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CLINICAL STUDY

Thromboembolic complications following implantation of durable left-ventricular assist devices

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ABSTRACT

INTRODUCTION: As the utilization of left-ventricular assist devices (LVADs) continues to rise and patients experience extended survival duration with these devices, the overall incidence of adverse events and complications has shown a notable increase. Among the major adverse events, thromboembolic complications are particularly significant. The aim of this study is to present our experience and assess the risk of thromboembolic complications after implantation of durable continuous-flow left-ventricular assist devices **(**CF-LVAD) in patients with end-stage heart failure.

PATIENTS AND METHODS: From 2007 to 2022, 169 left ventricular continuous-flow durable mechanical assist devices were implanted at our institute. Three types of devices were employed: HeartMate II (n = 54, 32%), HeartMate 3 (n = 70, 41.4%), and Heart Ware (n = 45, 26.6%). The data were extracted from the EUROMACS register.

RESULTS: Thromboembolic complication, pump thrombosis was observed in 11/169 patients (6.5%), with 2 patients experiencing stroke after embolism to the central nervous system. Among these cases, 10 patients (90.9%) were equipped with the Heart Ware device while 1 patient (9.1%) had the Heart Mate II device implanted. Nine patients received the durable device as a bridge to transplant therapy and two as a bridge to candidacy. The overall mean age of the patients was 47.6±10.2 years, with 2 women and 10 men. The pump thrombosis was managed through thrombolytic therapy, high-intensity heparin anticoagulation protocol, pump exchange, pump explantation, and early heart transplant. The combined hospital and long-term mortality rate was 4/11 patients (36.4%).

CONCLUSION: Based on our experience, thromboembolic complications presenting primarily as pump thromboses, were a relatively common phenomenon experienced in association with the second-generation continuous-flow devices, but rarely seen with the third-generation devices. Thrombolysis followed by early heart transplantation proved to be a safe treatment option *(Tab. 1, Ref. 14)*. Text in PDF *www.elis.sk*

KEY WORDS: durable mechanical assist device, durable left ventricular assist devices, outcomes, thromboembolic complications.

Introduction

The utilization of left-ventricular assist devices (LVAD) as bridges either to heart transplant (BTT), or candidacy (BTC), and as destination therapy (DT), has become an important option for treating patients with advanced heart failure refractory to medical therapy. Among LVAD devices currently available on the market, the HeartMate 3 (HM 3, Abbott Laboratories) distinguished by its fully magnetically levitated rotor is considered the most advanced. In the past, the technology of these devices used to be based on the axial-flow pump, as in HeartMate II (HM II, Abbott Laboratories) and centrifugal hybrid levitation, as seen in HeartWare ventricular assist device (HVAD, Medtronic Inc) (1).

The last several years have seen a shift in device indication and type, with 81.1% of patients now receiving implants as destination therapy and 92.7% receiving an LVAD with fully magnetic levitation in 2021 (1). The transition from pulsatile to continuous-flow devices, as seen in (CF)-LVADs, has been associated with a significant decline in overall adverse events, as well as with improved durability and significantly better long-term survival for both the BTT and DT indications.

However, as a result of prevalent utilization of left-ventricular assist devices (LVADs) and extended survival duration of patients with these devices, there has been a notable increase in the incidence of adverse events and complications The major adverse events are thromboembolic complications presenting as device pump thrombus occurring early (within 90 days after implant; 1.9%) or in a later period (5.1%), stroke occurring early (within

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90 days after implant, 6.2%) or in a later period (8.0%) and arterial non-central nervous system thromboembolism occurring early (within 90 days after implant, 0.6%) or in a later period (0.4%) (1).

The aim of this study is to present our experience and assess the risk of thromboembolic complications after implantation of CF-durable LVAD devices in patients with end-stage heart failure.

Patients and methods

From 2007 until the end of 2022, 169 CF-durable mechanical assist devices were implanted at our institute, and thromboembolic complications occurred in 11 patients (6.5%) The devices were utilized as follows: HM II (54/169;32%), HM 3 (70/169;41.4%), and HVAD (45/169; 26.6%). The strategy of LVAD implantation included: BTT (79, 46.7%), BTC (60; 35.5%), DT (14; 8.28%) and rescue therapy (16; 9.5%). Thromboembolic events presented as pump thrombosis, stroke or arterial non-central nervous system thromboembolism. The data were extracted from the EUROMACS register (European Register of patients with Mechanical Circulatory Support), where our data have been collected since 2019. All patients provided an informed consent to be included in the register, which is regularly updated and checked for data correctness. We identified two periods that varied in terms of the type of mechanical support devices primarily used and the clinical practice followed in our department. During the first period, from 2007 to 2015, the HM II device (Abbot Laboratories) and the HVAD (Medtronic, Inc) were employed, whereas, during the second time period, from 2016 to 2022, the main device used was the HM 3 (Abbot Laboratories) LVAD along with the HVAD device, until it was withdrawn from the market in 2021.

