Cardiovascular Pharmacology: Open Access
ISSN: 2329-6607
Perna et al., Cardiovasc Pharm Open Access 2016, 5:1
DOI: 10.4172/2329-6607.1000173
Case Report Open Access

Between Scylla and Charybdis: Difficult Balance between Anticoagulation and Bleeding in the Management of LVAD Thrombosis: A Case Report

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Abstract

Case: The patient was a 67 years old male. The patient experienced an episode of LVAD thrombosis. Device replacement was not possible due to high surgical risk. Pharmacological strategy was adopted with intraventricular fibrinolysis+intravenous Tirofiban infusion.

Outcome: Despite thrombosis resolution, two episodes of bleeding occurred. Thus we lowered antithrombotic drugs dose with subsequent relapse risk. At the end, a successful therapeutic strategy was achieved.

Conclusion: Our case report shows how the balance between anticoagulation and bleeding is a tricky feature of LVAD thrombosis management. When device replacement is not an option, trying to remove the clot soon with aggressive antithrombotic therapy can be a winning strategy and can quickly stop the haemolysis. Unfortunately, it can produce major bleeding events, harmful and potentially life-threatening. To be aware of potential cause of bleeding and looking for the appropriate dosage of antithrombotic drugs can be useful to manage these complications.

Keywords: Ventricular assist device; Thrombus; Pump thrombosis; Haemolysis; Lytic therapy; GpIIb/IIIa inhibitor; Anti-coagulation; Heart ware

Abbreviations

APTT: Activated Partial Thromboplastin Time; ASA: Acetylsalicylic Acid; CT: Computed Tomography; FDP: Fibrinogen Degradation Product; Hb: Haemoglobin; HF: Heart Failure; HVAD: Heart Ware Ventricular Assistance Device; INR: International Normalised Ratio; IV: Intravenous; LDH: Lactate Dehydrogenase; LVAD: Left Ventricular Assistance Device; MA: Maximal Amplitude; OAC: Oral Anticoagulant; pfHg: Plasma-Free Haemoglobin; PLTs: Platelets; TEG: Thromboelastography

Introduction

Continuous flow Left Ventricular Assist Devices (LVAD) is used in patients with advanced heart failure. Device-related hematologic complications remain an important associated morbidity. Pump thrombosis is a major and life-threatening adverse event. Despite chronic anticoagulation with warfarin, the Heart Ware Investigators noted high incidence (0.063-0.08 events/patient-year) of thrombosis in the Heart Ware HVAD Ventricular Assist System [1]. In this setting, the optimal treatment strategy is still uncertain. Treatment approaches include optimization of anticoagulation or antiplatelet therapy, fibrinolysis and device-exchange. However, when a surgical LVAD exchange is associated with a high morbidity and mortality, medical therapy can be an alternative strategy.

We report a case of pump thrombosis treated with medical therapy.

Case Presentation

The patient was a 67-years-old man, 170 cm × 72 Kg (BMI 24.9), with a long history of ischemic cardiopathy, type II diabetes mellitus and atherosclerotic disease of carotid arteries. On March 2013 he underwent Heart Ware HVAD implantation as destination therapy, through sternotomy. Surgery and postoperative progress were uneventful and the patient was home discharge. Standard antithrombotic therapy was administered (warfarin with INR range 2-3, ASA 100 mg/die, Dipyridamole 800 mg/die). During the following months he remained in satisfactory clinical condition and HVAD parameters were within normal limits. On May 2014, haematuria occurred and he was readmitted to our hospital. No clinical signs of pulmonary or abdominal congestion or signs of cardiogenic shock were observed during first physical examination. HVAD parameters showed a progressive increase of Power (P 2.8→3.6 W) and calculated flow (F 3.9→6 L/min), with a Speed (S) of 2360 rpm. Laboratory tests showed a significant elevation of serum lactate dehydrogenase (LDH) >1547 U/L and plasma-free haemoglobin (pfHg) >1046 mg/L, a decrease in haptoglobin and anemia (Hb 12.7 g/dL): major haemolysis was occurring. The anticoagulation profile was in range (INR 2.6, APTT 44 sec). Transesophageal echocardiography was performed: no clot was found at the inflow and outflow cannula site, but there was left ventricle dilatation with frequent aortic valve opening.

