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Impact of Hemolysis During Microaxial Flow Pump Support on Early Outcomes After Durable Left Ventricular Assist Device Implantation

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The impact of hemolysis during microaxial flow pump (mAFP; Impella, Danvers, Massachusetts, US) support on early outcomes after durable left ventricular assist device (d-LVAD) implantation is unknown. Three hundred and eleven consecutive patients undergoing d-LVAD implantation after mAFP support (Impella 5.0/5.5 72.3%) were retrospectively included. The incidence and predictors of hemolysis (plasma-free hemoglobin >20 mg/dl or lactic dehydrogenase (LDH) >2.5-fold the upper reference limit) before d-LVAD implantation were assessed, along with its impact on early post-d-LVAD outcomes. The primary outcome was a composite of hemocompatibility-related adverse events (HRAEs: stroke/gastrointestinal bleeding/pump thrombosis). Hemolysis occurred in 40.8%. Impella 2.5/CP *versus* 5.0/5.5 was the single independent predictor of hemolysis (adj-hazard ratio [HR] = 2.68, 95% confidence interval [CI] = 1.04–6.94, $p = 0.031$). Post-d-LVAD HRAEs occurred more frequently among patients with hemolysis (31.9% *vs.* 20.6%; $p = 0.041$), mainly driven by hemorrhagic stroke and gastrointestinal bleeding. At multivariate analysis, hemolysis remained independently associated with HRAEs (adj-HR = 1.62, 95% CI = 1.02–2.58; $p = 0.041$). Patients with hemolysis were more likely to need a temporary right ventricular assist device following d-LVAD implantation (28.3% *vs.* 16.8%; $p = 0.012$), with no difference in mortality (23.6% *vs.* 21.2%; $p = 0.355$). In conclusion, among patients undergoing d-LVAD implantation with mAFP bridge, hemolysis is common, occurs more frequently among patients supported with Impella 2.5/CP, and is an independent predictor of post-d-LVAD HRAEs.

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Key Words: left ventricular assist device, microaxial flow pump, impella, hemolysis, outcomes, bridge strategy

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D.L. and E.P. designed the study and collected the data. G.G. performed the statistical analysis. G.G., D.L., and A.L. drafted the manuscript. All authors contributed significantly to the writing and critical review of the manuscript and approved the final draft.

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The use of durable left ventricular assist devices (d-LVADs) has significantly increased in recent years, alongside remarkable progress in their design and clinical results.[1–3] These durable mechanical circulatory support systems have revolutionized the management of patients with end-stage heart failure, providing an increasingly effective treatment option even for the most critically ill individuals (INTERMACS 1–2).[1,2]

The growing success of d-LVADs among patients experiencing cardiogenic shock has led to a significant rise in the use of temporary mechanical circulatory support devices (tMCS) as a bridge to d-LVAD therapy.[4–6] Microaxial flow pumps (mAFP; Impella, Abiomed, Danvers, Massachusetts, US) have become a more popular choice.[7–10] This evolving practice has added new complexities in the periprocedural care of d-LVAD recipients, requiring focused attention on optimal management in patients supported by mAFP devices.[11] Despite growing experience, there is still a lack of information regarding the specific effects of mAFP support on early d-LVAD–related outcomes, making it essential to investigate this aspect comprehensively.

Hemolysis has emerged as a frequent complication of mAFP. The increased shear stress related to the pump impeller mechanically stresses the erythrocyte membrane resulting in cell damage and release of hemoglobin into the plasma (plasma-free hemoglobin [pfHb]). When the protective hemoglobin-scavenging mechanisms, such as haptoglobin, are saturated, pfHb accumulation depletes nitric oxide, causing vasoconstriction, platelet activation and aggregation, and arterial thrombosis.[12] Additionally, pfHb heightens inflammation and can cause pigment nephropathy, leading to acute kidney injury.[13–15] Moreover, the increased shear stress responsible for hemolysis might itself induce other hemocompatibility issues such as acquired von Willebrand Syndrome and thrombocytopenia that may concomitantly enhance the risk of bleeding events.[16–20]

Several small reports addressed the clinical impact of hemolysis in all-comers cohorts of patients supported with mAFP, with controversial results.[16,21,22] Conversely, the impact of hemolysis on clinical outcomes of patients undergoing d-LVAD implantation with mAFP devices remains unstudied. Therefore, the primary objective of this investigation is to characterize the incidence and clinical impact of hemolysis among patients requiring mAFP support as a bridge to d-LVAD therapy.

