Novel method using rotational thromboelastography analysis for intraoperative management of device patient with heparin-induced thrombocytopenia

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Heparin-induced thrombocytopenia (HIT) is a prothrombotic disease in response to previous heparin exposure. Direct thrombin inhibitors are suitable candidates for the prophylaxis of thrombosis in patients with HIT. Currently activated clotting time and activated partial thromboplastin time are used to guide dosing and monitor anticoagulation. These assays provide a measure of clot initiation and only account for a small fraction of the coagulation pathway. In this case study we performed rotational thromboelastography (ROTEM) analysis on a patient with HIT implanted with a continuous-flow CentriMag device for left ventricular support. ROTEM evaluation confirmed a decline in activated clotting time values and provided further information regarding intrinsic and extrinsic clotting times. Monitoring ROTEM parameters aided in the detection of coagulopathies and the decision to administer platelet or fresh frozen plasma products. Utilizing ROTEM can guide clinical decisions in transfusions, particularly in patients with HIT, where platelet and fibrinogen levels can be safely maintained to prevent thrombosis. *Blood Coagul Fibrinolysis* 27:943–947

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Background

Heparin-induced thrombocytopenia (HIT) is an immune-mediated prothrombotic disease in response to previous heparin exposure [1] Direct thrombin inhibitors (DTIs) are suitable candidates for the prophylaxis of thrombosis in patients with HIT [2–6]. Bivalirudin, a common DTI, can be considered as a therapeutic alternative to heparin [3,5–7]. Currently, in the clinical setting clotting assays such as activated clotting time (ACT) and activated partial thromboplastin time (aPTT) are used to guide dosing and monitor patient anticoagulation [2–4,8]. These assays provide a measure of clot initiation and therefore only account for a small fraction of the coagulation pathway [2,3]. Rotational thromboelastography (ROTEM) can offer additional information regarding intrinsic and extrinsic coagulation properties as well as fibrin polymerization and fibrinolysis [2,9].

The use of ROTEM has become very helpful in managing the hemostatic nature of complex patients and predicting the need for interventional coagulation therapy. Four different tests can be run simultaneously: EXTEM, INTEM, FIBTEM, and APTEM. The EXTEM function uses tissue factor to activate the extrinsic pathway of coagulation, whereas the INTEM function uses ellagic acid to activate the intrinsic process of coagulation. FIBTEM and APTEM results are correlated with EXTEM and are processed by adding a platelet inhibitor (cytochalasian D) to monitor fibrinogen contribution to clot firmness, and a fibrinolysis inhibitor (aprotinin) to screen for hyperfibrinolysis, respectively. Within each test many parameters can be measured to deduce coagulation factor deficiencies as well as irregular clot firmness and lysis. The clotting time (CT) parameter measures the time taken until a clot amplitude of 2 mm is reached. It is affected by coagulation factors as well as anticoagulants. The clot formation time measures the time taken to reach a clot amplitude of 20 mm, and the alpha angle (α) is indicative of the speed of clot formation. As α is a rate constant, it is usually inversely proportional to CT and clot formation time values; the longer the clot formation, the slower the rate of clot development and vice versa. The amplitudes after 10 and 20 min (A10 and A20) display clot firmness after a specified amount of time, reflecting the contributions of fibrinogen, platelets, and factor XIII to clot formation [4,10]. The A10 value has been reported as a predictor of the maximum clot firmness (MCF), allowing for early coagulopathy detection and therefore timely coagulation therapy [10].