A diagnosis of suspect HVAD thrombosis was made.

Our patient had a high surgical risk, so since the beginning we ruled out device replacement. A continuous infusion of intravenous heparin (target activated partial thromboplastin time of 50-60 seconds) was started, adding greater aspirin dose, 300 mg/die. Nevertheless, HVAD parameters continued to worsen (F>10) and after 24 hours patient became "cold and wet" (peripheral hypoperfusion, central venous pressure >19 mm Hg). Therefore, the decision to perform fibrinolysis

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Received January 04, 2016; **Accepted** February 10, 2016; **Published** February 15, 2016

Citation: Perna E, Cipriani MG, Marco DF, Macera F, Milazzo F, et al. (2016) Between Scylla and Charybdis: Difficult Balance between Anticoagulation and Bleeding in the Management of LVAD Thrombosis: A Case Report. Cardiovasc Pharm Open Access 5: 173. doi:10.4172/2329-6607.1000173

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was made: x-ray guided intra-ventricular thrombolysis was performed and Alteplase was administered (10 mg+10 mg+10 mg) (Figure 1). The injections were made directly into the device's inflow cannula through a 6Fr AL 2 catheter inserted through the radial artery. Every injection lasted 10 minutes and the interval between every bolus was 15-20 minutes. Blood tests were quite stable: PLTS 123 × 10^{-3}/microliter, INR 3.09, APTT 111.9 sec (six hours later 50.4 sec), D-dimer 21.78 mcg/mL. After an initial normalization, HVAD parameters showed a new slight increasing trend without worsening of clinical conditions (hemodynamically stable patient). Intravenous antithrombotic therapy with glycoprotein IIb/IIIa inhibitors (Tirofiban) was started. The infusion of Tirofiban was conducted at a rate of 0.1 mcg/Kg/min, without bolus. Within 12 hours since the beginning, we observed first results and complete resolution was evident at day 4 with stable flows and power consumption (Figures 2 and 3).

In the next 20 days patient was fine and we tried to optimize his therapy, but a severe major bleeding event occurred, and patient experienced massive bleeding from his urinary tract (bladder and prostatic tract of urethra). Endoscopic procedure and inferior bladder artery embolization were ineffective. The bleeding solved just after 25 days, multiple transfusions and frequent changes in dosage of antithrombotic therapy were performed (Aspirin 300 mg→100 mg and Intravenous Heparin APTT range <50 seconds). Five days after the resolution of haematuria, back pain with left lower limb irradiation showed up, a CT scan revealed a massive hematoma of the left psoas muscle, minimally stocked. The decision was made to stop heparin infusion and start OAC (warfarin) with INR range 2-2.5. No interventional procedures were necessary, bleeding stopped spontaneously.

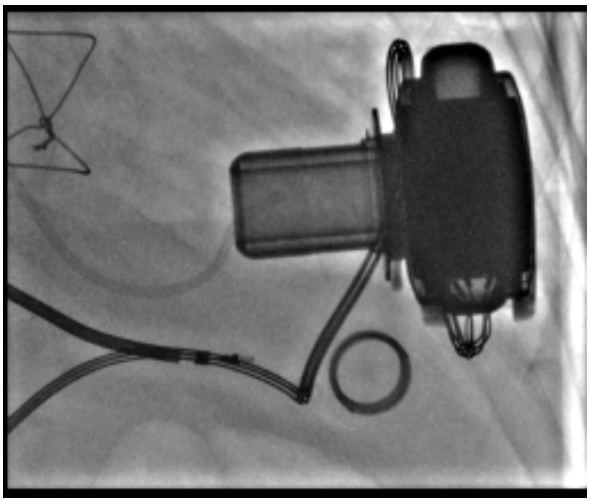

Figure 1: Intraventricular infusion of thrombolytic therapy: x-ray guided intra-ventricular thrombolysis with Alteplase. The injections were made directly into the device's inflow cannula through a 6Fr AL 2 catheter inserted through the radial artery.

