driveline and indwelling catheters in the peri-operative period. The concentration of infections during the first 30 days of support agrees with reports [1, 13] and hazard models [14, 15] seen in studies with other devices.

Granulocytes are an important first line of defense against infection, migrating from the vasculature to sites of injury to combat infectious agents. MAC-1 is an adhesion molecule expressed on stimulated granulocytes that mediates migration of the cell from the circulation into inflamed tissue. Upregulation of granulocyte MAC-1 expression in cardiovascular interventions is commonly associated with CPB circuit perfusion and sepsis as a biomarker for systemic inflammation [16, 17]. Extravasated granulocytes (following MAC-1 expression) release enzymes and reactive oxygen species that damage tissue and have been linked to increased edema and organ damage following surgery [18, 19].

Despite growing evidence of altered immune cell function in VAD patients, there is a paucity of information on granulocyte activation and the few papers that discuss it are incomplete or inconclusive. Diehl et al [20] investigated the prevalence of leukocyte-derived microparticles in several rotary or pulsatile VADs at 144 days post-implantation compared to a historical control population. Although the authors found that VAD patients had significantly elevated levels of circulating microparticles expressing MAC-1, the cellular origins of the microparticles were not reported. The authors discussed the possibility of increased microparticles caused by elevated wall shear stresses in various VADs disrupting the immune system but did not distinguish the results by type of circulatory support or provide information on infections for these patients.

Loebe et al [21] reported elevated circulating levels of various inflammatory biomarkers such as complement anaphylatoxins, cytokines and polymorphonuclear leukocyte elastase (PMNE, an indicator of granulocyte activation) compared to normal values for patients implanted with the pulsatile Novacor® or the rotary MicroMed DeBakey® VAD. While these investigators found that C5a and interleukin-6 were significantly increased in the rotary VAD population compared to the pulsatile cohort, PMNE values were nearly identical between the two groups. Additionally, each variable was condensed from 3 months of timepoints into a single averaged post-operative value and not compared to pre-operative levels, limiting the usefulness of this information.

In this study, HMII patients exhibited a rise in granulocyte MAC-1 expression on POD 14 which remained elevated to POD 60 (Figure 2B). Similarities among temporal trends for MAC-1 expression, white blood cell counts and infection events in HMII patients initially suggested that the elevated MAC-1 expression may be the result of blood samples withdrawn during active infections (Figures 1A, D and 2A, B). However, closer inspection of HMII patients that experienced at least one infection event revealed that peak MAC-1 expression occurred in the absence of infection (Figure 3).

Studies involving patients exposed to CPB circuits report only short-term leukocyte activation, with most subjects returning to pre-operative levels within 48 hours [22, 23]. The current study reveals that HMII patients experienced granulocyte MAC-1 expression elevated to levels comparable to that with CPB patients, but these findings continued to 60 days post-procedure. To the authors' knowledge, this is the first report demonstrating persistent circulating activated granulocytes this long after the early postoperative period. This study also suggests that the extended MAC-1 elevation phenomenon for the group of VADs studied was specific to the HMII pump and not attributable to differences in CPB time or blood product exposure (Figure 2A, B; Table 2). The MAC-1 data presented in this study does not appear to be predictive of infection events (Figure 3), but rather offers some insight into the underlying cellular immunological health of the patient. The prolonged expression of MAC-1 on circulating granulocytes has been shown by others to be detrimental to patients. The potential impact of ongoing and elevated granulocyte extravasation could help to explain prolonged tissue edema and organ dysfunction sometimes seen in patients supported by the HMII (such as pulmonary edema and kidney insufficiency). Expression of MAC-1 has been reported to be a modulator of granulocyte apoptosis, shortening lifespan and facilitating sequestration and clearance in the spleen [24]. Similarly, Shive et al [5] found increased neutrophil apoptosis following exposure to high fluid shear stresses, such as those assumed to be experienced in a continuous flow pump. While higher rotational speeds within an individual device is related to shear stress, comparisons of shear forces between devices based on pump speed was not considered in this study as differences in pump architecture is a critical variable in the estimation of fluid shear stress, and the local shear profiles at varying speeds in blood for each pump design were not available.