Recent studies have demonstrated the benefits of ROTEM use with argatroban [2,9] and the use of thromboelastography with bivalirudin [11,12]; however, to our best knowledge, a critical analysis of ROTEM use for

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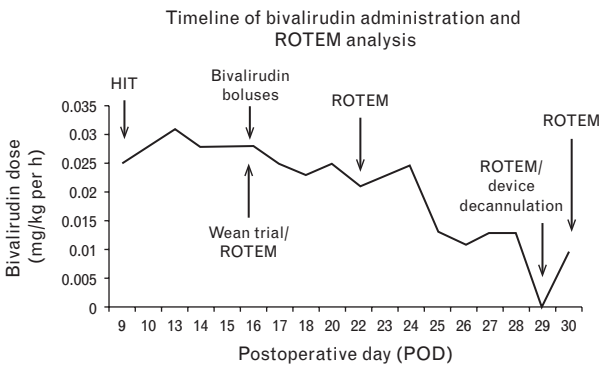
Fig. 1



Timeline of bivalirudin administration with dates of surgical occurrences and ROTEM testing. The patient was diagnosed with HIT on POD9 and subsequently switched to bivalirudin therapy. On POD16 a total bivalirudin bolus of 0.30 mg/kg was given intraoperatively in addition to a regular daily infusion of 0.028 mg/kh per h. HIT, heparin-induced thrombocytopenia; ROTEM, rotational thromboelastography.

device patients on bivalirudin has not been established. In this case study we performed ROTEM analysis on a patient with HIT implanted with a continuous-flow CentriMag device (Thoratec, Pleasanton, California, USA) for left ventricular support, with the intention of demonstrating the beneficial effects of viscoelastic assays on monitoring appropriate intraoperative anticoagulation therapy.

Case history

A 35-year-old man, previously healthy, active military personnel, presented as a transfer from an outside hospital for higher-level care, with dilated cardiomyopathy, left ventricular ejection fraction (LVEF) of 5%, and refractory cardiogenic shock of unknown etiology. He returned from a military base abroad with flu-like symptoms, 1 week prior to admission, presenting with tachycardia and hypoxia.

Upon admission he had acute respiratory distress syndrome and was in septic shock. The patient was taken to the cardiac catheterization laboratory for treatment of refractory cardiogenic shock via a 19-Fr TandemHeart catheter in the right femoral vein (tip placed transeptally into the left atrium) and artery, for percutaneous CentriMag placement. Heparin was started for anticoagulation therapy.

On POD6 (6 days after catheterization), the patient did not show signs of heart recovery. He was thus taken to the operating room (OR) for decannulation of peripheral cannulae, due to progressing leg ischemia, and subsequent central cannulation for left ventricular assist device (LVAD; CentriMag) support with Thoratec cannulae (34 Fr drainage and 24 Fr return cannula). The inflow cannula was placed through the apex of the left ventricle (LV) and the outflow cannula was placed through an 8 mm Dacron graft sewn onto the ascending aorta. Heparin was administered to achieve an ACT greater than 400 s for possible cardiopulmonary bypass support. Postoperatively the patient developed persistent thrombocytopenia; therefore, heparin platelet factor 4 (PF4) immunoglobulin G levels were monitored. Results were positive with optical densities of 0.785 and 1.875. After return of a positive serotonin-release assay, suggesting a diagnosis of HIT, heparin administration was stopped and bivalirudin was infused at 0.025 mg/kg per h to achieve an aPTT of 50–60 s and an ACT of 160–190 s (Fig. 1).

On POD13 the patient was able to tolerate low flows with inotropic support and cardiac index of 4.0 l/min per m^2. Therefore, on POD16 an LVAD weaning trial was completed in the OR. Three boluses of bivalirudin, totaling 0.30 mg/kg, were administered for possible cardiopulmonary bypass and LVAD recirculation. Subsequently, a citrated whole blood sample was collected for ROTEM analysis (ROTEM *delta* system; Tem Innovations, GmbH, Munich, Germany), before and after bolus administration. The CT, alpha angle or rate of clot formation (α), and MCF were measured for the INTEM, EXTEM, FIBTEM, and APTEM functions. The patient's LV function by transesophageal echo was poor (LVEF 10%) with epinephrine, milrinone, and iNO support; therefore, the decision was made not to decannulate the device. Bivalirudin administration was continued at 0.028 mg/kg per h after the wean trial.