After one week, HVAD parameters increased again. The patient was hemodynamically stable and a second infusion of Tirofiban 0.1 mg/Kg/min was started. After 48 hours parameters came back to normal and infusion was stopped; double antiplatelet therapy (Clopidogrel 75 mg+ASA 100 mg) was started. On July 22nd facing with haematuria relapse, clopidogrel was stopped and the following therapeutic regimen was set: ASA 100 mg+Warfarin INR 2-2.2+low-molecular-weight heparin 4000 UI/die.

Anticoagulation levels were reassessed twice a week according to thromboelastography. The last check (on the discharge day) showed stable anticoagulation status (native TPI 8,1) without platelets hyperaggregation (MA 69 in heparinase test). There were no more episodes of haematuria.

On August 8th the patient was home discharged with the following blood tests: PLTs 228 ×10^{-3}/microliter, Hb 10 g/dL, HcT 32.5%, INR 2.56, D-dimer 1.63 mcg/mL, FDP 482 mg/dL.

Discussion

In the last years the number of advanced HF patients supported with LVADs is increased. Device-related hematologic complications remain an important cause of associated morbidity. Bleeding continue to be one of the most common adverse event reported [2]. Although rates of pump thrombosis and thromboembolic complications occur less frequently than before, they are often life-threatening associated with increased risk of both stroke and mortality [3]. Therefore, it is well recognised that device thrombosis is a clinical syndrome with

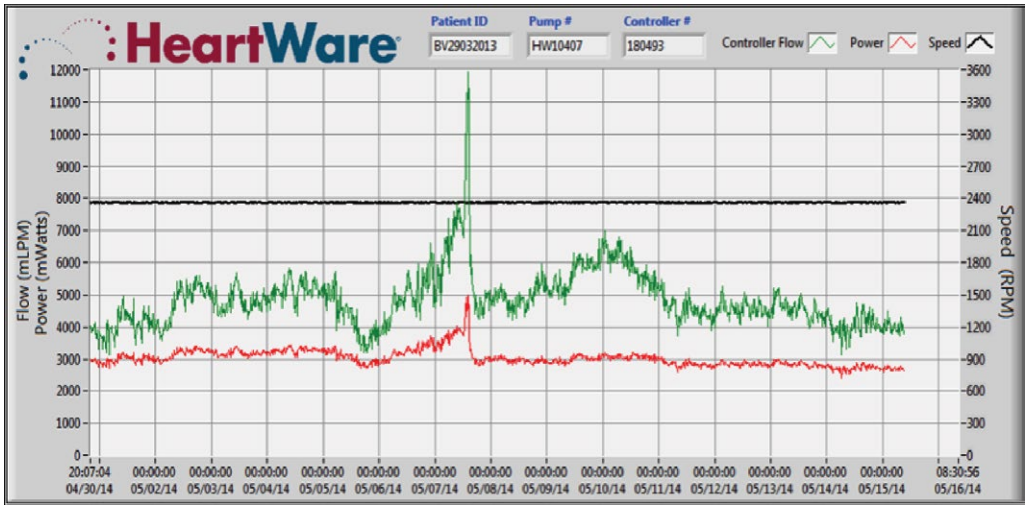

Figure 2: HVAD Parameters Log File: the high growth of the Flow value (red line) and of the Power (green line) and their reduction after fibrinolysis and anti-thrombotic therapy.