Methods

All consecutive patients with advanced HF undergoing implantation of a continuous-flow d-LVAD with mAFP bridging between January 2017 and December 2022, at 19 European Institutions were retrospectively analyzed. Data on patient history, clinical presentation, pre-d-LVAD temporary mechanical circulatory support use, management and complications, d-LVAD periprocedural course, and outcomes were collected in a predesigned dataset. Patients without available data on hemolysis before d-LVAD implant were excluded from the analysis. Hemolysis on mAFP support was defined as pfHb >20 mg/dl or LDH >2.5-fold the upper reference limit.[23,24] The study protocol was approved by the individual Health Research Ethics Boards.

Study Outcomes

The primary outcome was the composite of early hemocompatibility-related adverse events (HRAEs) including stroke, gastrointestinal bleeding, or pump thrombosis occurring within 90 days from d-LVAD implant. Secondary outcomes were the individual components of the primary endpoint, all-cause death, heart transplant, right ventricular assist device (RVAD) implantation, and renal replacement therapy (RRT) occurring within 90 days from d-LVAD implant. If patients underwent heart transplantation, d-LVAD explantation, or deceased, follow-up was censored. Outcomes were defined according to the updated INTERMACS definitions of d-LVAD adverse events.[23]

Statistical Analysis

Categorical variables are expressed as number and percentages, continuous variables are expressed as mean ± standard deviation or median and interquartile range (IQR) as appropriate. The unpaired *t* test or nonparametric Mann-Whitney *U* test was used for comparisons of continuous variables and χ^2 test was used for categorical variables. Univariate and multivariate logistic regression analyses were performed to identify the predictors of hemolysis before mAFP implant.

Kaplan-Meier survival curves and log-rank *p* values were used to evaluate the incidence of the primary outcome stratified by the occurrence of hemolysis. Univariate and multivariate Cox regression analyses were performed to identify the primary outcome predictors. The covariates associated with the outcome of interest at univariate analysis with a $p < 0.05$ were considered for inclusion in the multivariate models. Results are presented as hazard ratio (HR) and 95% confidence intervals (CIs). Sensitivity analyses were carried out according to concomitant use of extracorporeal membrane oxygenation (ECMO, ECMELLA strategy), to ECMO status at d-LVAD implant, and according to d-LVAD type. A $p < 0.05$ was considered statistically significant. Statistical analyses were conducted using SPSS (version 24.0; SPSS Inc., Chicago, IL) and STATA (version 17; StataCorp, College Station, TX).

Results

Study Population

Of 341 patients undergoing d-LVAD implant with previous mAFP support, 311 had hemolysis data before d-LVAD implant and comprised the study population. Patient characteristics before d-LVAD implant along with variables relating to the periprocedural course are depicted in Table 1. The median age was 58 years (IQR, 48–65 years), 82.6% were male, and 59.8% presented with ischemic cardiomyopathy. Almost one in three patients experienced cardiac arrest before mAFP placement (31.1%). Overall, mAFP duration was 8 days (IQR 5–14), 86 (27.7%) patients received an Impella 2.5/CP and 225 (72.3%) an Impella 5.0/5.5 (Figure 1). Microaxial flow pump was preferentially placed through the transaxillary access (71.1%). Ten percent had an intra-aortic balloon pump before mAFP implantation and, among patients with an Impella 5.0/5.5, in 36 (15.3%) cases, the device was placed as an upgrade from a less potent Impella (2.5 or CP). An ECMELLA strategy was deemed necessary in 119 (38.3%, n = 69 Impella 5.0/5.5; n = 50 Impella 2.5/CP) patients and ECMELLA duration was 7 days (IQR, 4–11).

