CFR Cardiac Failure Review

ORIGINAL RESEARCH

Therapy

Patient-specific Predictors of Haemolysis with Percutaneous Ventricular Assist Devices

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Abstract

Introduction: Percutaneous ventricular assist devices (pVADs) are increasingly used in cardiogenic shock but are associated with complications including haemolysis. The aim of this study was to investigate patient characteristics associated with haemolysis in cardiogenic shock patient population. **Methods:** Consecutive patients were identified using Current Procedural Terminology (CPT) codes for pVAD insertion. Patient characteristics, laboratory and imaging data, and patient outcomes were abstracted manually and using validated automated methods. Laboratory-defined haemolysis required a drop in haemoglobin ≥2 mg/dl with either lactate dehydrogenase ≥250 units/l or undetectable haptoglobin. Clinically significant haemolysis was defined as laboratory-defined haemolysis necessitating transfusion. Primary outcome was the association between haemolysis and on-device and 30-day mortality. **Results:** A total of 196 patients underwent pVAD insertion for cardiogenic shock during the study period and were included. Laboratory-defined haemolysis occurred in 46 patients (23.5%), of whom 12 (6.1%) had clinically significant haemolysis. Haemolysis occurred more often following emergency insertion, rather than elective insertion (84.8% versus 40.0%, p<0.001) in patients with elevated lactic acid levels (median 2.5 versus 1.6, p=0.016) and elevated heart rates (92.5 BPM versus 86.5 BPM, p=0.023). After multivariable adjustment, there was no association between laboratory-defined haemolysis and on-device (OR 0.6; 95% CI [0.1–3.4]; p=0.565) or 30-day mortality (OR 2.1; 95% CI [0.4–13.0]; p=0.391). **Conclusion:** Laboratory-defined haemolysis was common in patients with cardiogenic shock and pVAD, but clinically significant haemolysis was not. There was no association between haemolysis and on-device or 30-day mortality.

Keywords

Impella device, cardiogenic shock, mechanical circulatory support, ventricular assist device, high-risk coronary angioplasty

Received: 1 October 2024 **Accepted:** 29 November 2024 **Citation:** *Cardiac Failure Review* 2025;11:e04. **DOI:** https://doi.org/10.15420/cfr.2024.30

Disclosure: KVA has consulted for Guidepoint and Tegus and serves on a data monitoring and safety board for Fortrea. ASR has received consulting/speaking honoraria from Abiomed, Analog Devices, CareTaker Medical, Vectorious and Volumetrix and is on the *Cardiac Failure Review* editorial board; this did not affect peer review. All other authors have no conflicts of interest to declare.

Funding: AES is supported by an NIH T32 award (GM007569). KVA is supported by the NIH (K23HL166960), the International Society for Heart and Lung Transplantation Enduring Hearts Transplant Longevity Award, the Red Gates Foundation, and an AHA Career Development Award (#929347).

Data availability: The data are not publicly available due to privacy or ethical restrictions.

Authors' contributions: Conceptualisation: ASR; data curation: AES, HG, LD, JN, LT, EF-E; methodology: ASR; writing – original draft: AES, JLL, QSW, BDA, JMO, SB, KVA, ASR; writing – review & editing: AES, ASR.

Ethics: The study was approved by the Institutional Review Board of Vanderbilt University Medical Center.

Consent: The requirement to obtain informed consent was waived by the Institutional Review Board of Vanderbilt University Medical Center.

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Percutaneous ventricular assist devices (pVADs) are catheter-based miniaturised micro-axial flow pumps that provide circulatory support. Due to ease of placement and expanded indications, the usage of pVADs has increased recently to treat patients with various aetiologies of cardiogenic shock, including post-pericardiotomy shock.[1–3] Furthermore, pVADs are used for intra-procedural circulatory support during high-risk coronary interventions and ventricular tachycardia ablation.[4]

