

 Veli Burak Tackin¹,  İlhan Golbasi²,  Unal Atas³,
 İsmail Kakillioglu¹,  Ersin Ozer⁴,  Rauf Onder⁵,
 Sebahat Ozdem⁶,  İkbâl Ozen Kucukcetin⁶,
 Omer Bayezid²

¹Antalya City Hospital, Department of Cardiovascular Surgery, Antalya, Türkiye

²Akdeniz University Hospital, Department of Cardiovascular Surgery, Antalya, Türkiye

³Aksaray Training and Research Hospital, Department of Hematology, Aksaray, Türkiye

⁴Ordu State Hospital, Department of Cardiovascular Surgery, Ordu, Türkiye

⁵Hakkari Yüksekova State Hospital, Department of Cardiovascular Surgery, Hakkari, Türkiye

⁶Akdeniz University Hospital, Department of Biochemistry, Antalya, Türkiye

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Corresponding Author: Veli Burak Tackin
Antalya City Hospital, Department of Cardiovascular Surgery, Antalya, Türkiye
Email: brk.veli@gmail.com

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INTRODUCTION

Heart failure (HF), the prevalence of which is increasing, is an important health problem affecting approximately 26 million patients worldwide (1). While the incidence of HF is 1-3% in the general population, it increases to 10% after the age of 70 and it reaches 15-20 % after the age of 80 (2). According to Framingham Heart Study data; the 30-day mortality rate is

Is hemolysis a predictor of complications in patients implanted with a left ventricular assist device?

Abstract

Aim: Life-threatening complications such as intra-device thrombus, infection, bleeding, kidney and liver failure are frequently encountered due to the use of left ventricular assist devices (LVADs). We aimed to determine the incidence of hemolysis in patients implanted with LVAD, the mechanical complications detected in patients with hemolysis, and whether hemolysis can be used as a predictor of complications.

Material and Methods: In this single-center, retrospective clinical research study, we evaluated 40 patients with HeartWare (HeartWare International, Inc., MA, USA) LVAD implants to assess the incidence of hemolysis and its association with mechanical complications. Hemolysis parameters, including lactate dehydrogenase (LDH), bilirubin, serum-free hemoglobin (sfHb), corrected reticulocyte count (CRC), and haptoglobin, were measured in venous blood samples obtained from patients attending cardiovascular outpatient clinics. Patients were divided into two groups (group 1: without hemolysis, n=32; group 2: with hemolysis, n=8) based on the presence or absence of hemolysis, and demographic data, comorbidities, and laboratory results were compared. The time elapsed after implantation of the patients was min: 90 days, max: 3147 days.

Results: Hemolysis was detected in 20% (8 out of 40) of the patients included in the study. Patients with hemolysis demonstrated higher CRC, LDH, and total bilirubin levels (p<0.005), and lower haptoglobin levels compared to those without hemolysis (p<0.001). Intra-device thrombus was detected as a mechanical complication in 2 patients with hemolysis. One patient died and the other was discharged after medical treatment.

Conclusion: Our findings suggest that routine monitoring of hemolysis parameters in LVAD recipients may aid in the early detection of mechanical complications, such as pump thrombosis, before symptomatic manifestation, thus potentially reducing mortality. Assessing multiple parameters, including LDH, bilirubin, sfHb, CRC, and haptoglobin, is crucial for accurate hemolysis diagnosis and its association with mechanical complications. It should be supported by large series of studies with longer and similar follow-up periods and a larger number of patients.

Keywords: Hemolysis, heart-assist devices, hemoglobins, l-lactate dehydrogenase

approximately 10.1%, the annual mortality rate is 20%-30%, and the 5-year mortality rate is around 45%-60% (3). Despite all the pharmacological agents and support devices used, the gold standard treatment in end-stage HF (ESHF) is heart transplantation (4). However, due to the scarcity of donors and the resulting long waiting period, this treatment is not sufficiently accessible (5).

Left ventricular assist devices (LVAD) have begun to be widely used in recent years for the bridge to transplantation and destination therapy in patients with ESHF who do not respond to medical treatment. Developments in mechanical technology and surgical techniques in the last 2 decades have greatly increased the success rate and duration of use of LVADs. With similar survival rates achieved in patients using these devices and heart transplant recipients, it has become a standard treatment for ESHF (6). With LVADs implanted in more than 25,000 patients, overall survival is 83% at 12 months and 46% at 5 years, increasing survival compared to any conventional medical treatment (7). Despite advances in today's pump technology, postoperative device-related complications of LVADs still occur. Hemolysis is one of the hematological complications that potentially increases morbidity and is life-threatening (8). Parameters such as lactate dehydrogenase (LDH), bilirubin, serum-free hemoglobin (sfHb), corrected reticulocyte count (CRC) and haptoglobin, which are indicators of hemolysis caused by artificial surfaces and blood flow patterns, can be affected by many secondary causes. Therefore, it can be very difficult to clearly demonstrate and grade device-related hemolysis (9,10).

