Review Article

Excessive bleeding in cardiovascular surgery. Usefulness of viscoelastic testing

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ABSTRACT

Excessive bleeding due to coagulation disorders is a well-known complication in cardiovascular surgery. Traditionally, standard coagulation tests have been used for their management, and more recently, viscoelastic testing has gained ground. This is performed using a different methodology and provide information on clot initiation, firmness, and lysis. Viscoelastic testing can diagnose coagulation factor deficiencies, the presence of heparin and protamine, fibrinogen, fibrin or Factor XIII deficiencies, platelet deficiency, and hyperfibrinolysis. The correlation between viscoelastic testing and standard coagulation tests is strong only in a few assays, and they have limitations in detecting the absence of general preconditions for coagulation, platelet aggregation deficiency, von Willebrand factor deficiency, the effect of fractionated heparin, the effect of direct factor Xa inhibitors and low and moderate intensity local or systemic fibrinolysis. To facilitate the treatment of patients with excessive bleeding, algorithms guided by viscoelastic testing have been designed.

INTRODUCTION

1. Introduction

Excessive or severe bleeding is a known complication in cardiothoracic surgery (CTS) that occurs in up to 10% of patients. When present, it increases adjusted mortality in up to 4 times.[1]

In spite of some attempts, there is no universally used definition for excessive or severe bleeding in CTS. It could be useful to consider this diagnosis when chest drain output is:

a. More than 500 ml within 1 hour, with no signs of reducing in the following hour;
b. More than 300 ml/h during the first 3 hours, with no sign of reducing in the following hour;
c. More than 200 ml/h for more than 3 hours, with no signs of reducing in the following hour;
d. More or equal to 1200 ml within the first 12 hours after the surgery.

Another definition that could be valid is the one categorizing bleeding as excessive when drain output exceeds 2 ml/kg/h. Recorded visible excessive bleedings are around 8 ml/kg/h.

When faced with lower volumes of bleeding, but with moderate to severe mediastinal widening in chest X-ray, we should consider that part of the bleeding has remained in the chest and a diagnosis of excessive bleeding should be contemplated. We should also take into account a diagnosis of excessive bleeding when treatment has been administered for it, even though the previously mentioned values were not reached.

The possible causes for bleeding immediately after cardiothoracic surgery are:[2]

1. Surgical
2. Coagulopathies
2.1. Hyperfibrinolysis
2.2. Residual heparinemia or heparin rebound
2.3. Platelet dysfunction
2.4. Thrombocytopenia
2.5. Deficiency coagulopathy (hemodilution, insufficient replacement or consumption)
2.6. Excess protamine
2.7. Von Willebrand factor deficiency
2.8. A combination of the above items
2.9. Disseminated intravascular coagulation
3. Mixed (surgical plus coagulopathy).

In the case of bleeding, it is important to diagnose the possible presence of coagulopathy and to characterize it to be able to apply a treatment specifically addressed for it,

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as soon as possible. A non-directed therapy for excessive bleeding with blood products, due to the absence of identification of the culprit coagulopathy entails an unnecessary transfusion and it exposes patients to risks such as infections, lung injuries (TRALI), increase in total body water and immunomodulation.[3,4] All of the above do not include red blood cells replenishment, when considered necessary. Besides clinical history and signs, there are different auxiliary tests by which a diagnosis of coagulopathy can be reached. Traditionally, standard coagulation tests have been used, and more recently, viscoelastic testing (VET).

The benefits described for VET are a fast and full evaluation of coagulation, the identification of specific coagulopathies that are not always detected by standard testing, being useful as guides for the administration of blood products that may reduce excessive transfusion, postoperative monitoring, and a reduction in postoperative complications[5]

For more than two years, VETs have been used in this institution, so it seems timely to carry out an outline focused on their use.

2. TECHNIQUE AND DEVICES TO CARRY OUT VETS

Coagulation viscoelastic testing is based on placing citrated whole blood on a cup with a central pin within it. The cup or the pin (according to the manufacturer) oscillate, while the other element remains fixed. Resistance to movement, as blood coagulates, is measured, yielding the results. Different reagents and chemical products (platelet function inhibitors, antifibrinolytic agents, etc.) are added to the blood in the cup to assess the strength of the clot by different methods.

In *Table 1,* the best known devices and most used assays made by each device are provided.

The ClotPro® device, from the Haemonetics® company, also performs other analysis such as: RW-test: a test for direct anticoagulation (e.g.: rivaroxaban); ECA-test: a test for direct thrombin inhibitors; and TPA-test that detects antifibrinolytic treatments, activating fibrinolysis. The same company has TEG5000® and TEG6s® devices, which carry out similar assays, and the TEG PlateletMapping® assay, which analyzes platelet function.