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Table 1. Baseline Characteristics, mAFP Support Course, and Periprocedural d-LVAD Implant Characteristics in the Overall Cohort and Stratified by the Occurrence of Hemolysis

	Overall (n = 311)	No Hemolysis (n = 184)	Hemolysis (n = 127)	*p* Value
Patient characteristics				
Age (yrs)	58 (48–65)	59 (49–66)	56 (47–64)	0.061
Male sex (%)	257 (82.6)	155 (84.2)	102 (80.3)	0.227
BSA (m^2)	2.0 (1.8–2.1)	2.0 (1.9–2.1)	1.9 (1.8–2.1)	0.533
Ischemic cardiomyopathy (%)	186 (59.8)	104 (56.5)	82 (64.6)	0.096
Prior cardiac surgery (%)	49 (17)	31 (18.7)	18 (14.6)	0.229
Prior stroke (%)	34 (11.4)	19 (11)	15 (11.9)	0.472
Diabetes (%)	90 (29.3)	58 (32.2)	32 (25.2)	0.114
Atrial fibrillation (%)	117 (37.6)	77 (41.8)	40 (31.5)	**0.041**
Peripheral artery disease (%)	25 (8.2)	14 (7.8)	11 (8.7)	0.475
Patient course on impella support				
Impella 2.5/CP (*vs.* 5.0/5.5)	86 (27.7)	36 (19.6)	50 (16.1)	**<0.001**
Trans-axillary access (%) (*vs.* femoral)	221 (71.1)	143 (77.7)	78 (61.4)	**0.002**
Blood loss during Impella implant (ml)	150 (0–1,355)	190 (42–1,210)	130 (0–1,490)	0.288
Cardiac arrest before Impella (%)	96 (31.3)	53 (29.4)	43 (33.9)	0.243
Upgrade from IABP (%)	31(10)	19 (10.3)	12 (9.4)	0.479
Upgrade from Impella 2.5/CP to 5.0/5.5 (%)	36 (15.3)	22 (14.4)	14 (16.9)	0.371
ECMELLA (%)	119 (38.3)	66 (35.9)	53 (41.7)	0.237
ECMO support at LVAD implant	60 (21.3)	30 (18.5)	30 (25)	0.122
Mobilization out of the bed (%)	99 (33.7)	74 (42.8)	25 (20.7)	**<0.001**
Vasoactive-inotropic score (points)	3.5 (0-7.6)	3.3 (0–7.1)	3.6 (0–8.7)	0.118
Mechanical ventilation (%)	129 (42.4)	71 (39.9)	58 (46)	0.171
Renal replacement therapy (%)	89 (28.7)	51 (27.9)	38 (29.9)	0.394
Anemia (%)	35 (11.3)	21 (11.4)	14 (11)	0.534
Thrombocytopenia (%)	188 (60.5)	94 (51.1)	94 (74)	**<0.001**
Lactates >2 mmol/L (%)	27 (8.7)	10 (5.4)	17 (13.5)	**0.012**
Hyperbilirubinemia (%)	105 (33.8)	49 (26.6)	56 (44.1)	**0.001**
LDH >700 U/L (%)	123 (39.5)	0 (0)	123 (96.9)	**<0.001**
Plasma-free hemoglobin >20 mg/dl (%)	21 (11)	0 (0)	21 (25)	**<0.001**
Hypoalbuminemia (%)	238 (76.5)	135 (73.4)	103 (81.1)	0.143
INR <2 IU/L	309 (99.4)	183 (99.5)	126 (99.2)	0.651
Creatinine >2 mg/dl (%)	63 (20.3)	36 (19.6)	27 (21.3)	0.410
Periprocedural characteristics				
HeartWare d-LVAD (%) (*vs.* HeartMate III)	131 (42.1)	77 (41.8)	54 (42.5)	0.674
Mini-invasive implant (%)	21 (7.4)	10 (5.9)	11 (9.8)	0.158
Implant on CPB (%)	219(72.8)	131(74.9)	88(69.8)	0.202
Surgical time (min)	237 (178–291)	237 (170–295)	238 (189–286)	0.653
Concomitant cardiac surgery (%)	68 (21.9)	35 (19)	33 (26)	0.094
Blood loss during LVAD implant (ml)	605 (350–1,150)	190 (43–1,210)	630 (342–1,208)	0.946
RVAD implant (%)	67 (21.5)	20 (10–24)	36 (28.3)	**0.012**
RVAD duration (days)	18 (10–24)	20 (10–24)	17 (10–25)	0.652
Red blood cell transfusion (units)	6 (2–9)	5 (2–9)	6 (3–8)	0.206
Rethoracotomy (%)	76 (24.4)	43 (23.4)	33 (26.0)	0.346

Bold values denote statistical significance (p<0.05).BMI, body mass index; CPB, cardiopulmonary bypass; d-LVAD, durable left ventricular assist device; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; RVAD, right ventricular assist device.

