Early Aspirin Nonresponders Identification by Routine Use of Aggregometry Test in Patients With Left Ventricle Assist Devices Reduces the Risk of Pump Thrombosis

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ABSTRACT

Left ventricular assist device (LVAD) management is very challenging since many adverse events can occur in ongoing patients. Inadequate anticoagulation treatment can lead to life-threatening situations like ischemic stroke or pump thrombosis. The main intention of our study was to investigate if early identification of aspirin nonresponders by using aggregometry can improve anticoagulation management, reducing the risk of pump thrombosis.

Methods. From December 2010 to May 2018, 24 patients were implanted with a HeartMate II (HMII), 6 received a HeartWare HVAD system–full support VAD (HVAD), and 22 received a HeartMate III (HMIII). All patients were maintained with a target INR of 2.0 to 3.0. When the aggregometry test revealed a normal platelet function, 100 mg of aspirin were initiated. Only aspirin nonresponders were early identified by repeating the aggregometry after 7 days of aspirin administration. In acetylsalicylic acid nonresponder patients, 75 mg of clopidogrel was used, and the patients were tested again. Ticlopidine (250 mg) was used when clopidogrel was unsuccessful.

Results. Four patients required modification in antiplatelet therapy. Three patients (5%), 2 HVAD and 1 HMII, suffered from pump thrombosis. One patient died as a consequence of a large intracranial hemorrhagic event following thrombolytic treatment. One patient required a pump exchange; in 1 patient, thrombolytic infusion was conducted successfully.

Conclusion. Reported rates of pump thrombosis at 12 months for patients implanted with commonly used LVADs were 6% to 12% for axial-flow pumps and 8% with centrifugal-flow devices. In our series, the reported 5% overall incidence of pump thrombosis encourages the routine use of an aggregometry test for early identification of aspirin nonresponders.

LEFT ventricular assist devices (LVADs) are now widely used for the management of end-stage heart failure. During the last few years, an essential technological evolution has led to the latest-generation device that combines small size and high hemocompatibility [1]. Despite the well-recognized effect of LVADs on quality of life of the patients implanted, the mechanical devices are not entirely free from early and late adverse events. Despite technological improvements, anticoagulation remains mandatory, and inadequate anticoagulation treatment can lead to life-threatening situations like ischemic stroke or pump thrombosis [2]. Thrombotic complications are related to nonphysiological flow patterns, resulting in shear stress and platelet activation, as well as the interaction of blood with

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Table 1. Baseline Characteristics

POPULATION	52 PTS	
SEX	M 42 (80.7%)	F 10 (19.3%)
MEDIAN AGE	64.5 y ± 3.5	
TYPE OF LVAD	HMII 24 pts (46.1%)	
	HMIII 22 pts (42.3%)	
	HVAD 6 pts (11.6%)	
DIAGNOSIS	CMPD 22 (42.4%)	
	CMI 27 (51.9%)	
	Hypertrophic CMD 3 (5.7%)	

Abbreviations: CMD, dilated cardiomyopathy; CMI, ischemic cardiomyopathy; CMPD, idiopathic dilated cardiomyopathy; HMII, HeartMate II; HMIII, HeartMate 3; HVAD, HeartWare; LVAD, left ventricular assist device.

the artificial surfaces of the ventricular assist device (VAD) system [3]. Thrombus formation is a dynamic process that is regulated by components of the hemostatic system, which, under physiological conditions, form blood clots that limit blood loss from damaged vessels [4]. According to the International Society of Heart and Lung Transplantation guidelines [5], patients with VAD should receive anticoagulation with warfarin to maintain an international normalized ratio (INR) within a range as specified by each device manufacturer. Aspirin (81-325 mg daily) and other antiplatelet drugs may be used in addition to warfarin according to the recommendations of specific device manufacturers. Antiaggregation therapy is routinely prescribed, and so far few works have addressed the impact of the efficacy's monitoring of the antiaggregation therapy on the incidence of pump thrombosis. At the same time, no attention has been focused on the impact of the early identification of aspirin nonresponders on the incidence of pump thrombosis. The main intention of our study was to investigate if continuous monitoring of antiaggregation therapy efficacy by repeating an aggregometry test at different follow-up time can help to optimize anticoagulation management. Therefore, we worried if an early identification of aspirin nonresponders could have been useful in reducing the risk of pump thrombosis.