The Werfen® company also produces the ROTEM Sigma device® that includes the EXTEM, INTEM, FIBTEM, APTEM and HEPTEM assays. It also has the ROTEM Platelet® device, which has two additional channels to evaluate platelet function through impedance.

TABLE 1.
Viscoelastic coagulation tests. Most disseminated and used devices and assays.

			Purpose
Company	**Werfen®**	**Haemonetics®**	
Model	**ROTEM®**	**ClotPro® TEG®**	
Assay	EXTEM	EX-test	It examines the extrinsic pathway of coagulation
	INTEM	IN-test	It analyzes the intrinsic pathway of coagulation
	FIBTEM	FIB-test	It studies fibrinogen and fibrin, blocking platelet contribution
	HEPTEM	HI-test	It investigates the intrinsic pathway of coagulation adding a heparin inhibitor
	APTEM	AP-test	It detects hyperfibrinolysis by the addition of an antifibrinolytic agent

3. TYPICAL GRAPH, MAIN PARAMETERS AND NORMAL VALUES

The typical graph generated in viscoelastic testing can be seen in *Fig 1.*

Main parameters and normal values:

The main parameters for VETs can be classified according to the coagulation process characteristics on which they provide information.[6,7]

I. Clot onset:

a. Coagulation time (Werfen) or R time (Haemonetics) (CT). It is the time elapsed from the addition of the reagent to the sample and a width of 2 mm in the produced signal by the onset of clot formation. Its prolongation occurs due to deficit in coagulation factors and by the presence of anticoagulation agents such as heparin, depending on the assay used.
b. Clot formation time (CFT) (Werfen) or amplitude time (K) (Haemonetics). It is the time elapsed between CT and a 20 mm amplitude in the signal produced by the clot growth.

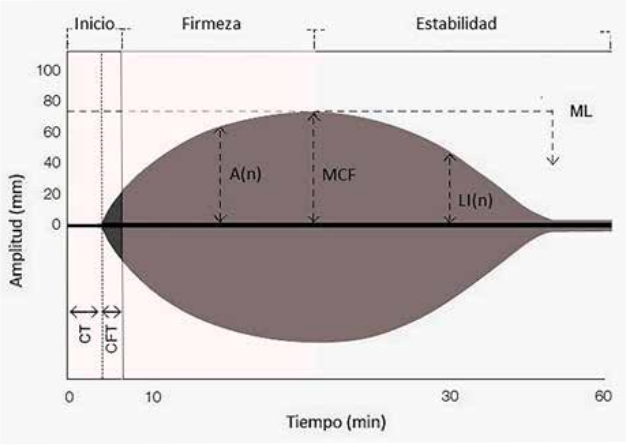

FIGURE 1.
Typical graph generated in a viscoelastic coagulation test
CT: coagulation time (Werfen) or R-time (Haemonetics); **CFT:** clot formation time (Werfen) or K-time (Haemonetics); **A(n):** amplitude in n min of CT (e.g.: A5); **MCF:** maximum clot firmness (Werfen) or maximum amplitude (Haemonetics); **LIn:** lysis index in n min of CT (e.g.: LI30); **ML:** maximum lysis.

TABLE 2.
Normal values of the main parameters of viscoelastic coagulation tests for hypocoagulable conditions.

	EXTEM	INTEM	HEPTEM	FIBTEM	EX-Test	IN-Test	HI-Test	FIB-Test
CT (s)	<80	<240	<240	<600	<65	<185	<185	
A5 (mm)	>35	>30	>30	>8	>39	>32		>6
A10 (mm)	>40	>40	>40	>8	>47	>41		>7
MCF (mm)	>50	>50	>50	>9	>50	>50		>9
LI 30(%)	>85	>85	>85	>85				
ML (%)	<15*	<15*	<15*	<15*				

CT: coagulation time or R-time; **A5:** amplitude in 5 min of CT; **A10:** amplitude in 10 min of CT; **MCF:** maximum clot firmness or maximum amplitude; **LI30:** lysis index in 30 min of CT; **ML:** maximum lysis. * reading in 60 min.

II. Clot strength:

a. Maximum clot firmness (Werfen) or maximum amplitude (Haemonetics) (MCF). It reports on the input by fibrinogen, fibrin and platelets to clot firmness.
b. Amplitude (A5, A10) (amplitude at 5 or 10 minutes of CT or R-time). It reports on the input of fibrinogen, fibrin and platelets to clot firmness and it is used to predict MCF in a shorter time.