Benefits of mechanical circulatory support devices must be balanced against their inherent risks. Bleeding, haemolysis, peripheral vascular complications, and stroke are among the most common complications with pVAD.[5] Patients with a pVAD have higher rates of bleeding compared with other cardiac intensive care unit (ICU) patients and have nearly threefold higher rates of bleeding than those with intra-aortic balloon pump (IABP).[6,7] There is also a higher incidence of haemolysis in pVAD

patients compared with IABP patients and an approximately 13% risk of vascular complications, including acute limb ischaemia.[8,9]

Several device-specific factors, including pump speed, pump size, inlet or outlet obstruction and high shear stress along the rotor blades, lead to haemolysis.[10] Many protocols currently exist to monitor for haemolysis while on pVAD support, including serial haemoglobin, lactate dehydrogenase (LDH), plasma free haemoglobin, and/or haptoglobin levels.[11] However, there remains a paucity of data on patient-specific factors that increase the risk of haemolysis while on pVAD support. In this study we investigated the patient characteristics most strongly associated with both laboratory and clinically significant haemolysis in patients admitted to our cardiac ICU with pVADs.

Methods

The Vanderbilt University Medical Center (VUMC) Mechanical Circulatory Support registry is a retrospective, single-centre registry at a quaternary care hospital. The study was approved by the Institutional Review Board of Vanderbilt University Medical Center and informed consent was waived.

Study Population

We retrospectively identified all patients aged ≥18 years who underwent pVAD insertion or removal at VUMC from 1 January 2018 to 30 June 2023. All pVAD types, including Impella 2.5, CP, 5.5 and RP were included. Patients were identified using Current Procedural Terminology (CPT) codes for insertion (CPT 33990).

Data Collection and Definition of Variables

Patient demographics and comorbidity data were abstracted from the medical record system using previously established methods.[12–16] Echocardiographic data, when available within 3 months prior to pVAD insertion, were abstracted from the official report. Haemodynamic and laboratory data immediately prior to pVAD insertion were extracted using the date of insertion. pVAD indication, urgency and details of the pVAD circulatory support course (including P-level, device type and insertion vessel) were determined through manual chart review.

Study Outcomes

Two definitions of haemolysis were used. Laboratory-defined haemolysis was described as a drop in haemoglobin ≥2 mg/dl and either LDH ≥250 units/l (greater than twofold the upper limit of normal) or an undetectable haptoglobin.[17] Plasma free haemoglobin was obtained very infrequently and, hence, not included in this definition. Clinically significant haemolysis was defined as the presence of laboratory-defined haemolysis necessitating transfusion with at least 1 unit of packed red blood cells in the absence of an alternate source of blood loss.

Statistical Analysis

Descriptive statistics are reported for demographics, clinical characteristics and outcomes stratified by the presence or absence of laboratory haemolysis. Continuous variables are reported as median and IQR, and between-group comparisons were conducted using Mann–Whitney *U*-test. Categorical variables are reported as total number and percentage, with comparisons made using Pearson chi-squared test or Fisher's exact test as appropriate. Multivariable logistic regression modelling was performed to assess the association of clinically relevant variables and the development of haemolysis. The primary outcome was the association of haemolysis with on-device and 30-day mortality, which was assessed using logistic regression models that adjusted for clinically relevant variables. Data were analysed using R version 4.2.2 (R Foundations for Statistical Computing).

Results

Baseline Cohort Characteristics

A total of 196 patients underwent pVAD insertion over the study period. The median (IQR) age of the cohort was 65.9 (55.2–75.1) years and included 60 women (30.6%) and 27 Black or Hispanic patients (13.7%; *Table 1*). Impella 2.5 and CP were the predominant devices implanted (89.8%) and were used in emergency implantation in 99 patients (50.5%). A total of 66 patients (33.7%) required device insertion in the setting of acute myocardial infarction (MI), while 43 (21.9%) underwent placement for heart failure-associated cardiogenic shock. The most frequent indication for implantation was bridge to recovery (40.8%), while 73 patients (37.2%) had pVAD for haemodynamic support during high-risk percutaneous coronary intervention, and 28 patients (14.3%) had pVAD for left ventricular unloading during veno-arterial extracorporeal life support.