There is limited data on the incidence, definition, and prognosis of hemolysis in patients with HeartWare (HW) LVAD implanted patients. Life-threatening mechanical complications such as pump thrombosis, kinking formation in the outflow graft, and graft thrombosis may occur in LVAD implanted patients in the early and late periods. Detection of these mechanical complications before clinical findings appear in the patient and early treatment will greatly reduce morbidity and mortality. Considering that these complications may occur in patients with hemolysis, examination and treatment can be performed for these complications. We aimed to detect this early diagnosis method using hemolysis parameters. Hemolysis detected using easily accessible blood parameters under outpatient clinic conditions may be a leading finding in the diagnosis of these complications.

MATERIAL AND METHODS

Characteristics of the Study Groups

The study was evaluated by the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee and approved with the decision dated 07/08/2020 and numbered 70904504/516. Before the study, patients and their relatives were informed and a written consent form was signed. It is a single-center, retrospective clinical research study. We included 40 patients who were implanted with HW (HeartWare International, Inc., MA, USA) LVAD at Akdeniz University Hospital between January 2012 and August 2021 and whose follow-up continues. Patients who underwent implantation of a different assistive device other than HW, who were younger than 16 years of age, who were followed up in another center, and who had malignancy, nutritional anemia, autoimmune hemolytic anemia, and chronic disease anemia were not included in the study. Complete blood count,

reticulocyte count, biochemical parameters (sfHb, haptoglobin, serum LDH, total bilirubin, direct bilirubin, total protein, albumin, liver enzymes, direct and indirect coombs, creatinine, electrolytes), coagulation parameters (prothrombin time (PT), activated partial thromboplastin time (APTT)) and nutritional parameters (folate, ferritin, vitamin B12) were obtained from venous blood samples taken from 40 patients who applied to the cardiovascular outpatient clinic for control purposes between July 2020 and January 2021. Blood samples were taken from the patients included in the study for hemolysis on the 90th day at the earliest and on the 3147th day (median: 502 days) at the latest after the implant. Hemoglobin and erythrocyte count were evaluated from a complete urine analysis. The peripheral smear of each patient was evaluated by a single hematologist, and the morphology and fragmentation status of the erythrocytes and the number of platelets were recorded. The earliest evaluation after LVAD implantation was made 72 hours after the procedure (5 patients).

LVAD Implantation Method

Under general anesthesia, a median sternotomy was performed. After heparinization, cardiopulmonary bypass was started with aorto-bicaval cannulation. In cardiopulmonary bypass support, an inflow cannula was placed from the apical left ventricle. The outflow cannula was anastomosed with 5.0 proline under the side clamp. Following air removal, LVAD flow was started. Cardiopulmonary bypass support was reduced and LVAD pump flow was increased. Heparin was neutralized. Mediastinal and hemithorax drains were placed. The layers were closed according to anatomy. Low molecular weight heparin and warfarin sodium were started on postoperative day 1 for patients who underwent LVAD implantation. He was discharged after the INR level was regulated to 2.5 -3.5.

Evaluation of Hemolysis and Serum-Free Hemoglobin Measurement

Hemogram

Hematological analysis: 2 mL whole blood samples taken into sample tubes (Vacusera, Izmir, Türkiye) containing K2 EDTA as an anticoagulant were analyzed by fluorescence flow cytometry method using the Sysmex XN 1000 (SysmexCorp., Kobe, Japan) analyzer.

PT, APTT(s)

Whole blood samples taken into sample tubes (Vacusera, Izmir, Türkiye) containing 3.2% sodium citrate as an anticoagulant were centrifuged at 4000 rpm for 10 minutes, and PT and APTT parameters were measured on the Siemens BCS XP (Siemens Healthineers, Germany) analyzer from the plasma obtained.

For the following parameters, blood samples taken into 5 mL vacuum tubes containing gel (Vacusera, Izmir, Türkiye) were centrifuged at 4000 rpm for 10 minutes in the laboratory, and serum was obtained, then measurements were made with the

specified analyzer and methods.