III. Clot stability and lysis:

a. Lysis index (at n minutes of CT or R-time; for instance, LI30) (LI). It represents the remaining firmness percentage of the clot in relation to MCF. It reports on fibrinolysis or severe Factor XIII deficiency.
b. Maximum lysis (ML). It reports on fibrinolysis or severe Factor XIII deficiency.

In *Table 2,* the normal values of the main VET parameters are shown, to be used in hypocoagulable conditions.[8,9,10]

4. VET DEVIATIONS FACED WITH BLEEDING-INDUCING CONDITIONS

VETs can be used to diagnose coagulation factors deficiency, presence of heparin and protamine, fibrinogen, fibrin or Factor XIII deficiency, platelet deficiency and hyperfibrinolysis.[6] The deviations that may occur in VETs in these scenarios can be seen in *Table 3.*

A recent study including 759 patients showed a significant reduction in the use of blood products, infections, intensive care unit stay times and total hospital stay times, and costs using VETs in heart surgery.[5]

5. VET LIMITATIONS

Although VETs may be used to diagnose many coagulation anomalies, not all can be detected by this method. Some alterations, in which VETs are not useful, are: 1) failure in general coagulation preconditions (hypothermia, acidosis, hypocalcemia and anemia); 2) platelet aggregation deficiency (there are special devices for this; e.g.: ROTEM Platelet® or TEG Platelet Mapping®), 3) Von Willebrand factor deficiency; 4) fractionated heparin effect; 5) effect of direct anticoagulants anti-Factor Xa or anti-Factor IIa; 6) local or systemic fibrinolysis of low and moderate intensity.

6. RELATIONSHIP BETWEEN THE DIFFERENT DEVICES AND STANDARD COAGULATION TESTS

Some authors have studied the relationship between the VET results when they are performed with the two most

TABLE 3.
Viscoelastic coagulation testing deviations in the case of conditions producing bleeding.

Prolonged CT	
In INTEM or IN-test	Intrinsic pathway factors deficiency
	Heparin excess (if associated to normal HEPTEM or HI-test)
	Protamine excess (if associated to prolonged HEPTEM or HI-test)
In EXTEM or EX-test	Extrinsic pathway factors deficiency
In FIBTEM or FIB-test	Hyperfibrinolysis
In HEPTEM or HI-test	Intrinsic pathway factors deficiency
	Protamine excess
Decreased A5, A10 and MCF:	
In EXTEM or EX-test	Fibrinogen/fibrin deficiency (if associated to decreased FIBTEM or Fib-test)
	Platelet deficiency (if associated to normal FIBTEM or Fib-test)
	Hyperfibrinolysis
In FIBTEM or Fib-test	Fibrinogen/fibrin deficiency (if associated to decreased EXTEM or EX-test)
Decreased LI and increased ML	
In EXTEM or EX-test	Hyperfibrinolysis (if associated to increased FIBTEM or Fib-test and normal APTEM or AP-test)

CT: coagulation time or R-time; **A5:** amplitude in 5 min of CT; **A10:** amplitude in 10 min of CT; **MCF:** maximum clot firmness or maximum amplitude; **LI:** lysis index; **ML:** maximum lysis.

used devices, and the standard coagulation tests in patients who undergo heart surgery.[6] The main findings were:

a. A strong correlation was found between the maximum clot firmness measures, in the tests evaluating the extrinsic and the intrinsic pathway, between ClotPro and ROTEM. The correlation was moderate for the time that points out the onset of coagulation (CT) between ClotPro and ROTEM, and maximum clot firmness in the tests for fibrin (Ex-test and EXTEM).
b. Prothrombin time strongly correlated with R-time (Extest ClotPro); while the correlation was low with coagulation time (EXTEM ROTEM).
c. Fibrinogen and plasma Factor XIII levels strongly correlated with the maximum clot firmness measure with the FIB-test (ClotPro) and the FIBTEM (ROTEM).
d. The number of platelets presented a moderate correlation with the difference between coagulation triggered by extrinsic pathway and the fibrin test (EXTEM-FIBTEM, Exttest Fib-test), both with ROTEM and with ClotPro.

