

Clinical application of viscoelastic point-of-care tests of coagulation-shifting paradigms

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ABSTRACT

Bleeding during cardiac surgery, liver transplant, trauma and post partum hemorrhage are often multifactorial and these factors are dynamic as new factors crop up during the course of management. Conventional tests of coagulation offer information of a part of the coagulation system and also is time consuming. Viscoelastic point of care tests (VE POCTs) like rotational thromboelastometry, thromboelastogram and Sonoclot, are based on analysis of the viscoelastic properties of clotting blood and provide information for the entire coagulation pathway. In this comprehensive review being presented here, we have examined the pros and cons of VE POCTs including clinical, cost and survival benefits. The recommendations of the various guidelines regarding use of VE POCTs in various scenarios have been discussed. The review also tried to offer suggestions as to their optimal role in management of bleeding during cardiac surgeries, extracorporeal membrane oxygenation, left ventricular assist devices, liver transplant and briefly in trauma and postpartum hemorrhage.

Keywords: Cardiac surgery, liver transplant, point of care tests, postpartum hemorrhage, rotational elastometry, sonoclot, thromboelastograph, trauma, viscoelastic

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INTRODUCTION

Blood and blood products are precious resources and demand is often in excess of supply. Mortality risk following allogenic blood transfusion increased in direct relation to the number of units of red blood cells (RBCs) transfused and was associated with risk adjusted reduction in survival for both, early (upto 6 months) and late (upto 10 years of follow-up) phases.^[1] Empirical therapy to control bleeding and to restore euolemia often leads to inappropriate use of blood products and indiscriminate use of crystalloid and colloids may further worsen the bleeding with adverse consequences. Perioperative monitoring of blood coagulation is important for prompt and accurate

diagnosis of the potential pathological causes of bleeding and to guide appropriate therapy.

Viscoelastic point-of-care tests of coagulation (VE POCTs) have been extensively used in recent years and have been evaluated for their utility in comparison to conventional coagulation tests (CCT) in different surgical settings.^[2-11] A comprehensive review presented here was necessitated by the reports^[3-8] and fresh guidelines^[9-11] that appeared since the last prominent review a couple of years ago^[2] and to offer suggestions as to their optimal role in management of bleeding during cardiac surgeries, extracorporeal membrane oxygenation (ECMO), left ventricular

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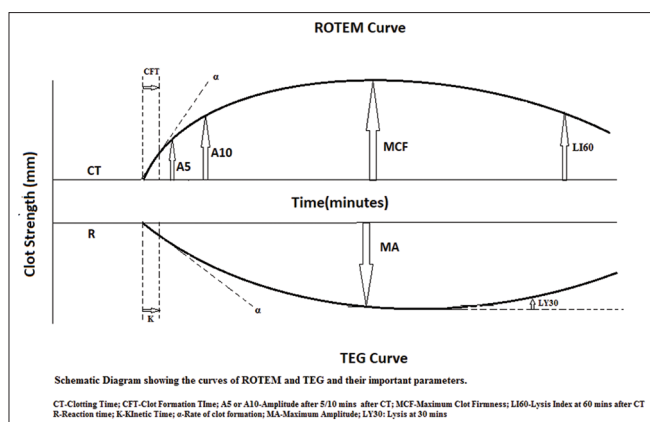


Figure 1: Schematic diagram of TEG® and ROTEM® curves with their corresponding parameters.

assist devices (LVAD), vascular surgeries, trauma, liver transplant (LT), and postpartum hemorrhage (PPH).

VISCOELASTIC MEASURES OF COAGULATION

Three viscoelastic assays of coagulation available are thromboelastogram (TEG), rotational thromboelastometry (ROTEM), and Sonoclot. The different TEG and ROTEM tracings are depicted in Figure 1.^[12]

These tests are based on analysis of the viscoelastic properties of clotting blood and provides comprehensive information for the entire coagulation pathway from clot formation, clot retraction, and to the dissolution of blood clot.

