

Monitoring hemostasis parameters in left ventricular assist device recipients – a preliminary report

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Abstract

Introduction: Mechanical circulatory support (MCS) therapy is associated with the improvement of long-term prognosis in patients with end-stage heart failure. For years it has been used as a bridge to transplant. However, more recently it is even being used as a destination therapy. Recently, clinicians have identified common MCS therapy-associated complications: pump thrombosis, bleeding, and hemolysis. These complications are very challenging with regard to both diagnosis and management.

Aim: To determine time-dependant changes of selected hemostasis/coagulation parameters in patients with end-stage heart failure treated with MCS and antithrombotic therapy.

Material and methods: Sixteen patients with end-stage heart failure on left ventricular assist device (LVAD) were followed for 6 weeks (six blood samples for each patient). Every week an extended hemostasis panel was assessed, including activated partial thromboplastin time, prothrombin time, international normalized ratio, von Willebrand factor (vWF) activity, factor VIII activity, fibrinogen level, D-dimer, platelet response to arachidonic acid (ASPI test) and adenosine diphosphate (ADP test), thrombin receptor activating peptide-6 (TRAP test) and collagen (COL test).

Results: The study population comprised 16 men. The median time from LVAD implantation was 120 days (100–150 days). During the study period the D-dimer and fibrinogen concentrations were elevated but remained similar throughout all six measurements. Meanwhile factor VIII and vWF activities were elevated in the first two measurements and then subsequently declined. Inhibition of platelet aggregation was greater early after LVAD implantation. During subsequent weeks the inhibition of platelet aggregation was less pronounced. No patient developed any bleeding or thrombo-embolic event during the study period.

Streszczenie

Wstęp: Mechaniczne wspomaganie układu krążenia (MCS) poprawia rokowanie chorych ze schyłkową niewydolnością serca. Przez lata metodę tę uznawano za leczenie pomostowe do transplantacji serca. Od niedawna stosuje się ją jako leczenie docelowe. Do częstych powikłań MCS należą: incydenty zakrzepowe (w tym zakrzepica urządzenia), incydenty krwotoczne oraz hemoliza. Powikłania te stanowią złożony problem kliniczny zarówno pod względem diagnostyki, jak i leczenia.

Cel: Ocena zmian w czasie wybranych parametrów układu krzepnięcia u chorych ze schyłkową niewydolnością serca leczonych za pomocą MCS i terapii przeciwzakrzepowej.

Materiał i metody: Przez 6 tygodni obserwowano 16 pacjentów ze schyłkową niewydolnością serca (sześć pobrań krwi dla każdego pacjenta). Co tydzień oceniano rozszerzony panel badań układu krzepnięcia, w tym czas częściowej tromboplastyny po aktywacji, czas protrombinowy, międzynarodowy współczynnik znormalizowany, aktywność czynnika von Willebranda (vWF), aktywność czynnika VIII, stężenie fibrynogenu, D-dimeru, czynność płytek pod wpływem kwasu arachidonowego (ASPI test) i dwufosforanu adenozy (ADP test), aktywującego receptora trombinowego peptydu 6 (TRAP test) i kolagenu (COL test).

Wyniki: W badaniu wzięto udział 16 mężczyzn. Mediana czasu od momentu wszczęcia urządzenia wspomagającego pracę lewej komory serca (LVAD) wynosiła 120 dni (100–150 dni). Podczas badania stężenia D-dimeru oraz fibrynogenu były podwyższone we wszystkich sześciu oznaczeniach, nie stwierdzono istotnych różnic między kolejnymi oznaczeniami. Aktywność vWF i czynnika VIII były podwyższone w pierwszych dwóch oznaczeniach, w kolejnych oznaczeniach obserwowano ich zmniejszenie. Zahamowanie agregacji płytek krwi było większe zaraz po implantacji LVAD. W następnych tygodniach stwierdzono zmniejszenie stopnia zahamowania agregacji płytek krwi. Podczas trwania badania u żadnego chorego nie wystąpił incydent zakrzepowo-zatorowy ani krwotoczny.