Clinical Characteristics of Patients with Haemolysis

Of 196 patients, 46 (23.5%) met the laboratory definition for haemolysis and 12 (6.1%) met criteria for clinically significant haemolysis. Patients with laboratory-defined haemolysis were more likely to have emergency, rather than elective, pVAD insertion (84.8% versus 40.0%, p<0.001) and lower baseline left ventricular ejection fraction (LVEF; median, 18.0% versus 32.3%, p=0.002). pVAD insertion was more often in the setting of acute MI (58.7% versus 26.0%, p<0.001) and intended for recovery (67.4% versus 32.7%, p<0.001) in those with laboratory-defined haemolysis, whereas the device was more often used for haemodynamic support during high-risk procedures in those without laboratory-defined haemolysis (6.5% versus 46.7%, p<0.001). Baseline lactic acid (median, 2.5 mmol/L versus 1.6 mmol/L, p=0.016) and heart rate (92.5 BPM versus 86.5 BPM, p=0.023) were significantly higher in those with laboratory-defined haemolysis and there was a trend toward lower pulse pressure (33.5 mmHg versus 38.5 mmHg, p=0.056).

Clinical Outcomes Associated with Laboratory Haemolysis

pVAD support duration was significantly longer (67.4 hours versus 4.28 hours, p<0.001) for patients with laboratory haemolysis than for those without. Median hospital length of stay was longer in the cohort with haemolysis although it did not reach statistical significance (7.9 days versus 4.8 days, p=0.06; *Table 2*). Renal failure was significantly more common in those with haemolysis than in those without haemolysis (37% versus 16.7%, p=0.011).

Predictors of Laboratory-defined Haemolysis

Clinically relevant predictors of laboratory haemolysis are listed in *Table 3*. In multivariable regression modelling adjusting for aetiology of cardiogenic shock, urgency of pVAD insertions, and pre-device insertion lactate, pulse pressure and LVEF, only emergency pVAD insertion remained a significant predictor of laboratory haemolysis (OR 12.3; 95% CI [1.1–137.3]; p=0.041).

Association of Laboratory Haemolysis with Mortality

The results of multivariable regression modelling examining the association between haemolysis and both on-device and 30-day mortality are listed in *Table 4*. After adjusting for clinically relevant variables, there was no association between laboratory-defined haemolysis and on-device mortality (OR 0.6; 95% CI [0.1–3.4]; p=0.565). There was similarly no association between laboratory-defined haemolysis and 30-day mortality (OR 2.1; 95% CI [0.4–13.0]; p=0.391).