The similar occurrence of infection events between the HMII and PVAD patients might be unexpected considering the substantially smaller exit site of the HMII driveline (Table 3). The increased levels of granulocyte MAC-1 expression found in HMII patients may have

negatively affected granulocyte reactivity and responsiveness in these patients. MAC-1 induced apoptosis of granulocytes could help to explain the relatively high incidence of infection among HMII patients during the first 60 days of implantation. In contrast, the HW device may have advantages over the other devices in that it has a smaller percutaneous exit site than the PVAD, and its patients had significantly lower levels of granulocyte MAC-1 expression than those of the HMII. Both of these factors could contribute to HW patients experiencing significantly less infection events than either the PVAD or HMII patients. It appears that there may be VAD design factors other than driveline exit site contributing to a risk of infection.

Limitations

This was a single institution study consisting of a relatively small number of patients; a larger multi-center study is warranted. The methodology of this study focused on assessing the prolonged effects of VAD implantation on circulating immune cells. Only patients supported for > 30 d were included in the study, which may have contributed to some selection bias. However, recent INTERMACS data suggest this still represents > 85% of all VAD patients [25]. Another limitation with this study was that only bridge-to-transplant patients could be implanted with the HW or PVAD pumps, which resulted in shorter enrollment periods in the prospective study due to pump explant or transplantation. Additionally, the PVAD was rarely utilized as an LVAD-only device, decreasing the number of available patients that were included in this cohort. All of these factors contributed to a smaller statistical power for the subset of patient whose granulocyte activation levels were followed, especially when evaluated to POD 120. Infectious event data was also limited by the size of the study, and confirmation of differences in infection rates between devices would require more patients followed for a longer period of time. Only driveline tunneling with partial velour exposure was used during the study. Other techniques have been described that may improve infection rates [26]; however, the presence of infection did not contribute to the increased MAC-1 levels in HMII patients (Figure 3). Another study limitation was that other parameters, such as markers of inflammation or granulocyte apoptosis were not measured. Simultaneous measurement of tissue edema as well as plasma interleukin-2, interleukin-6, complement anaphylatoxins and tissue necrosis factor- α along with granulocyte MAC-1 expression would be of interest in future studies.

Conclusions

Alterations in leukocyte numbers and granulocyte activation experienced by VAD patients may be device-specific. HMII patients experienced a significantly different trend of circulating granulocyte MAC-1 expression compared to PVAD and HW patients to POD 30, and HW patients to POD 120, as well as substantially longer elevation than was reported in temporal studies involving CPB circuits. Extravasation and apoptosis of activated granulocytes may contribute to persistent edema and continued infection risk among HMII patients. In contrast, HW patients exhibited little granulocyte activation and significantly less infection events. VAD design may thus influence circulating immune cell activation and infection risk, although the specific relationship between this activation and infection is not known.

Acknowledgments

We thank the nurses and engineers of the Artificial Heart Program at UPMC for coordinating patient consent and blood collection. We thank Dr. Vera Donnenberg for guidance on flow cytometry protocol development. We thank Michael McCall and Darrick Mowrey for providing expertise on data collection and analysis. We thank Gina Jackson and Cory Leeson for sample processing. Support was provided in part by the Cardiovascular Bioengineering Training Program (NIH Training Grant T32-HL076124), NIH Grant R01 HL089456-01, the McGowan Institute for Regenerative Medicine, and the Heart and Vascular Institute of UPMC.

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Figure 1.

Leukocyte and hematocrit changes and incidence of infection events in HMII, HW or PVAD patients following implantation of the device. A) White blood cell numbers. B) The percentage of white blood cells consisting of granulocytes. C) Total hematocrit. D) Infection events per day of patient support. Mean plus standard error of the mean for continuous data. Normal ranges are intra-hospital values. "0" on the abscissa indicates pre-operative values. HMII=HeartMate II; HW=HeartWare; PVAD=Thoratec PVAD pneumatic device.

Figure 2. MAC-1 expression on circulating granulocytes in a subset of VAD patients following implantation

A) MAC-1 expression in all 3 devices evaluated to 1 month post-implant. B) MAC-1 expression in HMII or HW patients to POD 120. Data presented as mean plus standard error of the mean. “0” on the abscissa indicates pre-operative values. HMII=HeartMate II; HW=HeartWare; PVAD=Thoratec PVAD pneumatic device.

Figure 3. Granulocytes expressing MAC-1 in HMII patients that experienced at least one infection event during study enrollment. Data presented as mean plus standard error of the mean. HMII=HeartMate II.