MATERIALS AND METHODS

Fifty-nine patients who underwent implantation of an LVAD (HeartMate II, Thoratec Corp., Pleasanton, CA, USA; HVAD, HeartWare Inc, Framingham, MA, USA; and HeartMate III, St. Jude Medical Inc., St. Paul, MN, USA) and who had given their consent were enrolled in this observational study between December 2010 and May 2018. In all the patients, the anticoagulation treatment started on the first postoperative day by infusing intravenous heparin without bolus with goal partial thromboplastin time (PTT) between 40 and 50 seconds. During the second postoperative day, an average PTT between 50 and 60 seconds was maintained. Warfarin was started on the third postoperative day, and a PTT between 60 and 70 seconds was ensured. Heparin infusion was maintained until the international normalized ratio (INR) reached a value between 2 and 3. Our protocol aimed

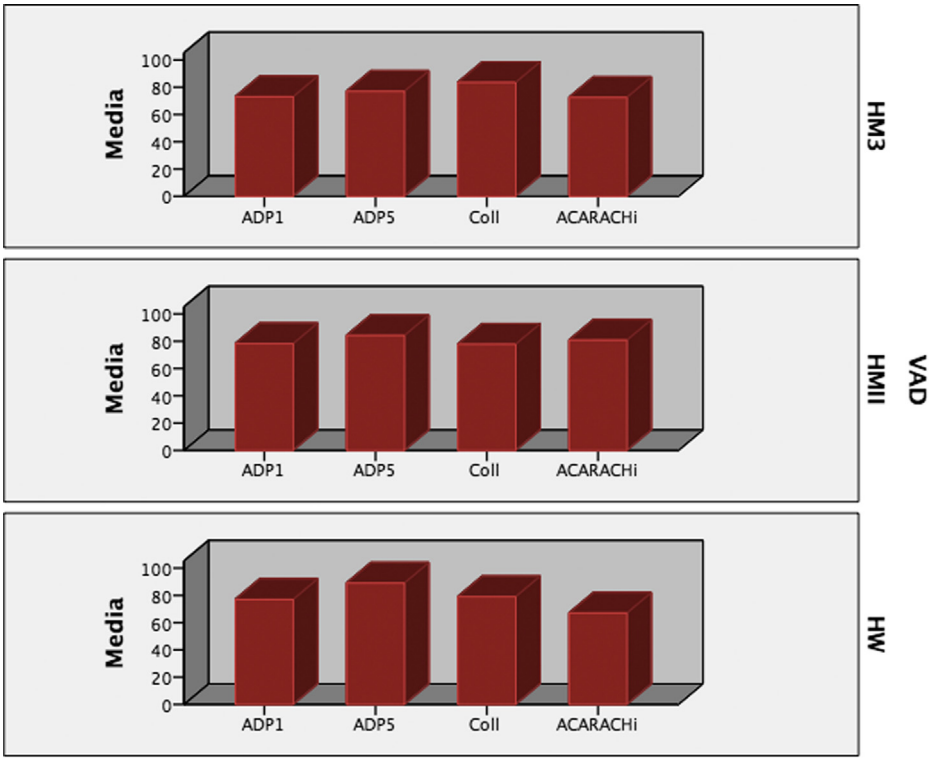

Fig 1. Platelet aggregation evaluated by AGP for each type of device in 4 different channels. Abbreviation: ACARACHi, arachidonic acid.