7. EXCESSIVE BLEEDING MANAGEMENT APPROACH

A practical approach to manage excessive bleeding immediately after cardiothoracic surgery should have the basic premise that any medical action should be taken in the shortest time possible, and preventing damage to the patient. The longer they take, the more blood the patient loses, the higher the need for blood products for replenishment, and the higher the risk of morbimortality in patients. The approach may be based on some basic questions:

1) Is there excessive bleeding or is it usual bleeding?

a) Before, it was stated that there is no universal definition for excessive bleeding. As usual bleeding varies with surgical and anesthetic techniques, with extracorporeal perfusion and other scenarios, it would be ideal for each service to analyze which are the volumes considered excessive. Or else, definitions such as the one included at the beginning of this summary can be used.
b) It is important to highlight that, if there is no excessive bleeding, patients should not be treated even when coagulations tests are altered. This is based on coagulation tests being made in vitro, with variables present in organisms that are not measured. This is expressed in the low positive predictive value of coagulation tests.[11]
c) In the case of excessive bleeding, if the systemic blood pressure of a patient is high or within the upper limit of normalcy, the patient should be treated to obtain values according to the situation of the patient (for instance, medium blood pressure of 70 for a previously normotensive patient). For this goal, an IV vasodilation agent is usually used.
d) In the case of excessive bleeding, and until a specific diagnosis and treatment are realized, the need to replenish red blood cells should be evaluated. In the case of hypotension, and until red blood cells concentrates arrive, crystalloid replenishment should be started immediately (for instance, saline solution). Five hundred cc should be replenished for every 500 cc of lost blood; however, the loss of the first 500 cc does not require replenishment.
e) Before excessive bleeding, it is convenient to report it to the surgical team to obtain their opinion, as well as to minimize reintervention times when needed.

2) Is excessive bleeding due to surgical causes, coagulopathies or both?

A differential diagnosis of the causes should be established by the history of the patient (e.g.: previous heart surgery, effect of antiplatelet agents), clinical signs (e.g.: bleeding only through drains or universal bleeding) and auxiliary tests (hemostatic values or non-hemostatic values in coagulation tests). A bleeding by surgical cause may be associated to coagulopathy. This happens when a) a bleeding by surgical cause undergoes incomplete blood product replenishment, and b) a bleeding by surgical cause is treated excessively with crystalloid fluids and hemodilution occurs in the patient.

If a patient is a carrier of bleeding by surgical cause, accompanied or not by coagulopathy, the patient should be urgently referred to the OR. Until the patient is moved to the OR, the coagulopathy should be treated.

3) If it seems there is a coagulopathy, are the general basic conditions for coagulation present?

For coagulation to work properly in the human body there should be:

a) Body temperature >35°C
b) pH >7.2
c) Hb >8 g/dl (lower levels lead to loss of laminar flow, preventing a proper plasma and platelet contact with the endothelium).12
d) Ionized calcium >1 mmol/l.

4) If there seems to be a coagulopathy, which is it?

In *Table 4,* the main features of VETs and the standard coagulation tests are shown, in some coagulopathies that are usually found during and after heart surgery.

5) What specific treatment is required for the coagulopathy?

One of the merits of VET devices has been the dissemination of treatment algorithms by their manufacturers. Thus, they made a contribution to disseminating knowledge on the therapy for coagulopathies. The manufacturer of the ROTEM device has designed an algorithm to manage excessive bleeding, based on the order of treatment: 1st hyperfibrinolysis, 2nd heparinemia, 3rd fibrinogen deficiency, 4th platelet deficiency, and 5th factor deficiency. However, other personalized approaches to treatment can be equally effective.

Next, the most frequent coagulation alterations in the immediate period after cardiothoracic surgery are mentio-

TABLE 4.
Coagulation tests in some coagulopathies associated to heart surgery.

Coagulopathy	Coagulation viscoelastic tests	Standard coagulation tests
Hyperfibrinolysis	ML (in EXTEM or EX-test and FIBTEM or FIB-test) ↑ (in 60 min) or A5 and A10 (in EXTEM or EX-test) ↓ or CT (in FIBTEM or FIB-test) ↑↑ with normal ML (in APTEM or AP-test).	Prothrombin time ↑ APTT ↑ Thrombin time ↑ Fibrinogen ↓↓ Euglobulin lysis time ↓ Factors V and VIII ↓ D-dimer ↑↑
Heparinemia	CT (in INTEM or IN-test) ↑ with normal CT (in HEPTEM or HI-test).	APTT ↑ Thrombin time ↑
Factor deficiency	CT (in EXTEM or EX-test) ↑ (vitamin K-dependent coagulation factors) CT (in INTEM or IN-test) ↑ with CT (in HEPTEM or HI-test) ↑ (intrinsic pathway factors) with normal FIBTEM or FIB-test.	APTT ↑ Prothrombin time ↑ (vitamin K-dependent coagulation factors) Normal fibrinogen or ↓ Normal number of platelets or ↓ (hemodilution)
Protamine excess	CT (in INTEM or IN-test) ↑ with CT (in HEPTEM or HI-test) ↑ normal CT (in EXTEM or EX-test)	APTT ↑ Thrombin time ↑ Normal prothrombin time
Platelet deficiency	A5, A10 and MCF (in EXTEM or EX-test) ↓ with Normal A5, A10 and MCF (in FIBTEM or FIB-test)	Number of platelets ↓ and/or Smear with no platelet aggregation
Fibrinogen/ fibrin deficiency	A5, A10 and MCF (in EXTEM or EX-test) ↓ with A5, A10 and MCF (in FIBTEM or FIB-test) ↓	Fibrinogen ↓