Of these, 44% had ECMO explanted 10 days (IQR, 4–17) before LVAD implant and 56% were still on ECMO support at d-LVAD implant. The median maximum vasoactive-inotropic score on support was 3.5 (IQR, 0–7.6), 42.4% required mechanical ventilation and 28.7% renal replacement therapy. While on mAFP support, 33.7% of the patients were mobilized out of bed. At the last evaluation before d-LVAD implant, 8.7% of the patients had elevated lactates (>2 mmol/L), 20.3% had renal damage (creatinine >2 mg/dl), and 11.3% of the patients had anemia.

Occurrence and Predictors of Hemolysis Before Durable Left Ventricular Assist Device Implant

Hemolysis before d-LVAD implant was present in 127 (40.8%) of the patients. Patients without atrial fibrillation, those supported with Impella 2.5/CP device, and those undergoing implant from a trans-femoral access were more likely to suffer from hemolysis (Table 1). Patients with hemolysis were more likely to also have thrombocytopenia and elevated lactates, and not undergoing mobilization out of bed (Table 1). Among patient- and device-related factors, Impella 2.5/CP device and trans-femoral access were associated with hemolysis (Table 2). At multivariate analysis, Impella 2.5/CP *versus* 5.0/5.5 was the single independent predictor of hemolysis (adj-HR = 2.68, 95% CI = 1.04–6.94; $p = 0.031$).

Impact of Hemolysis on Post-Durable Left Ventricular Assist Device Outcomes

At 3 months from d-LVAD implant, 69 (22.2%) patients had died, 28 (9.0%) were transplanted and 214 (68.8%) were alive on d-LVAD support. Early HRAEs had occurred in 74 (23.8%) patients (gastrointestinal bleeding 34 [10.9%], hemorrhagic stroke nine [2.9%], ischemic stroke 34 [10.9%], pump thrombosis 10 [3.2%]). Patients with hemolysis were more likely to experience post-d-LVAD HRAEs (31.9% *vs.* 20.6%, $p = 0.041$, Figure 2), mainly driven by hemorrhagic stroke (2.3% *vs.* 0.6%;

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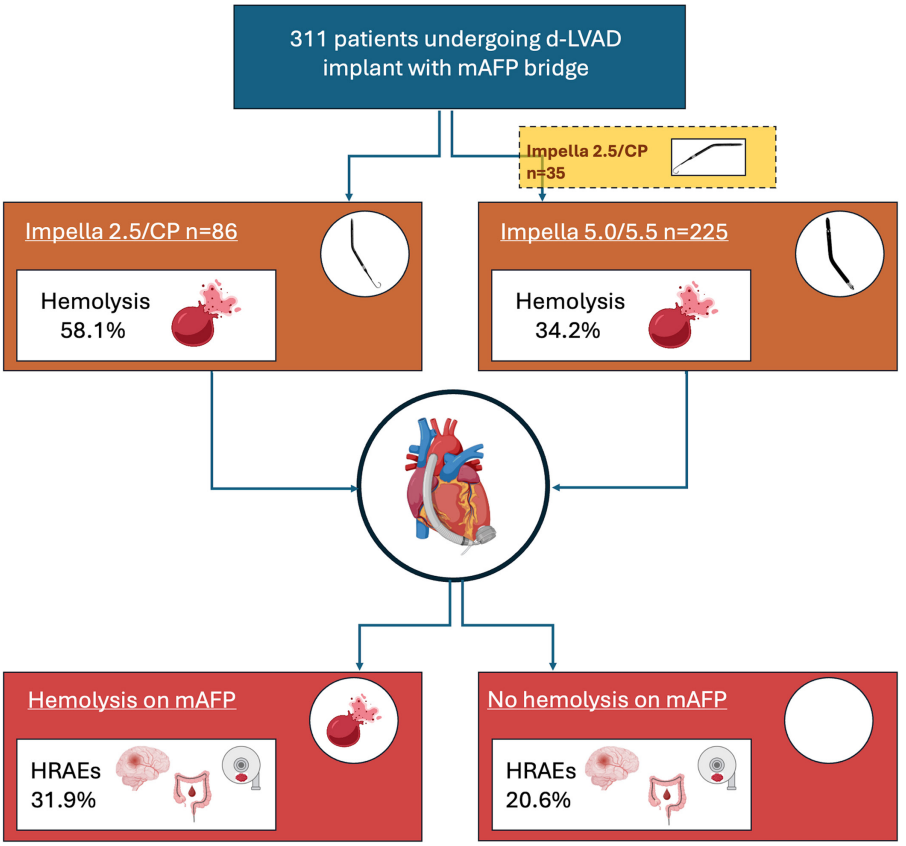