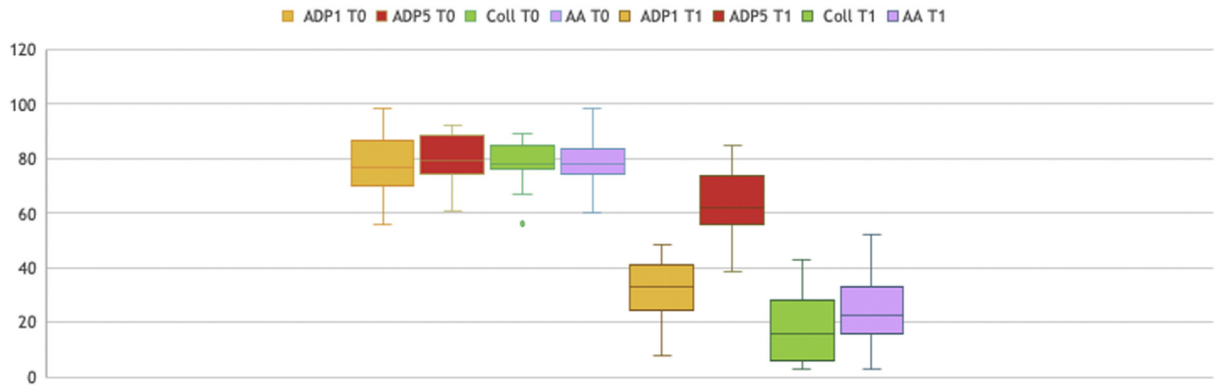

Fig 2. Comparison between AGP at T0 and T1 in responder patients.

to obtain early measurements of platelet aggregation to identify the individual response of each patient to antiplatelet therapy. Traditionally, monitoring of platelet aggregation involves exposure of platelets to a variety of stimuli in vitro, a technique known as platelet aggregometry [6]; the platelets aggregate following an addition of different agonists, and this aggregation leads to an increase in light transmission, which is measured by photometry. Agonists used to stimulate platelets commonly include adenosine diphosphate (ADP), collagen, epinephrine, thrombin, and arachidonic acid [7]. In vitro measurement of platelet aggregation (or agglutination with ristocetin) by light transmission aggregometry (LTA) is performed by employing platelet-rich plasma, and platelet-poor plasma is used as a reference to define the "theoretical" point of 100% light transmission. Following exposure to an agonist, formation of platelet aggregates results in a decrease in absorbance and a corresponding increase in light transmission through the platelet-rich plasma sample, and quantitative assessment of platelet aggregation can be obtained, most typically expressed as % aggregation. One week after the LVAD implantation, the first LTA test was performed. If a normal platelet aggregation was found, then acetylsalicylic acid (ASA) 100 mg was prescribed. The test was repeated after 1 week of treatment. A good efficacy of antiaggregation therapy was considered when a reduction in platelet aggregation of at least 50% was identified. In nonresponder patients, the suspension of ASA was recommended, and therapy with clopidogrel (75 mg) was started. The efficacy of the new pharmacologic treatment was investigated by repeating LTA 1 week later. If the new therapy was proven unsuccessful, clopidogrel was suspended, and ticlopidine (250 mg 2 times per day) was given. LTA was repeated 7 days after treatment. Once the efficacy of antiaggregation therapy was demonstrated, the test was repeated at 3 and 6 months during the follow-up period.

RESULTS

From December 2010 to May 2018, 24 patients were implanted with HM II, 6 received an HVAD, and 22 received an HM3 (Table 1). LTA evaluated platelet aggregation in 4 different channels: ADP1, ADP2, arachidonic acid (AA), and collagen (Coll) (Fig 1). We compared the patients' aggregometry at T0 (postoperative day 5) with the aggregometry performed after a week of treatment with ASA. In responder patients, there is a significant reduction in platelet aggregation (around 20%) in AA and Coll channels (Fig 2). The inhibition of platelet aggregation in these channels is maintained over time, as evidenced by repeated tests at 3 and 6 months (T3 and T6) (Fig 3). Nonresponder patients did not undergo a significant reduction in platelet aggregation, which remained around 75% in the AA and Coll channels before and after aspirin administration (Fig 4). In these patients, ASA treatment was discontinued, and treatment with clopidogrel started. Platelet aggregation, which in the ADP1 channel usually is around 75%, dropped to around 15% to20%. Platelet