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Conclusions: Patients on MCS therapy demonstrate significant time-dependant changes in hemostasis parameters (both in the coagulation system and platelet aggregation).

Key words: mechanical circulatory support, left ventricular assist device, bleeding, thrombosis.

Introduction

Heart transplantation remains the first-line therapy in the management of end-stage heart failure. However, the number of transplants is estimated at less than 3,500 yearly worldwide, which is obviously inadequate to meet the demand in this rapidly growing population of heart failure patients [1, 2]. Mechanical circulatory support (MCS) is an umbrella term describing various technologies used in both short- and long-term management of patients with either end-stage chronic heart failure (HF) or acute HF. Long-term devices are used either as a 'bridge to transplant' to support patients who are unable to wait any longer for a heart transplant, or, more recently, as 'destination therapy' for older patients suffering from end-stage heart failure and who have contraindications to heart transplantation [3, 4]. Mechanical circulatory support includes a left ventricular assist device (LVAD) or a bi-ventricular assist device (BiVAD). However, MCS therapy is not without risk. Recently, clinicians have identified common MCS therapy-associated complications: pump thrombosis, bleeding, and hemolysis [5]. These complications are very challenging with regard to both diagnosis and management.

The incidence of LVAD thrombosis is 2–13% of adult patients with a continuous-flow LVAD (axial flow 4–13%, centrifugal flow 2%) [6]. Therapeutic options include surgical procedures (device exchange, catheter-based thrombectomy) and medical therapy. The latter may consist of: thrombolytic therapy with recombinant tissue plasminogen activator, intensified anticoagulation treatment with unfractionated heparin, bivalirudin, intensified antiplatelet treatment with intravenous GP IIb/IIIa inhibitors, or with thienopyridine-derivative P2Y₁₂ ADP receptor inhibitor. However, there are no unified guidelines as to the anti-thrombotic therapy [7, 8]. The incidence of LVAD-associated bleeding, depending on its definition, varies widely between 10% and 50%, with no difference in the overall bleeding rates between axial- and pulsatile-flow devices [9]. Much of the bleeding risk is attributed to the anti-thrombotic regimen. However, there are reports that the observed increased risk of bleeding is higher than would be anticipated from antithrombotic therapy alone [10].

Given the coexistence of thrombo-embolic and hemorrhagic complications, monitoring of hemostasis using thromboelastometry/graphy and platelet function analysis is recommended during MCS therapy [11]. Hemostasis assays should be used to reduce the risk of bleeding and thrombo-embolic complications during MCS therapy and antithrombotic management.

Wnioski: U pacjentów stosujących MCS wykazano znaczne zmiany w parametrach hemostazy zarówno w układzie krzepnięcia, jak i aktywności płytek krwi.

Słowa kluczowe: mechaniczne wspomaganie układu krążenia, urządzenie wspomagające pracę lewej komory serca, krwawienie, zakrzepica.

Aim

Therefore, we set out to determine time-dependant changes of selected hemostasis parameters in patients with end-stage heart failure treated with MCS and anti-thrombotic therapy.

Material and methods

The study conforms to the Declaration of Helsinki. The study was approved by the local Bioethics Committee, and all patients gave written consent to participate in the study.

Sixteen patients with end-stage heart failure on LVAD were followed for 6 weeks (six blood samples for each patient). Given the various effects of continuous-flow LVAD and pulsatile-flow LVAD on hemostasis [12], we included in the current study only continuous-flow LVAD recipients.

HeartMate II is an intracorporeal pump with an axial flow pattern. The pump is driven by a rotating magnetic levitated impeller and has a capacity of up to 15,000 rpm, resulting in a theoretical maximal blood flow of 8–10 l/min.

HeartWare (HW) is an intracorporeal 3rd-generation pump. It is a rotational pump with a magnetic levitating rotor (similar to a propeller). The blood flow is not axial, because inflow and outflow axes are arranged in a 90 degrees angle. Moreover, this pump runs with a lower rotation speed of 1,000 to 2,500 rpm and generates up to 10 l/min flow.