Figure 1. Study flowchart of mAFP strategies, development of hemolysis on mAFP support, and post-d-LVAD HRAEs outcomes. d-LVAD, durable left ventricular assist device; HRAEs, hemocompatibility-related adverse events; mAFP, microaxial flow pump. full color online

p = 0.027) and gastrointestinal bleeding (15.0% *vs.* 8.2%; p = 0.045). At multivariate analysis, hemolysis remained independently associated with HRAEs (adj-HR = 1.62, 95% CI = 1.02–2.58; p = 0.041), together with higher body surface area (p < 0.001) and female gender (p = 0.004) (Table 3). Patients with hemolysis had a trend for more frequent RRT requirement following d-LVAD implantation (46% *vs.* 35.2%; p = 0.051), were more likely to need temporary RVAD following d-LVAD implantation (28.3% *vs.* 16.8%; p = 0.012) and to undergo early heart transplantation (17.4% *vs.* 8.6%; p = 0.031), while no difference in mortality was observed (23.6% *vs.* 21.2%; p = 0.355) (Table 4, Figure 3).

Sensitivity Analyses

By ECMO status. The baseline characteristics of the study population stratified by ECMELLA status and ECMO at d-LVAD implant status are reported in Supplementary Tables 1 and 2, Supplemental Digital Content, http://links.lww.com/ASAIO/B491. No difference in hemolysis was observed between patients requiring *versus* not requiring ECMELLA (44.5% *vs.* 39.7%; p = 0.237) nor among patients still on ECMO *versus* not on ECMO at d-LVAD implant (50.0% *vs.* 40.5%; p = 0.122). There was no interaction between ECMELLA requirement or ECMO at d-LVAD implant with the impact of hemolysis on early HRAEs (p for interaction 0.271 and 0.710, respectively).

By d-LVAD type. No differences in hemolysis were observed between patients undergoing d-LVAD implant with a HeartWare pump *versus* a HeartMate III pump (40.3% *vs.* 40.8%; p = 0.674). Patients undergoing d-LVAD implant with a HeartWare pump had higher odds of early HRAEs (2.09, 95% CI = 1.30–3.38; p = 0.003). However, there was no interaction between d-LVAD type with the impact of hemolysis on early HRAEs (p for interaction 0.434).

Table 2. Univariate and Multivariate Predictors of Hemolysis During mAFP Support Before d-LVAD Implantantion

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	***p* Value**	**HR (95% CI)**	***p* Value**
Male sex	0.76 (0.42–138)	0.370	-	ns
Age (per year increase)	0.98 (0.97–1.0)	0.167	-	ns
Impella 2.5/CP (*vs.* 5.0/5.5)	2.67 (1.61–4.44)	**<0.001**	2.68 (1.04–6.94)	**0.031**
Impella access (trans-femoral *vs.* trans-axillary)	2.21 (1.31–3.63)	**0.002**	-	ns

CI, confidence interval; d-LVAD, durable left ventricular assist device; HR, hazard ratio; mAFP, microaxial flow pump.