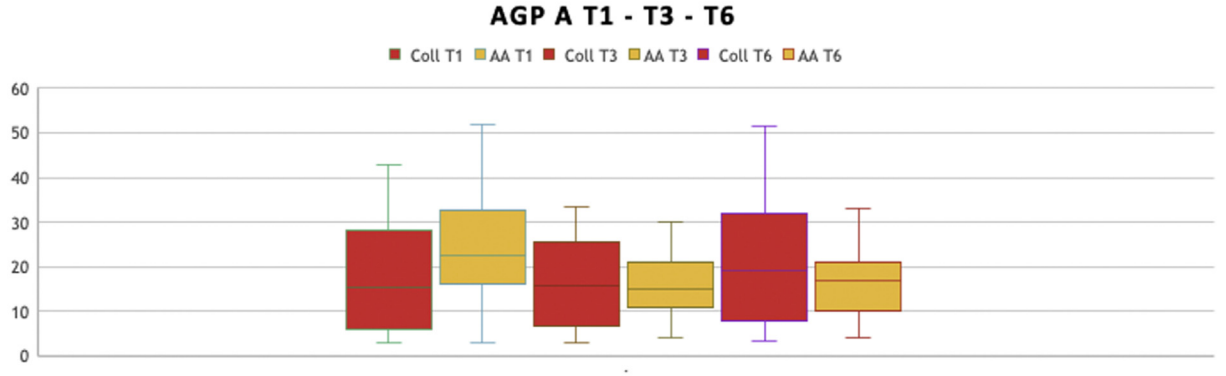

Fig 3. Platelet aggregation at T1-T3-T6 in Coll and AA channel.

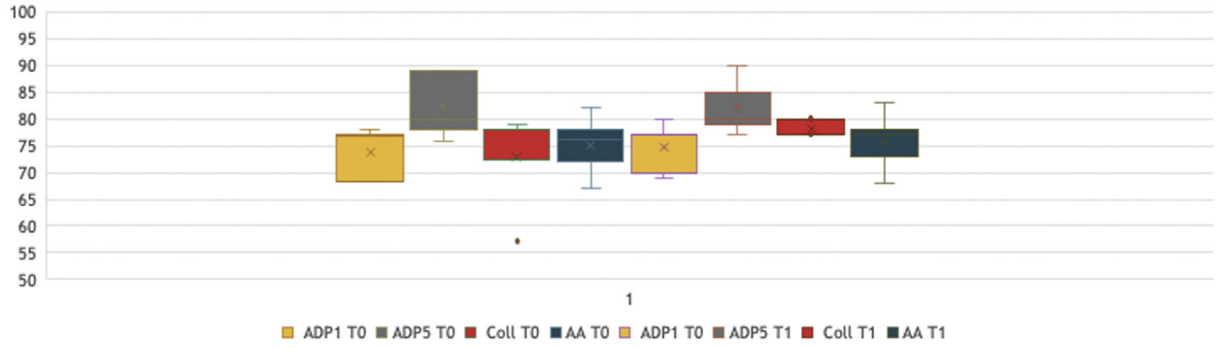

Fig 4. Comparison between AGP at T0 and T1 in nonresponder patients.

aggregation, which in the ADP5 channel is around 80%, dropped to around 40% (Fig 5). In 4 patients, an aspirin resistance was found. In 3 of them, an optimal antiaggregation treatment was obtained by administering clopidogrel instead of aspirin. Further resistance to clopidogrel emerged in the other patients who required clopidogrel to be suspended and ticlopidine (250 mg twice a day) to be started. No HM3 patient experienced a pump thrombosis event. Three patients (5%), 2 HVAD and 1 HMII, suffered from pump thrombosis. One patient died as a consequence of a large intracranial hemorrhagic event following thrombolytic treatment. One patient required pump exchange; in 1 patient, thrombolytic infusion was conducted successfully.