On POD21 a bedside mini ramp study was conducted. Patient LVAD flow was decreased to 1 l/min with an LVEF of 15%. The following day ROTEM analysis was performed, to assess hemodynamic status. Bivalirudin administration was maintained at 0.025 mg/kg per h at that time with aPTT values remaining steady at 62.4 s and a declining optical density of 0.367 as of POD26.

On POD28 bedside transesophageal echo and mini ramp study demonstrated stable LV function (LVEF 15%); therefore, bivalirudin administration was stopped on POD29 and the patient underwent a redo full sternotomy. The LVAD CentriMag was weaned and decannulated in the OR without using cardiopulmonary bypass. Heparin was not administered and ACT levels remained at 148–158 s. ROTEM analysis was performed before and after device decannulation as well as the following day. Bivalirudin infusion was administered at 0.01 mg/kg per h after decannulation. On POD34 the patient was extubated and his PF4 immunoglobulin G level dropped to normal with an optical density of 0.160.

Results

Bivalirudin administration was monitored over the course of care for this patient (Fig. 1). ROTEM analysis was completed intraoperatively and intermittently between

Table 1 Rotational thromboelastography values for the INTEM and EXTEM functions for perioperative and intraoperative care of patient

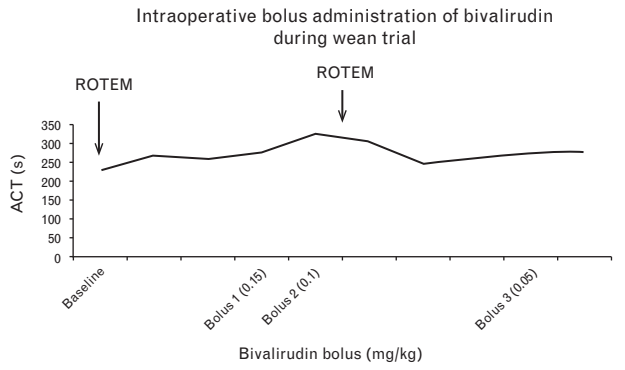
	Surgical wean (pre bolus)		Surgical wean (post bolus 2)		POD22		Oecannulation (Baseline)		Decannulation (post)		POD30	
ROTEM parameters	INTEM	EXTEM	INTEM	EXTEM	INTEM	EXTEM	INTEM	EXTEM	INTEM	EXTEM	INTEM	EXTEM
CT(s) (122–208 s) (43–82 s)	456	220	348	175	271	94	243	99	213	87	221	97
CFT(s) (45–110) (48–127)	161	167	183	187	175	182	98	107	78	87	92	103
A (°) (70–81) (65–80)	63	63	59	58	69	67	72	72	74	73	73	71
A10 (mm)	36	36	35	34	35	34	49	48	57	55	49	50
A20 (mm) (51–72) (50–70)	43	42	42	41	42	41	55	55	63	62	55	57
MCF (mm) (51–72) (50–70)	47	44	47	44	45	44	58	58	65	64	57	59

Ranges are listed in the left hand column for each parameter. INTEM ranges are displayed on top and EXTEM ranges are displayed on the bottom. CFT, clot formation time; CT, clotting time; MCF, maximum clot firmness; ROTEM, rotational thromboelastography.

surgical occurrences to detect CT changes with varying bivalirudin infusion (Table 1). During the weaning trial (POD16) anticoagulation was monitored with ACT values in relation to bivalirudin bolus administration (Fig. 2). ACT results did not reach the targeted 400 s; therefore, ROTEM analysis was performed. Baseline ROTEM results indicated CT values of 220 and 456 s for EXTEM and INTEM, respectively, whereas data collected after bolus administration (0.15 and 0.1 mg/kg) revealed declined CT levels of 175 and 348 s, respectively. This prompted further bivalirudin administration (0.05 mg/kg).

