Difficulties With the Use of Thromboelastometry in a Patient With Antiphospholipid Syndrome Undergoing Cardiac Surgery

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THE ANTIPHOSPHOLIPID SYNDROME (APLS) is an autoimmune syndrome characterized by a hypercoagulable state with vascular thrombosis and the persistent presence of phospholipid-directed autoantibodies. Cardiac surgery in such patients carries significant morbidity and mortality and is fraught with both thromboembolic and bleeding complications.[1–3] Management of perioperative anticoagulation is complicated by an intrinsic prothrombotic state and the paradoxical tendencies of lupus anticoagulant antibodies (LAC) to inhibit phospholipid-dependent coagulation during in vitro lab testing superimposed on the complex effects of cardiopulmonary bypass on coagulation and low tolerance for postoperative bleeding risk.

The use of viscoelastic hemostatic testing in this setting previously has been proposed as a possible adjunct to mitigate these complexities.[4] However, there are little published data on its use in APLS patients and, in particular, in those undergoing cardiac surgery requiring cardiopulmonary bypass.

The authors describe a case of a patient with primary APLS undergoing mitral valve replacement and their experience with the use of rotational thromboelastometry (ROTEM), and they provide a brief overview of the literature regarding its use in such patients.

CASE REPORT

A 59-year old Caucasian woman underwent mitral valve replacement for severe mitral regurgitation from a flail posterior leaflet secondary to a ruptured papillary muscle following an inferior ST-elevation myocardial infarction. She had undergone a successful and uneventful primary angioplasty 11 days earlier but, unfortunately, developed congestive cardiac failure on the third day post-procedure. Postinfarction echocardiography demonstrated (apart from the described mitral valve pathology) an ejection fraction of 60% and a pulmonary artery systolic pressure of 41 mmHg.

She had a significant past history of primary APLS with positive assays for lupus anticoagulant antibodies (B2 glycoprotein IgM [38.1 SMU] and anti-cardiolipin IgM [15.5 MPL]). Since her diagnosis 20 years ago, she has had several thrombotic episodes including bilateral deep vein thrombosis and pulmonary embolism, ischemic stroke, and digital gangrene of her right hand. She also had 3 episodes of atraumatic intracranial hemorrhage while on long-term warfarin and had been diagnosed with breast cancer a month prior to admission.

Preoperatively, the patient was treated with furosemide and digoxin. Aspirin was stopped three days prior in anticipation of surgery, and anticoagulation was maintained with subcutaneous enoxaparin, 50 mg twice daily, until discontinuation 14 hours before surgery. Preoperative testing the day before surgery revealed a mild thrombocytopenia (platelet count of 99 x 10^9/L) and slightly prolonged clotting times (prothrombin time [PT] of 15.7s, activated partial thromboplastin time [APTT] of 45.3s, international normalized ratio [INR] of 1.32).

Coagulation was monitored intraoperatively with a triple-reagent activated coagulation time (ACT; Actalyte MINI II Activated Clotting Time Test System, Helena Laboratories, Beaumont, TX; see Table 1 for ACT results) and ROTEM (Tem Innovations GmbH, Munich, Germany; see Table 2 for ROTEM results) before, during, and after bypass with intention to manage hemostatic product use in accordance with the recommendations of the ROTEM Expert Meeting Working Group, Munich 2007.[5] The initial pre-bypass baseline ROTEM was drawn 14 hours after the most recent dose of enoxaparin, and ROTEM was monitored on 4 channels; namely, INTEM (containing phospholipid and ellagic acid activators), EXTEM (with tissue factor activator), HEPTEM (containing heparinase for neutralizing heparin) and FIBTEM (with cytochalasin D, which blocks the platelet contribution to clot formation, allowing analysis of the fibrinogen component).

With a baseline ACT of 158s, anticoagulation for bypass was achieved with 600 units/kg of heparin. This resulted in an ACT of >1500s and an undetectable clot on INTEM analysis.

A repair using a size 28-mm Edwards Physio II annuloplasty ring was attempted, but the result was unsatisfactory, and hence, valve replacement surgery using a 27 mm St. Jude Medical Epic Bioprosthetic mitral valve was performed. Total bypass time was 128 minutes, and aortic cross-clamp time was 88 minutes. Separation from bypass was achieved with modest inotropic support, and a post-bypass transesophageal echocardiogram showed satisfactory valve function with good ventricular contractility.