Every week an extended hemostasis panel was assessed, including activated partial thromboplastin time (APTT), prothrombin time (PT), international normalized ratio (INR), von Willebrand factor (vWF) activity, factor VIII activity, fibrinogen level, D-dimer, platelet response to arachidonic acid (ASPI test) and adenosine diphosphate (ADP test), thrombin receptor activating peptide-6 (TRAP test) and collagen (COL test).

Fasting venous blood samples were taken each week, and all tests were performed within one hour of blood samples' collection. Whole venous blood samples were collected from each patient and placed in 2 tubes of 4 ml with 109 mmol of sodium citrate (3.2%) and in 2 tubes of 3 ml with > 15 µg/ml of hirudin. Plasma was separated by centrifugation at 2000 g for 15 min at ambient temperature (20–25°C). The vWF activity and D-dimers were evaluated by an immuno-turbidimetric assay, using a fully automated hemostasis analyzer (BCS XP system, Innovance Siemens Healthcare, USA). Factor VIII (% activity of normal plasma) and coagulant fibrinogen (mg/dl) were determined by chromometric techniques by means of fully automated hemostasis analyzers (BCS XP system, Siemens Healthcare, USA). Prothrombin time (PT, % time of normal plasma), INR, and APTT (s) were also assessed by chromometric techniques. Platelet aggregation was tested in

Tab. I. Baseline clinical characteristics

Parameter	Result
Age [years]	41 (24–49)
Men, <i>n</i> (%)	16 (100)
Time from LVAD implantation [days]	60 (45–120)
Non-ischemic cardiomyopathy, <i>n</i> (%)	9 (56.2)
LVAD type:	
– HeartWare, <i>n</i> (%)	13 (81.2)
– HeartMate II, <i>n</i> (%)	3 (18.8)
Left ventricular ejection fraction (%)	15 (10–18)
Body mass index [kg/m ²]	23 (19–26)

physiological calcium conditions by the Multiplate analyzer (Dynabyte, Munich, Germany), using agonists of thrombin receptor activating peptide-6 (TRAP-6), arachidonic acid (ASPI), adenosine diphosphate (ADP), and a collagen binding activity assay (COL).

The antithrombotic protocol involved the use of unfractionated heparin according to the APTT (60–80 s) starting on postoperative day (POD) 1. On POD 2 warfarin was started to achieve INR of 2.0–2.5 in continuous-flow pumps. In addition, aspirin and/or clopidogrel were used antiplatelet agents, starting from POD 2. The type and dose of antithrombotic regimen were at the discretion of the attending physician.

Statistical analysis

Continuous variables are presented as medians and interquartile ranges. Categorical variables are presented as frequencies. Friedman analysis of variance (ANOVA) test followed by Bonferroni correction and the Wilcoxon

matched-pairs signed-ranks test were employed to test the difference between repeated laboratory tests during 6-week follow-up.

Results

Baseline clinical characteristic are presented in Table I. The study population comprised 16 men with a median age of 41 (interquartile range: 24–49). The median ejection fraction was 15% (10–18%). The median time from LVAD implantation was 60 days (45–120 days). Coagulation assay results are presented in Table II. During the study period the D-dimer and fibrinogen concentrations were elevated but remained similar throughout all six measurements. Meanwhile factor VIII and vWF activities were elevated in the first two measurements and then subsequently declined. Platelet function tests are depicted in Table III. Inhibition of platelet aggregation was greater early after LVAD implantation. During subsequent weeks the inhibition of platelet aggregation was less pronounced. No patient developed any bleeding or thrombo-embolic event during the study period.

Discussion

We set out to determine time-dependant patterns in hemostasis parameters in patients with end-stage heart failure treated with LVAD. There are several key findings of our study. First, D-dimer and fibrinogen concentrations were elevated but remained similar throughout all six measurements. Second, factor VIII and vWF concentrations were elevated at the beginning of the study and then steadily declined. Third, inhibition of platelet aggregation was greater early after LVAD implantation. And finally, despite the fluctuation in hemostasis parameters, there were