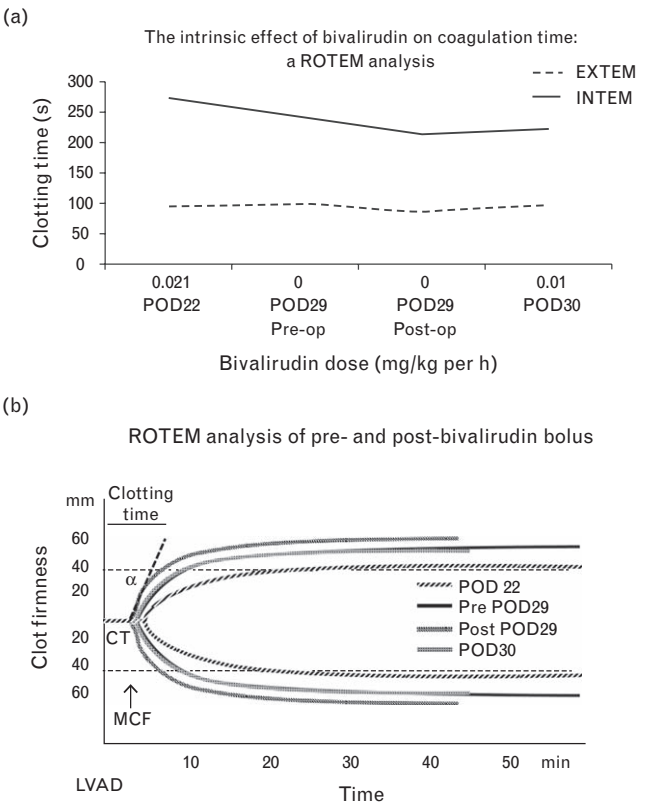
Clotting times were further monitored in relation to bivalirudin administration, from POD22 to POD30 to assess patient hemodynamic status (Fig. 3a). Both INTEM and EXTEM parameters were affected by changes in bivalirudin dosing; however, bivalirudin appeared to have a greater correlation to the INTEM function. As the infusion dose decreased, INTEM CT values demonstrated larger declines as compared with EXTEM. Figure 3b is a graphic representation of the ROTEM, illustrating the change in length of INTEM CT from POD22 to POD30. As bivalirudin administration was decreased the CT also decreased and subsequently when bivalirudin administration was increased on POD30, the CT was prolonged. The alpha angle remained within normal range (70–81°) from POD29 to POD30 indicating adequate platelet function as well as fibrinogen and coagulation factor contribution. However, POD22 had a slight decrease, most likely the

Fig. 2



Bivalirudin bolus administration versus ACT response. Three separate bivalirudin boluses were given to the patient on POD16 during the LVAD weaning trial. ACT values were measured concurrently with two ROTEM tests: one at baseline before bolus administration and the second following the administration of the second bolus. ACT, activated clotting time; ROTEM, rotational thromboelastography.

Fig. 3



Bivalirudin dose administration versus ROTEM clotting time values. (a) INTEM and EXTEM clotting times preceding and following device decannulation at varying bivalirudin infusion rates displays a pronounced effect on the INTEM function. On POD29 ROTEMs were run pre and post device extraction in the operating room. (b) Rotational thromboelastometry for the INTEM assay from POD22 to POD30. Monitoring of CT, α angle, and maximum clot firmness values intraoperatively required no platelet or FFP transfusions. α, alpha angle; CT, clotting time; MCF, maximum clot firmness; ROTEM, rotational thromboelastography.

Table 2 Clotting assays and laboratory results for perioperative care of patient

Test results	Surgical wean	POD22	Decannulation	POD30
aPTT (22.6–35.5 s)	76.5	62.2	52.9	40.3
Platelet count (150–425/1000/μl)	65	34	173	90
Fibrinogen levels (200–430 mg/dl)	200	291	354	339
ACT (90–130 s)	275 (Bolus l) 324 (Bolus 2) 273 (Bolus 3)		158	

Normal ranges are presented in parenthesis. Numbers signify values measured postoperatively. ACT, activated clotting time; aPTT, activated partial thromboplastin time.

result of low platelet levels (Table 2). In addition, MCF values were monitored for platelet and fibrinogen function with the aid of FIBTEM and APTEM analysis. MCF values were normal (51–72 mm) except on POD22, suggesting lowered platelet levels. Due to the patient's HIT status platelet transfusions and fresh frozen plasma products were not administered intraoperatively or on days when ROTEM analyses were completed to prevent thrombosis.