1. Rotational thromboelastometer, ROTEM® (Pentapharm, GmbH, Munich, Germany) offers four important assays—EXTEM, INTEM, FIBTEM, and APTEM—to assess different aspects of hemostasis and coagulation pathways.^[13]

EXTEM assay: In this assay, activity of extrinsic pathway of coagulation is explored by using tissue factor to activate the coagulation cascade. Information received from use of EXTEM assay are the clotting time (CT) and the measure of the maximum clot firmness (MCF) at 10 min (A10) after initiation of coagulation cascade. CT measures the time to the initiation of the fibrin formation and increase in CT reflects delay in initiation of coagulation cascade because of deficiency of thrombin formation. Reduced MCF at A10 (mm) suggests deficiency of either platelet function and or of fibrinogen.^[14]

INTEM assay: In this assay, unlike EXTEM, activity of the intrinsic pathway is explored and contact activator, ellagic acid (INTEM) is used to activate the coagulation process. INTEM assay is used to evaluate effect of heparin and of protamine.

FIBTEM assay: In this assay, cytochalasin D is added to the whole blood sample along with the tissue factor. The cytochalasin D inhibits platelet aggregation. The MCF thus obtained is entirely reflective of fibrinogen content and a reduced value of FIBTEM A10 is therefore suggestive of hypofibrinogenemia as the contribution of platelets to MCF had been negated.^[14] FIBTEM A-10 is also seen to have good correlation with Clauss measure of fibrinogen.^[7] No separate assay exists for assessing the platelet function, but it can be inferred from existing ROTEM® parameters. A10 EXTEM <35 mm and A10 FIBTEM >8 mm have been shown to suggest platelet dysfunction.

APTEM: It uses aprotinin or tranexamic acid in addition to tissue factor and provides information regarding the effect of antifibrinolytic drugs.

2. Thromboelastogram (TEG®) is another commonly used VE POCT based on measures of the viscoelastic forces of clotting blood. Two tests are commonly available.^[15]
 - (a) Kaolin (K) Test: Coagulation is activated by kaolin and provides global assessment of coagulation cascade.
 - (b) Functional Fibrinogen test: It uses abciximab to inhibit platelet activity and thus provides information about the coagulation cascade minus the contribution from platelet activity.

The various parameters available from TEG curve are described in Table 1.

3. Sonoclot: It is yet another VE POCT and uses a mechanism different from TEG and ROTEM. It evaluates the blood coagulation using changes in impedance to movement of Sonoclot probe imposed by the developing clot to yield a signature pattern from which different aspects of coagulation cascade may be inferred.

Espinosa A *et al.* (2014), compared TEG, ROTEM, and Sonoclot with CCT in setting of elective cardiac surgery with cardiopulmonary bypass (CPB). No correlations were found between international normalized ration (INR) and the TEG variable R (reaction time), the ROTEM CT (clotting time), or the Sonoclot Son ACT (time until fibrin formation). Neither did any of the VE POCTs showed correlations with platelet counts. However, TEG MA (clot strength), ROTEM MCF (clot strength) and the Sonoclot Clot Rate (rate of fibrin formation) correlated with fibrinogen levels at all time points. Authors concluded that TEG and ROTEM can be used to detect postoperative hemostatic changes following cardiac surgery, whereas Sonoclot was less suitable for the purpose.^[16] In a similar population, Sharma S *et al.* (2018) compared