Following separation from bypass, 250 mg of protamine were given, resulting in an ACT of 143s. As the clotting time (CT) (or time from start to when the waveform reaches 2 mm above baseline, thought to be most strongly influenced by plasma coagulation factors) was 418s on HEPTEM during bypass and remained prolonged following protamine (CTs for INTEM and EXTEM were 270s, and 125s, respectively), 613 mL of fresh frozen plasma were transfused. As the difference between post-bypass CTs for INTEM and HEPTEM (226s) was less than the 25% cutoff proposed to represent significant residual heparin effect, additional protamine was withheld.[5]

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Table 1. Activated Coagulation Time Results

Time		ACT (s)
Baseline		158
After IV heparin, 600 U/kg bolus		>1500
During Bypass	Time Following Initiation of Bypass	
	6 min	>1500
	21 min	>1500
	56 min	>1500
	90 min	987
	106 min	1020
After IV protamine, 250 mg		143

Abbreviations: ACT, abbreviated clotting time; IV, intravenous.

In view of the oozy surgical field, history of recent aspirin use, and preoperative thrombocytopenia, 300 mL of platelets were transfused. This was supported by the postbypass ROTEM reading, which demonstrated a prolonged clot formation time (CFT) (or time from 2 mm above baseline to 20 mm above baseline, thought to be influenced mainly by platelet function and fibrinogen) of 144s on the INTEM in the presence of a normal maximum clot firmness (MCF) (or clot strength) on FIBTEM and in consideration of the ROTEM's known insensitivity to aspirin effect. Antifibrinolytics were not administered as the LI30 (percentage clot lysis at 30 minutes, a marker of fibrinolysis) remained at 100% throughout.

Postoperatively, inotropes were rapidly weaned. A postoperative coagulation profile showed a PT of 18.9s, APTT of 38.5s and INR of 1.69. Chest drain output was low, allowing heparin to be restarted 8 hours postoperatively, achieving a therapeutic APTT of 99s.

In the early hours of the first postoperative day, the patient's hemodynamics deteriorated accompanied by mottling of her peripheries and a livedoid rash. An echocardiogram showed severe biventricular systolic dysfunction while the mechanical valve was seen to be positioned and functioning well. A small pericardial effusion was noted, but no features of tamponade were present. The patient subsequently suffered a brief episode of cardiac arrest after which extracorporeal membrane oxygenator (ECMO) therapy was instituted. Serial troponin I levels markedly increased during this period to a peak of 43.8 ug/L (reference range 0.000-0.039 ug/L), while a coronary angiogram demonstrated diffuse vessel narrowing but otherwise normal contrast flow. The patient was started on methylprednisolone and therapeutic plasma exchange for a presumptive diagnosis of possible catastrophic antiphospholipid syndrome (CAPS). Unfortunately, despite aggressive resuscitation, the patient remained in refractory circulatory shock. On the fourth postoperative day, she was found to have fixed dilated pupils and absent brainstem reflexes. A computed tomography (CT) brain scan demonstrated widespread borderzone infarcts. In view of the grave prognosis, ECMO support was withdrawn, and the patient passed away shortly after. A postmortem examination was performed, which demonstrated features of multi-organ ischemia and necrosis as consistent with the clinical course. However, it was unable to demonstrate findings pathognomonic of and completely specific to CAPS, such as the presence of microthrombi. Histologic examination in particular was made difficult due to autolytic changes possibly resulting from the prolonged period of hypoperfusion.

DISCUSSION

The APLS patient presenting for cardiac surgery requiring cardiopulmonary bypass is known to be at significant risk of morbidity and mortality.[6] Case series published by Berkun et al and Colli et al on APLS patients undergoing heart valve replacement reported an early mortality rate of 20% and 22%, respectively, and a combined rate of serious morbidity and mortality on longer followup of 60% and 55%, respectively.[2,3]

Table 2. Intraoperative ROTEM Results

	Prebypass		On Bypass		Postbypass	
	EXTEM*	FIBTEM†	EXTEM	FIBTEM	EXTEM	FIBTEM
CT (s)	302		177		125	
CFT (s)	69		181		141	
Alpha Angle (deg)	76		61		64	
MCF (mm)	61	29	49	38	57	16
LI30 (%)	100		100		100	

	Prebypass		On Bypass		Postbypass	
	INTEM‡	HEPTEM	INTEM	HEPTEM	INTEM	HEPTEM
CT (s)	358	X	4,504	418	270	226
CFT (s)	75	X	—	135	144	139
Alpha Angle (deg)	75	X	—	66	63	63
MCF (mm)	63	X	—	53	55	56
LI30 (%)	100	X	—	100	100	100

NOTE. Reference ranges provided by manufacturer.

Abbreviations: CFT, clot formation time; CT, clotting time; LI30, lysis index after 30 minutes; MCF, maximum clot firmness.

*CT 38-79s, CFT 34-159s, alpha angle 63-83 degrees, MCF 50-72 mm, LI30 94-100%.

†MCF 9-25 mm.

‡CT 100-240s, CFT 30-110s, alpha angle 70-83 degrees, MCF 50-72 mm, LI30 94-100%.