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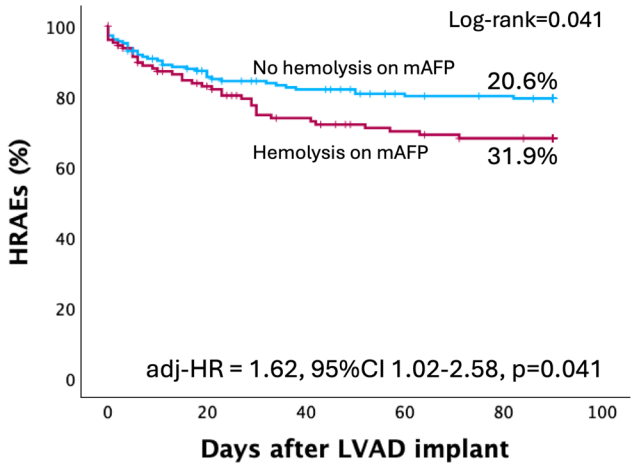


Figure 2. Kaplan-Meier estimates for the occurrence of post-d-LVAD early HRAEs based on the development of hemolysis during mAFP support. CI, confidence interval; d-LVAD, durable left ventricular assist device; HR, hazard ratio; HRAEs, hemocompatibility-related adverse events; mAFP, microaxial flow pump. full color online

Discussion

The aim of this study was to investigate the impact of hemolysis during mAFP support on early outcomes after d-LVAD implantation. The main results are as follows: hemolysis during mAFP before d-LVAD implantation is common, occurring in approximately 40% of patients. Among patient- and device-related factors, Impella 2.5/CP (*versus* 5.0/5.5) is the single independent predictor of hemolysis. Hemolysis on mAFP is an independent predictor of HRAEs following d-LVAD implant, mainly driven by bleeding events. No difference in mortality was observed.

In the recent DANGER-SHOCK trial, demonstrating the prognostic impact of mAFP in acute myocardial infarction-related cardiogenic shock, clinically significant hemolysis on mAFP was common (12.4%) and was associated with an increased risk of acute kidney injury and RRT.[25,26] Although earlier research has examined hemolytic complications in the wider mAFP population, the predictors, frequency, and effects of hemolysis events in d-LVAD patients bridged with mAFP are unsettled. Hemolysis heightens the risk of hemocompatibility events through several mechanisms, including pfHb-induced nitric oxide depletion and vasoconstriction, platelet activation and aggregation, inflammation, and acute kidney injury.[13–15] Although these factors enhance the risk of hemocompatibility events on mAFP support, they might conceivably have an impact on post-d-LVAD HRAEs as well. We thus designed this study to shed light on the complex relationships between hemolysis, tMCS management strategies, and post-d-LVAD outcomes, analyzing a large contemporary cohort of mAFP-bridged patients.

The findings of this study underscore several clinically relevant points. First, hemolysis before d-LVAD implant in mAFP patients is frequent and grossly in the range of what is reported in unselected mAFP cohorts (20.5–62.5%).[22,27] While a direct comparison with DANGER-SHOCK cannot be carried, as only clinically significant hemolysis was reported in the trial, the numerically higher rate observed in our cohort (40.8% of laboratoristic hemolysis in our cohort *versus* 12.4% of clinically significant hemolysis in DANGER-SHOCK) point at the different clinical settings, with a median support duration of 2.5 (IQR, 1.3–3.6) days in the trial and 8 (IQR, 5–14) days in our cohort, and a high rate of myocardial recovery in the trial as opposed to the "bridging purpose" of mAFP in this study.

Second, the use of new mAFP devices (Impella 5.0/5.5) as a bridge to d-LVAD is the sole independent predictor of a lower risk of hemolysis. This observation is plausible and grounded on the technological characteristics of the pump iterations. The hemocompatibility profile of the pump is directly related to

Table 3. Univariate and Multivariate Predictors of Post-d-LVAD Early HRAEs

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Male sex	0.49 (0.29–0.80)	**0.005**	0.47 (0.28–0.78)	**0.004**
Age (per year increase)	0.99 (0.97–1.01)	0.300	-	ns
BSA (per m^2 increase)	1.08 (1.02–1.13)	**0.006**	1.11 (1.05–1.17)	**<0.001**
Hemolysis on mAFP	1.60 (1.01–2.54)	**0.044**	1.62 (1.02–2.58)	**0.041**
Thrombocytopenia	1.68 (1.04–2.74)	**0.036**	-	ns

CI, confidence interval; d-LVAD, durable left ventricular assist device; HR, hazard ratio; HRAE, hemocompatibility-related adverse event.