CT: coagulation time or R-time; **A5:** amplitude in 5 min of CT; **A10:** amplitude in 10 min of CT; **MCF:** maximum clot firmness or maximum amplitude; **ML:** maximum lysis; **APTT:** activated partial thromboplastin time; **↑:** prolonged; **↓:** reduced or decreased.

ned, along with the most widely used therapeutic resources and their usual doses.

a) Treatment for hyperfibrinolysis:

* ***Epsilon aminocaproic acid***:[13]

Presentation: 2 g ampoule (Ipsilon®).

Dose: 4 to 5 g diluted in 250 ml of IV saline solution (SS) or dextrose (D5%) over one hour, followed by continuous infusion of 1 g/h over 8 hours or until bleeding control. Maximum dose 30 g/day.

* ***Tranexamic acid***[14]

Presentation: 5 ml ampoule with 500 mg (Arotran®).

Dose: in the postoperative period: 500-1000 mg (if not used during the surgery, a 1 g dose is probably the most appropriate) or 25 mg/kg. This dose can be repeated every 8 h. It can be directly administered by intravenous access slowly, over a time of no less than 1 ml/min, or diluted in SS or D5%.

b) Treatment for heparinemia:

* ***Protamine***[15]

Presentation: 5000 U ampule in 5 ml (protamine 1000 Rivero®).

Dose: 2500-5000 U or 30-60 U/kg. Administration: IV access, diluted in 100 ml of SS over 20 minutes.

c) Treatment of fibrinogen deficiency:

* ***Cryoprecipitate***[16]

Dose: initially 1 unit/10 kg of weight and later following clinical control.

* ***Fibrinogen concentrate***:[16]

Presentation: ampoule. One gram of lyophilized powder, reconstituted with sterile water (Haemocomplettan®).

Dose: 1-2 g or 25 mg/kg initially, with successive administration as required.

d) Treatment of platelet deficiency:

* ***Desmopresin***[17]

Presentation: ampoule: 1 ml, with 4 μg/kg (maximum 20 μg – 5 amp).

* ***Platelet concentrates (individual)***[18]

Presentation: platelets suspended in plasma volume of 50-70 ml.

Dose: 1 individual concentrate per each 10 kg of weight or 1 apheresis.

e) Treatment for factor deficiency:

* ***Fresh frozen plasma***[5]

Dose: 10-15 ml/kg – usually 4 U (increase the coagulation factors of the patient by 10%).

* ***Prothrombin complex*** (Factor II, factor VII, factor IX and factor X)[19]

Protromplex Total Tim 4®: presentation: 600 IU/20 ml, Beriplex P/N®: presentation 500 IU, Octaplex®: presentation 500 IU.

Dose: initial 15-25 IU/kg or desired increase in Quick value (in % of normal) x body weight (Kg) x 1.2

* ***Recombinant activated factor VII*** (rFVIIa) (Novoseven®)

Presentation: ampoule of 1 mg (50 KIU) and of 5 mg (250 KIU).

Dose: 40-80 μg/kg have been used, or even higher. Recently, using doses less than <20 μg/kg has been proposed, in early and rescue therapy, with no unwanted effects.[20] Use is controversial and requires a risk/benefit evaluation of individual patients.

6) Does bleeding require surgical treatment, even in the presence of coagulopathy?

Before, it was mentioned that a bleeding by surgical

cause could be associated to a coagulopathy (bleeding by surgical cause with incomplete replenishment of blood products or excessively treated with crystalloid fluids, producing hemodilution). Furthermore, if pericardial clots appear, producing coagulopathy by factor consumption, the latter will not improve until they are surgically removed.

On the other hand, bleeding by coagulopathy can produce cardiac tamponade, requiring urgent surgical treatment.

8. CONCLUSION

Excessive bleeding by coagulation alterations is still observed in cardiothoracic surgery, and it worsens the outcome. To help with diagnosis, there are standard coagulation tests, and more recently, viscoelastic tests. These two types of tests differ in their methodology and both have advantages and disadvantages. Having both types of tests increases the diagnostic capacity in the perioperative periods of heart surgery patients.

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