Haptoglobin (g/L): Haptoglobin measurements were performed by the immunoturbidimetric method on the Spa Plus® analyzer (Binding Site, Birmingham, UK).

Serum LDH (U/L): It was measured by the enzymatic colorimetric method with commercial kits on the Siemens ADVIA 2400 (Siemens Healthcare Diagnostics, Forchheim, Germany) autoanalyzer.

Total bilirubin (mg/dL) and direct bilirubin (mg/dL): were measured by Vanadoxidation method with commercial kits on the Siemens ADVIA 2400 (Siemens Healthcare Diagnostics, Forchheim, Germany) autoanalyzer.

C-reactive protein (mg/L): Measurement was carried out with commercial kits on the Siemens ADVIA 2400 (Siemens Healthcare Diagnostics, Forchheim, Germany) autoanalyzer, according to the immunoturbidimetric test principle.

Folate (µg/L), ferritin (µg/L), vitamin B12 (ng/L): Analysis was carried out on serum samples using the chemiluminescent immunoassay method with the Siemens Centaur XP device (Siemens Healthcare Diagnostics, Forchheim, Germany).

Corrected reticulocyte count: It was calculated with the formula "Patient's Hematocrit value/45 x % Reticulocyte".

Plasma-free hemoglobin level measurement was performed spectrophotometrically according to the method of Harboe E., which is based on the measurement of the maximum absorbance of oxyhemoglobin at 415 nm (Soret band) and from the measurement at 415 nm at 380 and 450 nm, subtracting turbidity and other nonspecific absorbances. Plasma-free hemoglobin reference level was defined as <5 mg/dL (11).

In the diagnosis of hemolysis, high serum LDH (12-15), high total bilirubin (13), high CRC (16), high sfHg (11), and low haptoglobin (14) levels were used as criteria when direct bilirubin was normal. We defined hemolysis as follows:

1. Serum LDH>225 U/L
2. Total bilirubin>1.2 mg/dL
3. Reticulocyte count>1.36%
4. Haptoglobin<1.97 g/L

We considered patients who had at least 3 of the above 4 criteria positive and whose sfHg value was high (>5 mg/dL) as having hemolysis. Patients evaluated for hemolysis were divided into 2 groups: no hemolysis (group 1, n=32) and hemolysis present (group 2, n=8). Demographic data, comorbidities, and laboratory data of the 2 groups were compared.

Statistical Analysis

Categorical variables were expressed as n (%) and numerical variables as mean±standard deviation (SD) or median (min-

max) values. The assumption of normality was checked with the Shapiro-Wilk test. Fisher's Exact test was used to analyze the relationships between categorical variables. In the analysis of the difference between the measurement values of patients with and without hemolysis, the Mann-Whitney U test was used if it did not comply with normal distribution. Spearman correlation test was applied to determine the correlation between the numerical data of the patients. Multivariate logistic regression analysis was performed to determine independent risk factors associated with the development of hemolysis in patients, and the results are presented with Odds ratio (OR) and 95% confidence intervals (CI). All analyses were performed with the IBM SPSS 23.0 software package (IBM Corp., Armonk, NY). P values less than 0.05 were considered statistically significant.

RESULTS

Of the 40 patients included in the study, 37 (92.5%) were male and 3 (7.5%) were female, and the average age was 49.37±11.3 (17-71). 50% of the patients had a history of ischemic cardiomyopathy (CMP), and 50% of the patients had a history of dilated CMP. Out of the patients, 24 (60%) had coronary artery disease (CAD), 17 (42.5%) had hypertension (HT), 9 (22.5%) had diabetes mellitus (DM), and 7 (17.5%) had stage 3 or higher chronic kidney disease (CKD) not requiring hemodialysis. The median postoperative time from the patients' LVAD implantation to the present was 502 (90-3147) days.

Hemolysis was detected in 8 (20%) of 40 patients included in the study, 7 males and 1 female. Although the mean age in patients with hemolysis was higher than in patients without hemolysis, it was statistically similar (p=0.065). There was no significant difference between patients with hemolysis and those without hemolysis in terms of body weight, smoking, and the presence of comorbidities such as hypertension, DM, CAD, and CKD. However, the rate of ischemic CMP was higher in patients with hemolysis (87.5%), and the rate of dilated CMP was higher in those without hemolysis (59.4%) (p=0.044). Although the median post-operative time of patients with hemolysis (986 days) was higher than that of patients without hemolysis (439.5 days), it was statistically similar (Table 1).