Table 4. Univariate Association Between Hemolysis on mAFP Support and Early Outcomes Post-d-LVAD

90 Day Outcomes	HR (95% CI)	*p* Value
All-cause mortality	1.16 (0.72–1.86)	0.550
Urgent heart transplant	2.13 (1.01–4.51)	**0.046**
HRAEs	1.10 (1.04–1.16)	**<0.001**
Gastrointestinal bleeding	1.69 (1.03–2.76)	**0.038**
Hemorrhagic stroke	5.29 (1.10–25.45)	**0.020**
Ischemic stroke	1.27 (0.63–2.58)	0.510
Pump thrombosis	0.98 (0.28–3.48)	0.978
RRT requirement	1.57 (0.95–2.60)	0.078
RVAD requirement	1.95 (1.13–3.37)	**0.016**
Driveline infection	1.00 (0.41–2.45)	0.996

CI, confidence interval; d-LVAD, durable left ventricular assist device; HR, hazard ratio; HRAEs, hemocompatibility-related adverse events; mAFP, microaxial flow pump; RRT, renal replacement therapy; RVAD, right ventricular assist device.

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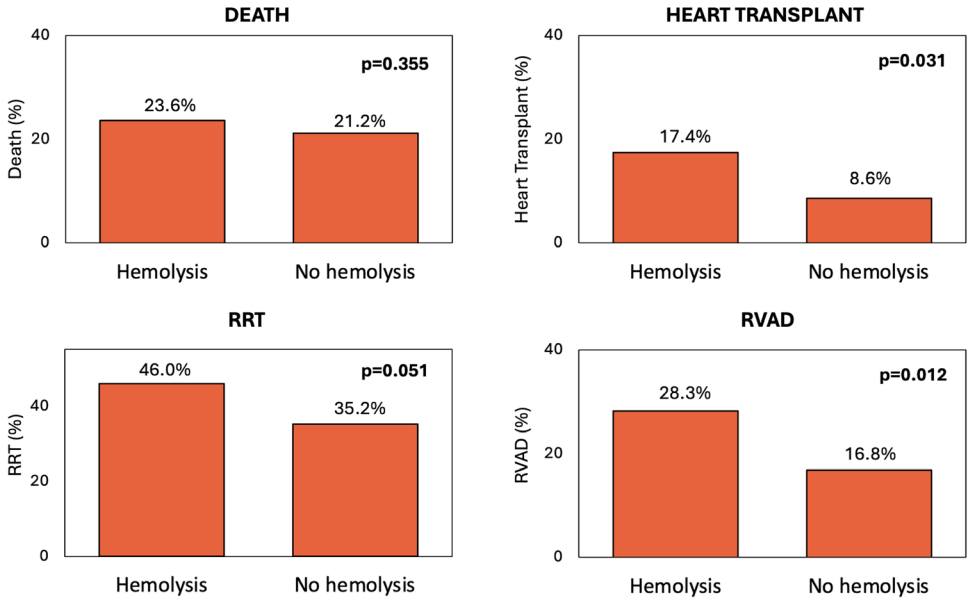


Figure 3. Association of hemolysis during mAFP support with post-d-LVAD early (90 days) secondary outcomes. d-LVAD, durable left ventricular assist device; mAFP, microaxial flow pump; RRT, renal replacement therapy; RVAD, right ventricular assist device. full color online