Table 1**Patient Demographics and Heart Failure Information^a**

Demographics	HMII (N=32)	HW (N=12)	PVAD (12)	P
Implant Age (yr)	56 ± 3	64 ± 2	42 ± 3	0.008 ^b
Sex (male)	84	75	58	0.246
Destination Therapy	59	NA	NA	
Diabetic	38	67	17	0.049 ^c
Smoker	59	67	67	0.808
Hemodynamics				
Body Surface Area (m ²)	2.1 ± 0.1	2.0 ± 0.1	1.8 ± 0.1	0.054
Cardiac Output (L/min)	4.3 ± 0.2	4.6 ± 0.5	3.6 ± 0.3	0.180
Cardiac Index (L/min/m ²)	2.1 ± 0.1	2.2 ± 0.2	1.9 ± 0.1	0.406
LVEF (%)	13.8 ± 1.0	15.8 ± 1.6	14.8 ± 1.5	0.552
Blood Pressure Mean (mmHg)	83 ± 2	78 ± 3	74 ± 2	0.033 ^d
PAP Mean (mmHg)	38 ± 2	39 ± 2	40 ± 3	0.899
Central Venous Pressure (mmHg)	12 ± 1	11 ± 1	16 ± 2	0.128
Pre-operative Support				
Milrinone Dosage (mg)	0.5 ± 0.2	0.6 ± 0.2	0.3 ± 0.1	0.510
IABP	56	42	75	0.265
IABP (avg days)	4 ± 1	3 ± 1	3 ± 1	0.508
ECMO	3	0	0	>0.999
ECMO (days)	5	NA	NA	
Concomitant Support				
Temporary RVAD	16	17	25	0.889
RVAD (avg days)	8 ± 2	9 ± 2	12 ± 5	0.889
Pre-operative Diagnosis				
Ischemic	50	42	42	0.688
Non-ischemic	44	50	33	
Other	6	8	25	

^a Continuous data shown as mean ± standard error of the mean and categorical data as percent;

^b HMII v HW P=0.330, HMII v PVAD P=0.006, HW v PVAD P=0.001;

^c HMII v HW P=0.306, HMII v PVAD P=0.646, HW v PVAD P=0.108;

^d HMII v HW P=0.419, HMII v PVAD P=0.039, HW v PVAD P>0.999;

ECMO=Extracorporeal Membrane Oxygenation; HMII=HeartMate II; HW=HeartWare; IABP=Intra-Aortic Balloon Pump; LVEF=Left Ventricular Ejection Fraction; PAP=Pulmonary Artery Pressure; PVAD=Thoratec PVAD Pneumatic; RVAD=Right Ventricular Assist Device

Table 2Cardiopulmonary Bypass Support, Post-operative Bleeding and Blood Product Exposure^a

	HMII (N = 32)	HW (N = 12)	PVAD (N = 12)	P
Cardiopulmonary Bypass Support (min)	107 ± 6	110 ± 12	124 ± 14	0.466
Chest Tube Drainage (ml) ^b	2484 ± 291	1641 ± 381	1744 ± 243	0.144
Total Blood Products (Units) ^c	14 ± 3	11 ± 4	10 ± 3	0.697
Red Blood Cells (Units) ^c	5 ± 1	4 ± 1	3 ± 1	0.504
Platelets (Units) ^c	4 ± 1	3 ± 1	2 ± 1	0.560

^aData presented as mean ± standard error of the mean^bDuring first 24 hrs post-implantation^cDuring first 48 hrs post-implantation

HMII = HeartMate II; HW = HeartWare; PVAD = Thoratec PVAD Pneumatic

Table 3Infection Events in Ventricular Assist Device Patients to Post-operative Day 120^a

	HMII (N = 32)	HW (N = 12)	PVAD (N = 12)	P
Infection Adverse Events	1.28 ± 0.32 53%	0.17 ± 0.11 17%	1.42 ± 0.36 75%	0.009 ^b
INTERMACS Categories				
Sepsis	0.38 ± 0.13 28%	0.08 ± 0.08 8%	0.25 ± 0.13 25%	0.411
Percutaneous Site and/or Pocket	0.06 ± 0.04 6%	0.00 0%	0.50 ± 0.23 33%	0.012 ^c
Localized Non-device	0.84 ± 0.23 47%	0.08 ± 0.08 8%	0.67 ± 0.28 42%	0.057

^aData presented as mean ± standard error of the mean and percentage of patients that experienced at least one event during the study^bHMII v HW P=0.039, HMII v PVAD P>0.999, HW v PVAD P=0.012^cHMII v PVAD P=0.036, HW v PVAD P=0.186

HMII = HeartMate II; HW = HeartWare; INTERMACS = Interagency Registry of Mechanically Assisted Circulatory Support; PVAD = Thoratec PVAD Pneumatic