Table 1: Baseline Characteristics of Cohort

	Laboratory Haemolysis, n (%) or median (IQR)		p-value
	Absent	Present	
Total sample	150	46	
Age (years)	68.22 (56.25–76.77)	63.33 (51.30–72.04)	0.109
Gender			
Male	102 (68.0)	34 (73.9)	0.563†
Female	48 (32.0)	12 (26.1)	
Race			
Caucasian	114 (76.0)	40 (87.0)	0.536‡
Black	20 (13.3)	4 (8.7)	
Hispanic	3 (2.0)	0 (0.0)	
Other	13 (8.7)	2 (4.3)	
BMI (kg/m^2)	28.50 (25.40–34.45)	27.70 (25.72–32.62)	0.518
Hypertension	61 (40.7)	22 (47.8)	0.491†
Diabetes	91 (60.7)	31 (67.4)	0.516†
Smoking history			0.296†
• Current	14 (9.3)	6 (13.0)	
• Former	66 (44.0)	13 (28.3)	
• Never	53 (35.3)	20 (43.5)	
Hyperlipidaemia	119 (79.3)	30 (65.2)	0.078†
Coronary artery disease			
Acute	82 (54.7)	29 (63.0)	0.356†
Chronic	40 (26.7)	7 (15.2)	
None	23 (15.3)	7 (15.2)	
Baseline serum creatinine (mg/dl)	1.28 (0.96–1.85)	1.45 (1.14–1.81)	0.374
AF	4 (2.7)	1 (2.2)	1‡
Stroke	18 (12.0)	4 (8.7)	0.790‡
Peripheral artery disease	24 (16.0)	6 (13.0)	0.8†
Prior MI	134 (89.3)	40 (87.0)	0.857†
History of aortic valve replacement	11 (7.3)	2 (4.3)	0.736‡
History of mitral valve replacement	3 (2.0)	1 (2.2)	1‡
Baseline haemoglobin (g/dl)	10.80 (9.33–13.17)	12.95 (10.43–14.83)	<0.001
LVEF (%)	32.31 (23.09–48.00)	18.00 (13.00–25.00)	0.002
Anticoagulation	66 (44.0)	14 (30.4)	0.143†
Warfarin	28 (18.7)	4 (8.7)	0.169‡
Dabigatran	1 (0.7)	0 (0.0)	1‡
Apixaban	21 (14.0)	5 (10.9)	0.804‡
Rivaroxaban	7 (4.7)	2 (4.3)	1‡
Enoxaparin	43 (28.7)	9 (19.6)	0.302†
Antiplatelet	114 (76.0)	32 (69.6)	0.495†
Prasugrel	14 (9.3)	5 (10.9)	0.777‡
Clopidogrel	96 (64.0)	24 (52.2)	0.205†
Ticagrelor	28 (18.7)	13 (28.3)	0.233†
Device intent			
Bridge to decision/ candidacy	4 (2.7)	5 (10.9)	<0.001‡
Bridge to recovery	49 (32.7)	31 (67.4)	
Bridge to transplant	3 (2.0)	0 (0.0)	
Bridge to LVAD	2 (1.3)	1 (2.2)	
Haemodynamic support during high-risk procedure (e.g. Impella-assisted PCI)	70 (46.7)	3 (6.5)	
LV venting during ECMO	22 (14.7)	6 (13.0)	
Impella class			
Emergency Impella	60 (40.0)	39 (84.8)	<0.001†
Elective Impella	90 (60.0)	7 (15.2)	
Device type			
Impella 2.5/CP	132 (88.0)	44 (95.7)	0.242‡
Impella 5.0/5.5	8 (5.3)	2 (4.3)	
Right-sided RP Impella	10 (6.7)	0 (0.0)	
Pump speed (p-level)	8.00 (4.00–9.00)	7.00 (5.00–8.00)	0.096
Aetiology of cardiogenic shock			
Acute MI	39 (26.0)	27 (58.7)	0.005‡
Acute decompensated heart failure	32 (21.3)	11 (23.9)	
Post-cardiotomy	1 (0.7)	0 (0.0)	
Myocarditis	2 (1.3)	2 (4.3)	
Ventricular tachycardia	5 (3.3)	3 (6.5)	
Other/unknown	26 (17.3)	3 (6.5)	
LDH (units/l)			
Baseline	1.60 (1.00–4.40)	2.55 (1.40–5.47)	0.016
1 day after insertion	2.60 (1.50–4.10)	2.10 (1.12–4.70)	0.41
≥2 days after insertion	1.30 (1.00–2.20)	1.40 (0.92–2.00)	0.827
Baseline pulse pressure (mmHg)	38.50 (28.25–50.75)	33.50 (25.00–41.75)	0.056
Baseline heart rate (BPM)	86.50 (71.00–102.00)	92.50 (80.50–109.00)	0.023
Device run time (hours)	4.28 (1.57–45.02)	67.36 (45.52–110.53)	<0.001

p-values calculated using the Mann–Whitney U-test for continuous variables, and either the †Pearson chi-squared test or ‡Fisher's exact test for categorical variables; ECMO = extracorporeal membrane oxygenation; LDH = lactate dehydrogenase; LV = left ventricle; LVAD = left ventricular assist device; LVEF = left ventricle ejection fraction; PCI = percutaneous coronary intervention.