CONCLUSION

The use of LVAD as a treatment for terminal heart failure is well established. The common indications for the implantation of an LVAD are the bridge to transplant, bridge to candidacy, and destination therapy. Recent studies have confirmed the effectiveness and improvement that they bring to the quality of life of patients and also to the prolongation of their life expectancy [8]. Among the associated risks, LVADs are still associated with thromboembolic events, which remain at 8% to 15%, despite developments in device technology, anticoagulation, and antiplatelet strategies [9]. This kind of adverse event and their management are subject to numerous discussions. However, a shared anticoagulant and antiaggregation protocol have not yet been defined; the therapeutic indications are still suggested by the producing industries and by expert consensus. There are various factors that contribute to the formation of the thrombus, like the "foreign" surfaces of LVADs that alter rheologic conditions (by affecting the ability of platelets to hook up to adhesive proteins that are exposed on the vessel wall [platelet adhesion] or are bound on the surface of other platelets [platelet aggregation]) [10], shear stress and blood stasis within the chambers of the native heart can induce activation of coagulation. The different antithrombotic strategies adopted and the lack of a standardized definition of bleeding between studies limited the ability to compare antithrombotic regimens, so the primary intention of our study was to investigate if early identification of aspirin nonresponders by using aggregometry can improve anticoagulation management, reducing the risk of pump thrombosis. Even if aspirin is commonly recommended and used as the first-line therapy in patients with LVAD since the first clinical experiences [11], mechanisms of platelet activation in patients with VADs (shear-induced platelet aggregation) make the efficacy of aspirin questionable.

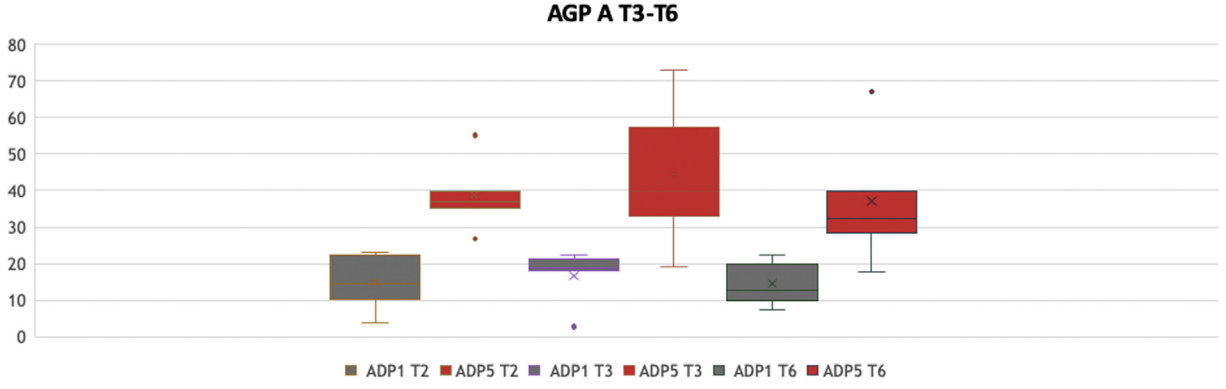

Fig 5. Platelet aggregation at T1-T3-T6 in ADP1 and ADP5 channel.

Furthermore, an experimental study conducted in a small sample of patients with external VAD implantation [12] has documented a nontrivial risk of aspirin hyporesponsiveness, defined by persistent platelet aggregation in 26% of the patients under arachidonic acid exposition. From these premises comes the desire to identify the ASA nonresponders to minimize the thromboembolic risks. Reported rates of pump thrombosis at 12 months for patients implanted with commonly used LVADs are 6% to 12% for axial-flow pumps and 8% with centrifugal-flow devices. In our series, the reported 5% overall incidence of pump thrombosis encourages the routine use of the aggregometry test for the early identification of aspirin nonresponders.

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