Tab. II. Coagulation assay results in studied patients

Variable	D-dimer (N < 0.5) [mg/l]	Fibrinogen (N < 400) [mg/dl]	INR (N 1.2–1.8)	APTT (N < 38) [s]	Factor VIII (N < 150) IU/dl	vWF (N < 150) IU/dl
Week 1	3.2 (2.0–8.9)	633 (611–669)	2.3 (2.0–2.9)	45 (38–51)	289 (221–586)	295 (183–329)
Week 2	4.1 (3.3–7.3)	698 (531–813)	2.5 (2.1–3.1)	48 (40–53)	201 (143–367)	192 (141–231)
Week 3	3.5 (3.2–10.0)	680 (602–713)	2.2 (1.9–2.8)	45 (35–49)	200 (131–275)	171 (101–263)
Week 4	3.9 (3.6–5.9)	653 (527–701)	2.3 (2.0–2.9)	46 (38–49)	160 (120–233)	188 (144–247)
Week 5	3.0 (2.1–6.3)	671 (603–739)	2.6 (2.3–3.0)	49 (45–53)	157 (131–189)	161 (134–211)
Week 6	2.8 (2.0–5.6)	641 (584–714)	2.5 (2.2–3.3)	48 (41–55)	162 (129–197)	159 (130–218)
<i>P</i> -value	0.3	0.3	0.7	0.5	< 0.001	0.01

Tab. III. Time-dependant changes in platelet function

Variable	ASPI (N > 494) area under the curve (AUC)* [min]	ADP (N > 691) area under the curve (AUC)* [min]	COL test (N > 708)	TRAP test (N > 920)
Week 1	371 (193–1015)	181 (101–1430)	194 (166–749)	320 (292–1411)
Week 2	753 (530–1382)	266 (215–376)	503 (255–914)	561 (432–1232)
Week 3	516 (211–649)	596 (509–734)	289 (197–410)	831 (700–1464)
Week 4	493 (229–564)	511 (395–583)	268 (220–373)	889 (793–1158)
Week 5	537 (289–638)	479 (229–552)	317 (245–438)	873 (741–1097)
Week 6	512 (312–681)	461 (315–580)	411 (344–589)	853 (665–1142)
<i>P</i> -value	0.009	0.007	0.01	0.01

no hemorrhagic or thrombo-embolic events during the study period.

Currently, long-term survival in carefully selected patients on MCS is much better than with medical therapy. However, MCS therapy is hampered by, sometimes life-threatening, complications including bleeding and device thrombosis [13]. Other complications include right ventricular failure, aortic insufficiency, and infection. Left ventricular assist device thrombosis etiology is multifactorial and thus presents complex and challenging problems in the diagnosis and management of such patients [14]. The conditions associated with LVAD thrombosis are divided into three large groups: (a) pump-related, (b) patient-related, and (c) management-related [14]. Left ventricular assist device thrombosis occurs in 2–13% of adult patients with a continuous-flow LVAD (axial-flow: 4–13%, centrifugal-flow: 2%) [6]. Thrombus may be formed at various sites, i.e. left ventricle, inflow cannula, pump housing, outflow cannula, outflow graft, or the aortic root, thus leading to serious cardiovascular events including thromboembolic stroke, peripheral thromboembolism, LVAD malfunction with reduced systemic flows or life-threatening hemodynamic impairment, cardiogenic shock, and even death [6, 15]. The four clinical signs of LVAD thrombosis recognized are as follows: (a) isolated power elevations, (b) isolated LDH rise, (c) evidence of hemolysis, and (d) new heart failure symptoms [14]. The multidisciplinary and multi-institutional ISHLT group proposed an algorithm for the diagnosis and management of LVAD thrombosis [13].