The employed antiplatelet and anticoagulation strategies were based on recommended guidelines and common clinical practice, including post-operative bridging with heparin (targeting an active partial thromboplastin time of 45–65 s), a goal INR of 2.0–3.0, and early initiation of aspirin and warfarin treatment (2).

Categorical values were reported as numbers, mean value±SD, and percentages. The patients provided an informed consent for the presentation of this study.

Results

Thromboembolic complications were observed in 11 out of 169 patients (6.5%). The HVAD was implanted in 10 patients (90.9%) and the HM II LVAD was provided to 1 patient (9.1%). Nine patients received the durable LVAD as part of the BTT therapy strategy, while two received it as part of the BTC strategy.

The overall mean age of the patients was 47.6±10.2 years, with 2 women and 10 men. The mean age in the BTT group was 46.6±9.8 years while in the BTC group, it was 45.5±23.3 years.

The heart failure was caused by dilated cardiomyopathy in 5 patients, ischemic cardiomyopathy in 5 patients, and familial cardiomyopathy in 1 patient.

The overall mean duration of the durable LVAD support was 16.8±11.8 months in the BTT group and 17±14.1 months in the BTC group.

All patients received aspirin and warfarin treatment with a target international normalized ratios (INR) of 2–3 after HVAD implantation and 2–2.5 after HM II implantation. The mean INR value of the group of 10 patients with thromboembolic complications after HVAD at the time of the event was 2.52±0.85, while the INR of the patient after HM II implantation was 2.24.

During the study period, the thromboembolic complications presenting as pump thrombosis occurred in 11 patients, while two patients experienced a stroke after embolism to the CNS. Only three events of pump thrombosis occurred early, within 90 days after implantation. The pump thrombosis was successfully resolved in six patients after thrombolytic therapy. One patient was successfully treated with a high-intensity heparin anticoagulation protocol, another patient underwent pump explantation and implantation of short-term left- and right-ventricular assist devices and the subgroup of two patients after CNS embolism were managed only with a conservative approach due to the bad prognosis stemming from CNS ischemia. Finally, one patient had the LVAD replaced, but unfortunately died due to severe postoperative bleeding. The median time from pump thrombosis to heart transplant was 4.5 (2–30) months. Five patients, after the pump thrombus resolution, underwent successful heart transplant and are still alive. One patient died 8 months after the heart transplant procedure (complicated postoperative course), 3 patients died while on LVAD support waiting for heart transplant (LVAD complications) and 1 patient died during the BTC period due to oncologic disease.

Details of the patients are shown in Table 1.

Discussion

Despite antithrombotic treatment, thromboembolic complications are common. They include stroke, transient ischemic attack, arterial non-CNS embolism and pump thrombosis.

During the study period, thromboembolic complications occurred in 11 patients (6.5%), all presenting as pump thrombosis, while two patients experienced also a stroke after embolism to the CNS, with only three events presenting early. These results are consistent with other registries. In the INTERMACS registry (1), late pump thrombosis occurred in 5.1% of the patients, with the incidence rate of early pump thrombosis being only 1.9%. Furthermore, in the EUROMACS registry (3), the adverse event rate per person-year for early and late pump thromboses was the same. Contrary to the above registries, in our study we did not observe any other thromboembolic complications such as stroke, transient ischemic attack or arterial non-CNS embolism.

Our study revealed that there were two periods differing in the incidence of pump thrombosis. Compared to the second period, the incidence of pump thrombosis in the first period was higher, specifically occurring in 6 patients after the HVAD device implantation and in one patient after the HM II device implantation. In the second period, pump thrombosis occurred in 4 patients, all of them after the HVAD device implantation. During the second period, the main device used was the HM 3 along with the HVAD device, until it was withdrawn from the market in 2021.

Tab. 1. Patients characteristics.

Patient	Gender	Age	Device	Duration of operation (year)	Duration of complication (months)	Complication	INR	Treatment
1	Male	51	HVAD	2013	36	Pump thrombosis	2.3	Thrombolysis, good effect
2	Female	46	HVAD	2014	10	Pump thrombosis	2.43	Thrombolysis, good effect
3	Male	46	HVAD	2014	3	Pump thrombosis	2.88	Thrombolysis, good effect
4	Male	53	HVAD	2014	6	Pump thrombosis	3.91	Short-term RVAD, LVAD implantation
5	Male	56	HVAD	2015	6	Pump thrombosis, CNS embolism	1.57	Conservative management
6	Male	40	HVAD	2016	2	Pump thrombosis	1.98	Thrombolysis, good effect
7	Male	62	HVAD	2016	20	Pump thrombosis	1.55	High-intensity heparin protocol
8	Male	56	HVAD	2017	9	Pump thrombosis	2.34	Thrombolysis, good effect
9	Female	33	HVAD	2019	9	Pump thrombosis	2.25	Thrombolysis, good effect
10	Male	52	HVAD	2019	7	Pump thrombosis, CNS embolism	3.97	Conservative management
11	Male	29	HM II	2013	3	Pump thrombosis	2.24	Durable LVAD reimplantation, death