Clinically Significant Haemolysis

Clinically significant haemolysis was rare, occurring in 12 patients (6.1%). Baseline characteristics of those with clinically significant haemolysis are listed in *Supplementary Material Table 1*. Patients with clinically significant haemolysis were of similar age and gender and had similar baseline haemoglobin levels compared with the rest of the cohort. They more frequently had emergency pVAD insertion for acute MI, decompensated

Table 2: Outcomes Associated with Laboratory-defined Haemolysis

	Laboratory Haemolysis, n (%) or median (IQR)		p-value
	Absent	Present	
Total sample	150	46	
Clinically significant haemolysis	0 (0.0)	12 (26.1)	<0.001
Mortality			
Total	22 (14.7)	12 (26.1)	0.118
30 days	40 (26.7)	26 (56.5)	0.001
Length of stay (days)	4.78 (1.82–12.07)	7.89 (2.71–16.34)	0.06
No. of transfusions	0.00 (0.00–4.00)	1.00 (0.00–4.00)	0.01
Outcomes			
• Recovery	1 (0.7)	2 (4.3)	0.275
• Transplant	1 (0.7)	1 (2.2)	0.959
• Renal failure	25 (16.7)	17 (37)	0.011

p-value calculated using the Mann–Whitney U-test for continuous variables and Pearson chi-squared test for categorical variables.

Table 3: Predictors of Laboratory-defined Haemolysis

	OR [95% CI]	p-value
Origin of cardiogenic shock: acute MI	1.507 [0.299–7.612]	0.619
Emergency Impella insertion	12.330 [1.107–137.306]	0.041
Lactic acid prior to device insertion	0.850 [0.661–1.093]	0.206
Pulse pressure prior to device insertion	0.964 [0.915–1.015]	0.160
Left ventricular ejection fraction	0.955 [0.906–1.007]	0.089

Table 4: Association of Laboratory-defined Haemolysis with On-device and 30-day Mortality

	On-device Mortality		30-day Mortality	
	OR [95% CI]	p-value	OR [95% CI]	p-value
Laboratory haemolysis	0.605 [0.109–3.357]	0.565	2.181 [0.367–12.952]	0.391
Origin of cardiogenic shock	1.288 [0.295–5.628]	0.736	0.821 [0.185–3.638]	0.794
Emergency Impella insertion	2.347 [0.315–17.467]	0.405	1.266 [0.212–7.552]	0.795
Lactic acid prior to device insertion	1.136 [0.940–1.371]	0.186	1.004 [0.838–1.203]	0.966
Pulse pressure variation	1.016 [0.983–1.050]	0.351	1.017 [0.983–1.051]	0.334
Left ventricular ejection fraction	0.973 [0.929–1.019]	0.244	0.973 [0.934–1.015]	0.205

Laboratory haemolysis defined as a drop in haemoglobin ≥2 g/dl and either undetectable haptoglobin or lactate dehydrogenase ≥250 units/l (twofold the upper limit of normal).

heart failure, or ventricular tachycardia and had longer device run times. Outcomes for these patients are summarised in *Supplementary Material Table 2*. Patients with clinically significant haemolysis had greater number of blood transfusions (4.0 units versus 0.0 units).

Discussion

In this single-centre retrospective study of patients receiving pVADs, we examined the impact of patient-specific factors associated with both laboratory as well as clinically significant haemolysis. The key findings of our study are, first, that rates of clinically significant haemolysis while on pVAD support were very low, although 1 in 4 patients met laboratory criteria for haemolysis; second, all of the patients with clinically significant haemolysis received either Impella 2.5 or CP device; third, laboratory-defined haemolysis was more common in patients with higher severity of presenting illness (including higher baseline lactate level, and lower LVEF and pulse pressure) requiring emergency circulatory support; and last, that haemolysis was not independently associated with higher on-device or 30-day mortality.

Haemolysis is a known complication of pVADs caused by non-laminar flow across the pump, resultant shear stress, and direct contact with mechanical device.[18] Smaller pump size results in greater turbulent flow and shear stress. Higher performance levels also lead to increased likelihood of haemolysis in addition to improper device position, pump thrombosis, and longer pump run.[19] In our cohort, Impella 2.5/CP pump and longer pump run times were indeed both associated with greater rates of laboratory haemolysis. The incidence of haemolysis with pVADs is reported to be between 10% and 62.5%.[20,21] Rates of laboratory haemolysis in our cohort were in that range at 23.5%.