When both groups were compared, CRC, serum LDH, and total bilirubin levels were higher in patients with hemolysis (p<0.001, p<0.001, p=0.048, respectively), while haptoglobin levels were lower (p<0.001). Additionally, red cell distribution width (RDW) was higher in patients with hemolysis (p=0.027), and mean platelet volume (MPV) (p=0.001) was higher. There was no significant difference between the two groups in Sfhg levels and other laboratory data (Table 2). The Sfhg value was above the specified value in all patients with hemolysis. Except for total bilirubin value, CRC, LDH, and sfHg levels used in the definition of hemolysis were found to be high in all patients in the hemolysis group. Haptoglobin level was found to be low in all patients in the hemolysis group.

Table 1. Clinical characteristics of patients

Variables	All patients (n=40)	Patients without hemolysis (n=32)	Patients with hemolysis (n=8)	p
Age (year)	49.38±11.34	47.96±11.35	55±10.05	.065
Gender				
Male	37 (92.5%)	30 (93.8%)	7 (87.5%)	.498
Female	3 (7.5%)	2 (6.2%)	1 (12.5%)	
Weight (kg)	80.68±14.7	78.84±13.92	88±16.38	.153
Smoke	19 (47.5%)	14 (43.8%)	5 (62.5%)	.442
Hypertension	17 (42.5%)	14 (43.8%)	3 (37.5%)	.999
DM	9 (22.5%)	6 (18.8%)	3 (37.5%)	.348
CAD	24 (60%)	17 (53.1%)	7 (87.5%)	.114
CKD	7 (17.5%)	4 (12.5%)	3 (37.5%)	.128
Etiology				
ICM	20 (50%)	13 (40.6%)	7 (87.5%)	.044
DCM	20 (50%)	19 (59.4%)	1 (12.5%)	
Post-op time (day)	502 (90-3147)	883.96±852.48	1016.12±951.12	.829

Findings are presented as median (min-max) or n (%). Mann-Whitney U test, Fisher's Exact test. DM: diabetes mellitus, CAD: coronary artery disease, CKD: chronic kidney disease, ICM: ischemic cardiomyopathy, DCM: dilated cardiomyopathy

Table 2. Laboratory results of all patients with and without hemolysis

Variables	All patients (n=40)	Patients without hemolysis (n=32)	Patients with hemolysis (n=8)	p
Hemoglobin (g/dL)	12.59±2.26	12.5±2.12	12.93±2.86	.728
Serum free hemoglobin (mg/dL)	25.39±25.08	22.52±17.18	36.84±44.63	.278
Htc (%)	37.83±6.95	37.46±6.54	39.27±8.75	.584
Erythrocyte count (10 ⁶ /mm ³)	4.73±1.01	4.77±1.02	4.58±1.00	.778
Platelet count (10 ³ /mm ³)	264.8±101.19	278.37±98.86	210.5±97.75	.055
MCV (fL)	82.05±5.41	81.46±5.80	84.37±2.44	.209
RDW (%)	14.85±1.96	14.56±1.97	16±1.51	.027
MPV (fL)	10.19±0.89	9.95±0.71	11±0.95	.001
Corrected reticulocyte count (%)	1.51±0.54	1.34±0.38	2.16±0.58	<.001
PT (sec)	31.6±9.75	32.31±9.00	28.75±12.58	.342
APTT (sec)	42.8±7.53	43.12±7.94	41.5±5.85	.829
INR	2.41±0.78	2.46±0.73	2.20±0.97	.415
Haptoglobin (g/L)	1.18±0.74	1.39±0.63	0.31±0.47	<.001
Folate (ng/ml)	8.35±4.12	8.21±4.06	9.93±3.31	.126
Ferritin (ng/mL)	177.9±239.7	177.72±259.49	178.6±148.00	.434
Vitamin-B12 (pg/mL)	411.05±216.12	399.93±218.11	455.5±216.15	.415
LDH (U/L)	376.1±450.66	279.21±63.71	787.62±933.59	<.001
Total bilirubin (mg/dL)	0.85±0.58	0.74±0.40	1.27±0.93	.048
Direct bilirubin (mg/dL)	0.29±0.23	0.25±0.18	0.41±0.34	.278
CRP (mg/L)	36.03±42.9	34.77±40.45	44.37±55.14	.986

Findings are presented with median (min-max). Mann-Whitney U test. Htc: hematocrit, MCV: mean corpuscular volume, RDW: red cell distribution, MPV: mean platelet volume, PT: prothrombin time, APTT: activated partial thromboplastin time, INR: international normalized ratio, LDH: lactate dehydrogenase, CRP: C-reactive protein