HVAD = Heart Ware ventricular assist device, HM II = Heart Mate II device, INR = international normalized ratio, RVAD = right-ventricular assist device, LVAD = left-ventricular assist device

The decline in the incidence of pump thrombosis might have been affected by the learning curve of caregivers, as is also reported by other authors (4). On the other, hand both HVAD and HM II patients are susceptible to pump thrombosis. An increase in the incidence rate of pump thrombosis from 2.2% to 8.4% at 3 months post-implantation has been reported for the period from 2002 to 2013 (5). Additionally, the incidence rate for HVAD thrombosis requiring replacement was reported as 4% (with at rate of 0.04 per patient per year), and the overall incidence for suspected pump thrombus was reported as 8.1% at rate of 0.08 per patient per year) (6). Our results are also supported by the fact that the Heart Ware device was withdrawn from the market in 2021 after the comparative analysis of Heart Ware and HM 3 data from the EUROMACS register, where the HAVD device had a higher incidence of thrombosis with subsequent neurological complications (7). Compared to the HM II device, the superiority of HM 3 device regarding pump thrombosis and disabling stroke was confirmed by the MOMENTUM 3 (8) trial where the incidence rates of pump thrombosis and disabling stroke in association with HM 3 device were 1.4%, and 5%, respectively and in association with HM II device, they were 13.9%, and 7.5%, respectively.

As a response to the past research showing high incidence rate of pump thrombosis (5), the PREVENT trial (9) reported that specific practices applied during the study were beneficial to lowering the incidence rate of pump thrombosis at 3 months post-implant (2.9%),. These practices were focused on the implantation technique (maximizing the flow through the LVAD), anticoagulation regimen (post-operative heparin bridging, goal INR of 2-2.5, early initiation of warfarin and aspirin therapy), early optimal speed management (>9,000 rpm), and blood pressure management (mean arterial blood pressure <90 mm Hg). Similarly, based on previous experience, during the second period, anticoagulation was intensified, the patients were educated and trained in self-monitoring of INR (practice introduced by us in 2016), and optimal antithrombotic and antihypertensive treatment (10).

The ideal strategy for treating pump thrombosis has not been definitely established. Medical therapy treatment often involves the administration of unfractionated heparin, direct thrombin inhibitors, thrombolytics (local or systemic), and glycoprotein llb/IIIa inhibitors such as eptifibatide used individually or in combination (11). Intravenous thrombolysis with alteplase may be used in patients with pump thrombosis who are poor candidates for redo procedures. However, these therapies are not without risk and are primarily associated with severe side effects, particularly bleeding (11). Moreover, identifying patients with the potential to respond positively to medical therapy remains uncertain, and the common practice in most centers is to weigh the risks associated with pump exchange against those linked to thrombolytic therapy on an individualized basis. In cases when the patient is hemodynamically unstable, the recommended treatment of pump thrombosis is LVAD replacement or urgent heart transplant after stabilizing the patient hemodynamically (12). Six patients from our study were successfully treated with thrombolysis, and one patient underwent the high-intensity heparin anticoagulation protocol. A study showed that when pump thrombosis was managed through heart transplantation or pump replacement, the mortality rate was similar to that of individuals without pump thrombosis. However, in patients who were treated with medication, the mortality rate was twice as high within six months after the diagnosis of pump thrombosis (13). In our study, one patient died after pump replacement and another patient died after LVAD explantation and implantation of short-term left- and right-ventricular assist devices. Moreover, 5 patients underwent early successful heart transplantation, while conversely, 3 patients who did not undergo heart transplantation died while on LVAD support.

The maintenance of INR within the therapeutic range is recommended for patients on warfarin and CFs-LVADs, and when the time in therapeutic range (TTR) correlates with the clinical outcome (2). However, high TTR is difficult to achieve despite intense monitoring by LVAD teams. A meta-analysis of five studies showed TTR of only 46.6% in CF-LVADs. This low TTR may contribute to thromboembolic complications (14). In our opinion, the development of pump thrombosis is likely attributed to the low TTR even though the mean INR values for HVAD and HM II

patients were within therapeutic ranges at the time of the diagnosis. To mitigate these complications, and drawing from our past experience, the patients were educated and trained in self-monitoring of INR, a practice we introduced in 2016.

In conclusion, based on our experience, thromboembolic complications linked to implantation of durable LVAD devices were relatively common, particularly those associated with the second-generation CF- devices, where pump thrombosis emerged as the primary complication. Thrombolysis followed by early heart transplantation proved to be a safe treatment option. Importantly, during the study period, we did not observe any thromboembolic complications with third-generation LVAD devices (HM 3).

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