the shear stress induced by the pump impeller on the blood, that is in turn related to rotational speed.[16,21,28] Impella 2.5/CP as compared with 5.0/5.5 devices necessitate higher rotational speed per flow generated, resulting in higher hemolysis. Furthermore, Impella 2.5/CP devices present higher pump position instability that may further contribute to increased shear stress and related complications.[11,29,30] Third, beyond observing well-described predictors of HRAEs like female gender and body mass index (BMI), we demonstrated that hemolysis on mAFP support is an independent predictor of post-d-LVAD early HRAEs and is associated with more frequent RVAD requirement and trends for higher RRT requirement. While no difference in mortality ensued, the increased need for early HT among patients with hemolysis suggests that HRAEs and/or early severe right heart failure might mediate the link between hemolysis and failure of the pump-patient interface. These results are hypothesis-generating, and we cannot provide a definite mechanistic explanation, nor establish the causal nature of this link. The relationship between hemolysis on support and post-d-LVAD HRAEs is likely complex and multifactorial. The heightened thrombotic risk related to pfHb-induced nitric oxide depletion and vasoconstriction, platelet activation, and aggregation might exacerbate the precarious hemostatic balance of patients with critical illness and might trigger more intense anticoagulation, resulting in higher vulnerability to both thrombotic and bleeding events.[24] The acute kidney injury related to pigment nephropathy with a higher requirement for RRT and related intensity of care may further contribute. On the other hand, hemolysis may be a marker of higher shear stress, concomitantly resulting in acquired von Willebrand syndrome and platelet depletion, that represent other potential mechanisms of post-d-LVAD HRAEs.[16,24] Both circumstances would call for aggressive prevention and management of on-support hemolysis, aiming at reducing shear stress at the pump-patient interface. Of note, the HRAEs event curves tend to diverge the most between 15 and 30 days post-d-LVAD implant. Although we do not have a definitive answer to explain this finding, we believe that the mechanisms heightening the risk of hemocompatibility events among patients with hemolysis, including pfHb-induced nitric oxide depletion and vasoconstriction, platelet activation and aggregation, inflammation, and acute kidney injury may require time to reach the threshold of a clinical event, especially in the very dynamic setting of the post-LVAD critical care. Specifically, these processes may interact with "second-hit" factors, including the need for prolonged RRT, the initiation and titration of antithrombotic regimens, and extended exposure to continuous-flow physiology, collectively contributing to a clinical event only at a later stage.

Several strategies can be used to mitigate the risk of hemolysis during mAFP support.[16] Optimal positioning of the device is crucial, with echocardiography or fluoroscopy used to ensure proper alignment relative to the LV axis. Regular monitoring of the device's position can prevent or promptly address device displacement. Adequate volume management is essential to maintain left ventricular preload, preventing hypovolemia and suction events. Addressing underlying conditions such as vasoplegia or right ventricular failure is vital for optimizing fluid balance and hemodynamics.[16,31] Adjustments of device settings based on hemodynamic status can further minimize shear stress. Protocols for device insertion and rotation should be implemented to ensure optimal placement and minimize the risk of bleeding and hemolysis associated with device malrotation.[30] Finally, strategies aiming to increase the clearance of pfHb might be beneficial.[32] Of note, there is an inherent trade-off between higher mAFP support (with its benefits for unloading) and the risk of hemolysis. While it is difficult to define a precise "sweet spot" for mAFP support to balance unloading and hemolysis risk, this decision should be individualized based on the patient's hemodynamic status, anemia, renal function, and overall treatment goals.

Finally, the observed association between hemolysis and RVAD requirement is thought-provoking. Despite heightened

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awareness and careful patient selection, early right ventricular failure remains a frequent and ominous complication of d-LVAD implantation.[33–35] While the morpho-functional metrics of preprocedural right ventricular function and adaptation can help predict post-d-LVAD right ventricular failure, their accuracy remains modest,[33,34] suggesting a more complex underlying biologic process. Whether hemolysis-induced inflammatory activation may exert detrimental cardiodepressive effects is a hypothesis that merits exploration.

Limitations

The results of the study should be interpreted considering several limitations. First, this study is hypothesis-generating and associative in nature. Second, the retrospective design may introduce bias, and practice variations among different institutions may influence outcomes. Third, we used the definition most widely accepted and recommended to report hemolysis in trials and registries of mechanical circulatory support.[23] However, the definition best representing clinically relevant hemolysis is currently unclear. Fourth, we did not collect data on clinical manifestations of hemolysis, tMCS escalation patterns, mAFP support level, purge solution type and concentration, antithrombotic regimens, and device malposition or malrotation. These factors might have further enriched the analysis and remain to be comprehensively explored. Finally, longitudinal measurements of hemolytic markers were not available, accordingly, the reported incidence and clinical impact refer to hemolysis just before d-LVAD implant.

Conclusions

Among patients undergoing d-LVAD implantation with mAFP bridge, hemolysis during Impella support is common, occurs more frequently among patients supported with Impella 2.5/CP, and is an independent predictor of post-d-LVAD early HRAEs. Whether a standardized approach to the prevention, detection, and treatment of hemolysis on mAFP might improve post-d-LVAD outcomes should be assessed in dedicated studies.

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