In addition to the aforementioned factors, significant variability in reported incidence of haemolysis may be driven by a lack of consistent definition of haemolysis. Traditionally, serum LDH level is used to diagnose haemolysis. The INTERMACS Registry defines major haemolysis as LDH 2.5-fold the upper limit of normal range or plasma free haemoglobin >20 mg/dl obtained 72 hours after device implantation with clinical signs of haemolysis such as jaundice, haemoglobinuria or hyperbilirubinemia.[22] A major limitation of LDH as an independent marker of haemolysis is that this metabolic enzyme is found in almost all tissues in the body and can be elevated during MI, skeletal muscle damage and multi-organ failure: all common findings in patients with cardiogenic shock.[23–25] In their single-centre retrospective analysis of 116 patients in cardiogenic shock, Esposito et al. found that serum LDH is significantly elevated even prior to device implantation.[19] Higher acuity of cardiogenic shock at the time of device implantation was also associated with increased risk of laboratory haemolysis in our patients. In our study, patients with acute MI as the aetiology of their cardiogenic shock were indeed more likely to meet criteria for laboratory haemolysis. Although plasma free haemoglobin has been shown to be a more reliable marker of haemolysis in patients with pVAD, it was not included in our definition of haemolysis because this was not routinely checked at our institution during the study period. Instead, low haptoglobin was used as an additional marker of haemolysis given its propensity to bind free haemoglobin.[19,26]

Our study found that emergency pVAD insertion was an independent risk factor for laboratory-defined haemolysis. It is plausible that this may be driven by a higher likelihood of improper positioning with emergency placement, which has been shown to be associated with increased incidence of haemolysis.[27] Alternatively, emergency placement is more likely to be performed in a sicker patient cohort requiring higher performance levels.[18,19,28] pVAD support as a bridge to recovery was also associated with higher rates of haemolysis in our cohort and is likely to have been due to longer exposure to the device.[29]

Renal injury is a common consequence of intravascular haemolysis. By-products of red blood cell breakdown, such as haem, are directly cytotoxic

to the proximal tubule and lead to renal vasoconstriction, which can precipitate an acute kidney injury.[30] High rates of renal failure have been confirmed in patients supported with pVAD.[21] This finding is often confounded by the propensity for patients in cardiogenic shock to develop acute renal failure regardless of mechanical support. In our cohort, renal failure was more common in patients with laboratory-defined haemolysis (37% versus 16%, p=0.011), but the same patients had more severe cardiogenic shock, as indicated by the higher serum lactate levels and lower pulse pressure and LVEF. It is important to note that although laboratory haemolysis may contribute to this comorbidity for patients on pVAD support, it was not associated with on-device or 30-day mortality. It is likely that the risk of such comorbidities is offset by the mortality benefit from restoration of adequate circulatory support, as was seen in the recently published DanGer Shock trial.[31]

There are a few notable limitations of our study. First, this is a retrospective analysis and is subject to all limitations inherent in such a design. Second, this is a single-centre cohort, which limits the generalisability of our findings. Lastly, we attempted to adjust for all clinically relevant confounders, but we appreciate that not all potential confounders may have been captured in our database. For example, at our institution it is standard practice for all patients with a pVAD to be on a heparin drip titrated to an unfractionated level of 0.2–0.4 IU/ml, but we are unable to quantify time in the therapeutic range.

Conclusion

Laboratory-defined haemolysis was common in patients with pVADs, but clinically significant haemolysis was relatively uncommon. There are many potential confounders when using a laboratory-defined diagnosis of haemolysis in the setting of pVAD. Haemolysis on pVAD was not associated with on-device or 30-day mortality in our cohort. ❑

Clinical Perspective

- Plasma free haemoglobin may be a more reliable marker of haemolysis in Impella patients, given that lactate dehydrogenase may be elevated from non-red blood cell turnover in clinically ill patients.
- The incidence of laboratory haemolysis increases as the severity of acute illness increases in critically ill patients.

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