Discussion

Due to the pharmacokinetic and pharmacodynamic profiles of bivalirudin it has been commonly monitored using ACT and aPTT assays [2–4,8]. Although these conventional tests provide important clinical data, they only account for a minimal portion of the coagulation pathway. Thus the use of ROTEM has become very beneficial in managing hemostasis in complex patients [10,13]. For the purposes of this case report only INTEM and EXTEM data were analyzed to determine the correlation between CT and bivalirudin administration. FIBTEM and APTEM were monitored; however, due to the patient's HIT status, platelet transfusions were not given intraoperatively.

During the first weaning trial on POD16, ROTEM analysis displayed decreased INTEM and EXTEM CT values after bolus administration. This confirmed that the patient required an additional bivalirudin bolus for anticoagulation despite low FIBTEM and platelet levels. Therefore, ROTEM analysis served as a useful marker, aiding in the proper intraoperative anticoagulation management of the patient.

Further analysis of the relationship between bivalirudin and ROTEM CT values demonstrated a strong correlation with the INTEM function. This suggests that DTIs can be monitored more precisely with the INTEM parameter. Similar results were reported by Sucker *et al.* [14] demonstrating increased hirudin sensitivity with ellagic acid as compared to tissue factor or ecarin-activating agents [14]. In addition alpha angle and MCF parameters provided useful information regarding the rate of clot formation and clot firmness. These measures guided the decision not to administer platelet transfusions intraoperatively and allowed us to maintain appropriate levels to prevent thrombosis.

The benefits of ROTEM analysis have been reported beyond this case report [10]. A recent randomized clinical trial demonstrated decreased erythrocyte, plasma, and fresh frozen plasma transfusion rates as well as decreased length of stay, adverse events, and 6-month mortality with combined ROTEM and platelet analysis as compared to conventional testing [15]. Furthermore, it has been reported that increased aPTT values have been associated with normal ROTEM CT values. Therefore, without ROTEM data clinicians are inclined to administer unnecessary coagulation products [16].

The use of ecarin clotting time (ECT) has emerged as another modality for measuring the dose-dependent effects of DTIs. Ecarin is a metalloproteinase, which cleaves prothrombin into meizothrombin. In the presence of a DTI, meizothrombin will be inhibited and will prolong the ECT. Once the given amount of DTI in a blood sample has been utilized, the remaining meizothrombin will continue along the coagulation pathway, cleaving fibrinogen into fibrin [17]. Multiple studies have shown that ECTs are superior to aPTT analysis as they yield more sensitive results at doses as low as 0.05 μg/ml. Furthermore these tests are not affected by other oral anticoagulants such as heparin or warfarin [17]. In comparison to the INTEM function of the ROTEM assay, which utilizes ellagic acid as an activator, Sucker *et al.* [14] demonstrated that sensitivity for thromboelastography was greatest with ellagic acid use as opposed to ecarin or tissue factor. Sensitivity with ellagic acid was noticed at concentrations of 0.1 μg/ml of hirudin as opposed to 0.5 μg/ml, respectively.

This case report has presented useful results in the intraoperative management of a mechanical device patient with HIT, on bivalirudin therapy. ROTEM parameters were valuable in determining the effect of bivalirudin on hemostatic function and anticoagulation. Viscoelastic tests can be utilized in the perioperative care of device patients, to closely monitor coagulopathies, platelet levels, and clot formation. Furthermore they have proven effective in providing critical data not accounted for in the conventional ACT or aPTT assays. This is useful to clinicians as there is growing consensus to use ROTEM analysis over aPTT assays for hemostatic therapy due to increased test accuracy associated with thromboelastographs [10]. As these tests are becoming

more commonly available at the bedside, their prophylactic use for complex prothrombotic and thromboembolic disorders is becoming integral to patient therapy.

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Conflicts of interest

There are no conflicts of interest.

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