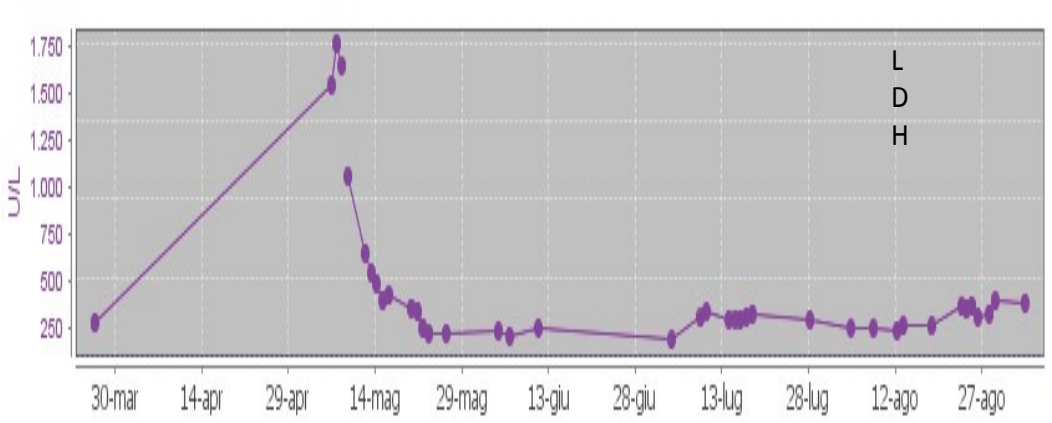

Figure 3: Lactate dehydrogenase's trend during the hospitalization with the sharp drop after fibrinolysis infusion: LDH is emerging as the most sensitive serial marker of thrombosis, with suggestions that an LDH value greater than 600 IU/L should prompt further evaluation.

several clinical, laboratory, echocardiographic and hemodynamic features. The most common clinical presentation of this adverse event is laboratory evidence of haemolysis [4-6]. The INTERMACS registry recently (2014) recategorized haemolysis in minor and major. Minor haemolysis is defined by the LDH or pfHb elevation in the absence of clinical signs/symptoms, and the management consists of anticoagulation optimization, increased aspirin doses or addition of a second antiplatelet therapy. Major haemolysis requires clinical symptoms or abnormal pump function to be diagnosed; hospital admission is recommended, as well as IV therapy with heparin and/or others additional treatment such as glycoprotein IIb/IIIa inhibitors or fibrinolytics especially if surgical intervention is contraindicated [6-7].

Our clinical case represents as a case of major haemolysis.

The decision to treat the patient just pharmacologically was driven by his clinical condition (fragility, organ damage) and his high surgical risk. The first step was antithrombotic therapy optimization with IV heparin infusion and increased aspirin dose. Careful monitoring of anticoagulation was performed with thromboelastography. Due to the rapid clinical deterioration with signs of shock, we decided to perform fibrinolysis. The benefit lasted 48 hours, and then the device parameters increased again, this time without clinical symptoms. To manage this second event, we decided to perform glycoprotein IIb/IIIa inhibitor (Tirofiban 0.1 gamma/Kg/min, no bolus) infusion. In 4 days we obtained complete resolution of pump dysfunction.

In literature optimal treatment and primary approach for patients with pump thrombosis has not established yet. Support for currently available therapeutic strategies derived from case reports and small case series (single centre experience) [4]. Multiple conflicting reports have been published about the use of fibrinolytics and GpIIb/IIIa, because of the low treatment success, the significant rate of morbidity (hemorrhagic stroke) and death. Moreover Stulak et al. recently observed a significant incidence of pump thrombosis recurrence (57%) in patients in whom a treatment success was initially obtained [8].

Our philosophy was *"to play heavily in attack and then wait in defence"*. At the beginning, our strategy was to be more aggressive as possible, to save the device, considering the surgical replacement was not feasible. We used all possible treatments to dissolve the clot and to stop the haemolysis.

Obviously the difficulty was to achieve a good balance between necessary anticoagulation and bleeding complications. In fact, while "waiting", the other side of the coin was the huge risk of bleeding linked to the therapy itself, with prolonged hospitalization, the need to change dose of antithrombotic drugs and the subsequent risk of thromboembolic recurrence. In our case after the acute thrombotic event, patient experienced a severe major bleeding from urinary tract and a massive spontaneous hematoma of the psoas muscle. First step was slight reduction in anticoagulant therapy. Then we decided to stop the bleeding with local invasive procedure.

At the end we decided to associate low dose warfarin (INR 2-2.5) with low molecular weight heparin (enoxaparin 4000 UI/die) as anticoagulation and Aspirin 100 mg as anti-platelet agent.

There were no more episodes of bleeding or thrombosis for 6 months.

Conclusion

We report a case of successful medical therapeutic strategy after acute thrombosis of Heart Ware LVAD. Clinical complexity reflects the difficult pharmacologic management of this adverse event, including the ideal agent and dose, the treatment duration and the impact of antithrombotic therapy on subsequent bleeding risk.

However, when patient cannot be a surgical-candidate, drug therapy is the only possible way out.

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