Multivariate logistic regression analysis was performed for risk factors associated with the development of hemolysis in patients. As a result of the analysis, age, RDW, and MPV were not found to be independently associated with the development of hemolysis in all models created ($p>0.05$). It was determined that increasing corrected reticulocyte count in patients also increased the risk of hemolysis (Odds ratio [OR]: 1.58; 95% Confidence interval [CI]: 1.011-2.469; $p=0.044$). It was observed that decreasing haptoglobin value positively affected the development of hemolysis (OR: 0.028; 95% CI: 0.001-0.678; $p=0.028$). It was determined that the risk of hemolysis development increased as the LDH value increased (OR: 1.045; 95% CI: 1.006-1.086; $p=0.023$).

2 of the 8 patients with hemolysis had elevated watts and liters and were followed up in intensive care with the diagnosis of pump thrombosis. One of the 2 patients died on the 2nd day due to low cardiac output and sepsis despite intravenous thrombolytic therapy, heparin infusion, and intra-aortic balloon pump support. In the other patient, LVAD parameters returned to normal on the 2nd day after intravenous thrombolytic therapy and heparin infusion. He was discharged with full recovery seven days later.

DISCUSSION

In this study, in which we evaluated 40 patients with HW LVAD implants, we detected hemolysis in 8 patients as a result of our evaluation of all LDH, bilirubin, sHgb, CRC, and haptoglobin parameters, which are indicators of hemolysis. 6 of 8 patients were asymptomatic and were diagnosed during routine cardiovascular outpatient clinic examination. LVAD mechanical complications were detected in 2 patients with hemolysis.

Data obtained early after LVAD implantation indicate that hemolysis occurs due to the surgical procedure and multiple transfusions. However, hemolysis is common immediately after implantation due to shear stress caused by LVAD support (10). Incorrect positioning and displacement of the cannula, device, pannus, and thrombus in the outflow graft, and thrombus formation inside the pump are among the complications that frequently cause hemolysis. Hemolysis should be suspected in cases of newly developing anemia, symptoms of heart failure, sudden change in urine color, sudden increases in wattage, changes in flow, and pulsatility index. Early diagnosis of pump thrombus has the potential to improve patient outcomes through closer monitoring, aggressive anticoagulation, or earlier pump replacement (14).

Due to its miniaturized housing and pericardial placement, it can be effectively used to support the left ventricle (17). Furthermore, complications such as life-threatening perioperative bleeding, gastrointestinal bleeding, driveline site infections, intracavitary thrombus formation, hemolysis, postoperative renal and hepatic failure, right ventricular failure, aortic valve insufficiency, and hemorrhagic or ischemic cerebrovascular events are commonly observed with the use of LVAD devices (18,19). Hemolysis is an

expected condition to be seen during and after cardiopulmonary bypass and in all extracorporeal circuits. Hemolysis, a common complication among patients treated with short-term LVADs, has been reported in approximately 1 in 10 patients. Data on hemolysis are limited, and although the incidence of hemolysis after LVAD implantation is known to be low in the first 60 days, its incidence in long-term use is not clearly known (16).

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) defines sHgb >40 mg/dl 72 hours after implantation as hemolysis (20). Additionally, in other studies conducted on patients implanted with LVAD, LDH (12-15), sHgb (12,13), bilirubin (13), and haptoglobin (14) parameters were used as hemolysis criteria. In the HeartMateII (HMII) bridge to transplant study, hemolysis was defined as two measurements of plasma-free hemoglobin >40 mg/dl within 24 hours and one measurement of LDH $>1,000$ U/L within the same 24-hour period (12). In one study, hemolysis was detected in 32 patients (18%) according to INTERMACS criteria and in 68 patients (37%) according to the LDH criteria (more than 2.5 times the upper limit of laboratory normal) (13). In studies conducted on LVAD patients, hemolysis rates were found to be 5% (16), 3% (12), 18%-37% (13), 18% (14), 13% (15). Again, different studies involving 100 and 367 HMII patients were examined in two studies, hemolysis was reported in 18 (18%) and 49 (13%) patients, respectively (14,15). In our study, we detected hemolysis in 8 of 40 patients (20%), a rate similar to the literature. Different parameters were used in the evaluation of hemolysis in the studies and different results were obtained. The most important reason for this situation is that many parameters that may be indicators of hemolysis, especially LDH, can be affected by different reasons. Therefore, in our study, we evaluated all the 5 most important parameters associated with hemolysis in patients using the HW LVAD device, which has not been discussed much before, unlike the literature. We aimed to exclude laboratory changes due to secondary causes and to minimize false positivity in terms of hemolysis.