Left ventricular assist device patients experience significant baseline activation of endothelial and coagulation systems, further accentuated in the early postoperative period [16]. More importantly, prolonged activation of the endothelial and coagulation systems was also reported, which may indicate activation of the extrinsic (tissue factor) pathway of thrombosis mediated by sustained endothelial dysfunction in these patients [16]. Elevated D-dimer concentrations, as found in our study, may reflect chronic, ongoing activation of the coagulation system [17]. Elevated concentrations of fibrinogen, factor VIII, and vWF might result in a hypercoagulable state resulting in LVAD thrombosis. Elevated factor VIII levels have been associated with an increased risk of thrombosis [18]. Conditions leading to the increase of factor VIII levels can be genetic or acquired. More importantly, we have to keep in mind that factor VIII is an acute-phase protein (malignancy, chronic diseases, infections). Thus, genetic or acquired conditions determining high factor levels might predispose patients to LVAD thrombosis. The vWF has a pivotal role in thrombogenesis, and high plasma levels of vWF have been associated with increased risk of thrombosis [19]. A varied response to the antiplatelet regimen, as demonstrated during the study period, may also predispose to thrombosis, namely white thrombus formation. One study found that ASA doses at or below 81 mg/day were an independent predictor of device thrombosis [20]. Pacholewicz *et al.* reported that pump thrombosis was preceded by an almost surprising increase

in platelet aggregation induced by ASPI and ADP [21]. Thus the authors argue that an increase of platelet reactivity or non-response (or low response) to antiplatelet therapy may, in part, play a role in pump thrombosis. Indeed, elevated expression of platelet membrane receptors, namely CD62P and CD63, have been reported in patients on LVAD [22]. Moreover, highly variable platelet aggregation induced by different agonists was also observed [23]. Left ventricular assist device thrombosis has been reported in non-responders to aspirin [24] and clopidogrel [25].

In addition to thrombosis, bleeding has recently been identified as one of the most common adverse events of LVAD therapy and is the major cause of morbidity [9]. Much of the bleeding risk may be associated with the antithrombotic regimens. Having said that, some authors report that the increased risk of bleeding is higher than would be attributed to antithrombotic therapy [10]. The most commonly reported sources of bleeding are epistaxis, GI bleeding, bleeding of the mediastinum and thorax, and intracranial hemorrhage. The incidence of bleeding, depending on its definition, varies widely between 10% and 50%, with no difference in the overall bleeding rates between axial- and pulsatile-flow devices [9]. The prevalence of GI and intracranial bleeding is 30% and 11% respectively [26]. Consequently, hemorrhagic adverse events are more prevalent than thrombo-embolic events. The mechanisms underlying bleeding in LVAD patients are complex and not yet fully understood, and include colonic dysplasia, concomitant use of anticoagulant and antiplatelet agents, and the presence of acquired bleeding diathesis (acquired von Willebrand syndrome type 2A resulting from the deficiency of high-molecular-weight vWF multimers). As such, high-molecular-weight vWF multimers declined in patients with LVAD [27, 28], but returned to normal in 6 patients after heart transplantation [29]. However, in the present study we measured only vWF antigen, which is generally within the normal range or elevated and cannot be used in the confirmation or exclusion of acquired von Willebrand syndrome type 2A. The sensitivity of various laboratory tests for vWS2A in patients with bleeding GI dysplasia is as follows: gel electrophoresis (quantification of HMWM) > PFA-100 closure time > vWF:RCo > bleeding time > vWF:Ag [15, 30].

The coagulation system response to LVAD presence varies greatly between patients. It would seem that LVAD recipients achieve a new equilibrium between prothrombotic and prohemorrhagic states [31]. More importantly, there is a fine and complex balance in the management of such patients of overcoagulation and undercoagulation.

Management protocols for LVAD are usually institution-dependent, and unfortunately, there is a large variability in clinician-related factors. We have to keep in mind that the “one size fits all” approach is impractical and ineffective. Therefore, individually tailored antithrombotic therapy protocols must exist in centers managing LVAD recipients.

It has to be noted that our study has some limitations. We did not assess the dysfunction of vWF (in particular the

deficit of high molecular weight multimers of vWF assessed in gel electrophoresis). Moreover, we did not use thromboelastographic (TEG) monitoring, which could have provided additional information, as TEG is uniquely capable of showing the combined interaction of coagulation factors, platelet content, and platelet function in the process of clot production in whole blood.

Conclusions

Patients with end-stage heart failure on LVAD therapy demonstrate significant time-dependant changes in hemostasis parameters that could be attributable to the risk of developing both thrombotic and bleeding events. However, further studies are needed to determine whether these changes could serve as biomarkers of such events.

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Disclosure

Authors report no conflict of interest.

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