In previous studies, in terms of demographic characteristics, post-LVAD hemolysis has been reported to be higher in younger patients (14,16,21), patients with higher body mass index (16,21), female gender (16), and Caucasian race (21). While age and body mass index were similar in both groups in our study, there were not enough female patients for comparison. In previous studies, no relationship was found between hemolysis and comorbidities such as DM, CAD, peripheral artery disease, and cerebrovascular disease, other than chronic obstructive pulmonary disease (13,16). We did not detect a relationship between hemolysis and comorbidities such as HT, DM, and CKD, which we evaluated. Having an ischemic CMP etiology made a significant difference. 7 of 8 patients with hemolysis have ischemic CMP. However, this difference detected in a small number of patients with hemolysis should be supported by studies with high patient volumes and the effect of CMP etiology on hemolysis can be investigated.

In two different studies conducted on patients implanted with HMII LVAD, LDH and total bilirubin levels were found to be statistically higher, and international normalized ratio (INR) levels were found to be statistically lower in the group with hemolysis (14,19). Plasma hemoglobin level was found to be statistically higher and platelet (PLT) count was found to be statistically lower in the group with hemolysis (19). In addition, low INR levels were found to be a highly predisposing factor for the formation of morbid conditions (14). However, in our study, while PT, aPTT, INR and PLT values were similar in both groups, we found that CRC, serum LDH, and total bilirubin levels, which we used as parameters, were higher and haptoglobin levels were lower in the group with hemolysis. LDH levels were high as expected in all patients with hemolysis. On the other hand, LDH levels were above the normal range in 21 of 32 patients without hemolysis, and no additional signs of hemolysis were detected in these patients. LDH level, which has different isoenzymes in different tissues, can increase liver damage, megaloblastic anemia, bone fractures, muscle trauma, myocardial infarction, encephalitis, meningitis, and infections such as Human Immunodeficiency Virus (22). LDH serum level increases not only during hemolysis but also due to other secondary causes. Therefore, LDH level should be evaluated together with other parameters rather than used alone as a hemolysis parameter. Sfhg was found to be negative (<5 mg/dL) in only two of 32 patients without hemolysis. In our study, the sfhg level was expected to be significantly higher in the group with hemolysis, but there was no significant difference between the two groups. Therefore, as a result of the study, it was thought that the sfhg level alone was not a reliable parameter in the diagnosis of hemolysis and that it should be supported by other parameters or a different cutoff value should be used.

Checking for signs of hemolysis during patient follow-up is important to assess the proper function of the LVAD. The appearance of hemolysis findings may indicate a thrombus inside the LVAD or at the anastomosis, a kink formation in the LVAD access cannula, or incorrect positioning (10). For this reason, routine evaluation of these parameters, which are associated with hemolysis, at regular intervals would be an appropriate approach to prevent and diagnose such complications in the follow-up of patients. Diagnosis and early treatment of life-threatening mechanical complications such as pump thrombosis, outflow graft kink formation, and intra-graft thrombosis before patients become symptomatic can significantly reduce mortality.

The limitations of our study are that we included patients in whom a single LVAD system (HW) was implanted, that our number of patients was lower than in other studies, and that the velocity of the outflow graft was not compared by measuring echocardiography in patients with hemolysis. Another limitation was that there were no patients with similar follow-up periods and who underwent LVAD implantation in the same period. Hemolysis comparisons could be made in patients during the preoperative period, 3 months, 6 months, and 1 year follow-up.

CONCLUSION

In conclusion, intravascular hemolysis may be a predictive finding of some mechanical complications that may be encountered in patients after LVAD implantation and may cause serious morbidity and mortality. It is important to determine the necessary laboratory parameters for early and easy detection of hemolysis findings. In our study, the sfhg level, which is expected to be used as the sole criterion in the diagnosis of hemolysis, was similar in both groups. Based on the results of our study, measuring LDH, sfhg, total or indirect bilirubin, haptoglobin, and CRC in LVAD patients at regular intervals, even if the patients are asymptomatic, can predict mechanical complications that may develop in these patients. Studies with higher volume patient series, more similar follow-up periods, and patients implanted with similar indications may reveal the reliability of these parameters and their importance in early diagnosis.

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