Table 1: Description of parameters used in TEG® and ROTEM®

Parameter	Description
TEG® parameters	
R	<i>Reaction Time</i> , represents the initiation of clot formation and is defined as the time from the start of the test till 2 mm amplitude is reached. Correlates with coagulation factor activity and thrombin generation. Prolonged R time reflects a deficiency of coagulation factors
ACT	<i>Activated Clotting Time</i> , surrogate of R time in the rapid TEG assay, in which tissue factor activates coagulation and accelerates measurements.
K	<i>Kinetics</i> , describes kinetics of clot formation and denotes time taken by clot amplitude to increase from 2 mm to 20 mm
Alpha angle	Slope between r and k, indicates the rate of clot strength achieved. Correlates with fibrinogen concentration and function
MA	<i>Maximum Amplitude</i> , indicates platelet-fibrin interaction
A	<i>Amplitude</i> at a fixed time, A5 (Amplitude at 5 minutes), A10 (Amplitude at 10 minutes),
CL or LY30	<i>Clot Lysis</i> or TEG lysis at 30 mins after MA, Reflects fibrinolysis
ROTEM® Parameters	
C	<i>Clotting time</i> , the time from the start of measurement until initiation of clotting, i.e., initial thrombin formation. CT is mainly dependent on the availability of coagulation factors and heparin action. Assesses the initiation of clotting, thrombin formation, start of clot polymerisation. CT-EXTEM >90 sec implies poor clot initiation.
CFT	<i>Clot Formation Time</i> , the time from initiation of clotting until a clot firmness of 20 mm is detected. Assesses the function of fibrin polymerization, stabilization of the clot with thrombocytes and factor XIII
Alpha angle	Slope of tangent at 2 mm amplitude
MCF	<i>Maximum Clot Firmness</i> , Assesses the firmness of the clot. Increased stability of the clot by the polymerized fibrin, thrombocytes as well as factor XII. It depends upon platelet function and fibrinogen
LY	<i>Clot Lysis</i> , Reduction of the clot firmness after MCF. Indicates stability of clot. A maximum lysis (ML) <15% is considered normal, ML >15% indicates hyperfibrinolysis
A10 EXTEM®	Amplitude of clot firmness (10 mins after CT in EXTEM assay. Value of 35 mm implies impaired clot formation either because of low platelet count or hypofibrinogenemia
A10 FIBTEM®	Amplitude of clot firmness 10 mins after CT, detects hypofibrinogenemia as platelet aggregation is inhibited. Correlates well with Clauss measure of fibrinogen, when less than equal to 8 mm. Suggests severe hypofibrinogenemia (<100 mg/dl) when it is <5 mm
ROTEM® Assays	
FIBTEM®:	Fibrin-based extrinsically activated thromboelastometric test with tissue factor and cytochalasin D for platelet inhibition. It can isolate fibrin polymerization from platelet-fibrin interactions and so provides better detection of hyperfibrinolysis, performed in citrated samples. Correlates with functional fibrinogen test in plasma
APTEM®	Tissue factor and phospholipids activation with tranexamic acid/aprotinin
INTEM®	The intrinsic pathway is activated by a contact activator, ellagic acid, to assess the clot formation and fibrinolysis, performed in citrated samples
EXTEM®	Extrinsic initiation of coagulation pathway is activated by tissue factor (thromboplastin from rabbit brain), performed in citrated samples,
HEPTEM®	Heparinase-modified intrinsic activation which identifies potential heparin effects

TEG® parameters with CCT and reported that there was significant correlation of platelet count with MA values (postoperative samples), fibrinogen levels, and alpha angles with MA (preoperative and postoperative samples). Further, in the postoperative period, r time, k-time, and MA values were found to be significantly better predictors of bleeding, whereas, none of the CCTs showed any such correlation.^[17] Singh SA *et al.* (2020) compared TEG with ROTEM in liver transplant (LT) recipients and established that significant linear association could be found for only CFT (ROTEM) with K (TEG) and of MA (TEG) with MCF (ROTEM).^[6] For the other parameters, there was either moderate or poor correlation. Thus, neither the values of these two tests are interchangeable nor are the guidelines that govern use of either of the devices.^[6] The differences may be explained by different cups and pins used in both systems (ROTEM® cups and pins use plastic with greater surface charge, thus allowing greater contact activation compared with cups and pins used in TEG®) and different composition and concentrations of the coagulation activators.^[18]

CONVENTIONAL COAGULATION TESTS VERSUS POINT-OF-CARE TESTS OF COAGULATION

Conventional coagulation laboratory tests (CCT) like prothrombin time (PT), activated plasma thromboplastin time (APTT), INR, fibrinogen assay, etc., test the individual components of the coagulation cascade in isolation, whereas the VE POCTs are performed on whole blood and all the activities that otherwise occur *in vivo* during the natural course of clot formation, like platelet aggregation, interaction of platelets with coagulation factors, fibrin cross-linking, and clot lysis are studied.^[19]

Advantages of VE POCTs over CCTs thus include:

1. CCTs assess the function of a part of the coagulation system, whereas the thromboelastometric tests provide information about the entire clot formation kinetics and simultaneously evaluate intrinsic and extrinsic pathways of coagulation.^[7]
2. VE POCTs provide graphical representation of coagulation activity in real time besides providing with the actual values for different measured parameters

Table 2: Classes of recommendation given by the Guidelines

Classes of Recommendation	Definition
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful and effective.
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III	Evidence/general agreement that the given treatment/procedure is not useful/effective and may sometimes be harmful.

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Table 3: List of acronyms and explication

Abbreviation	Acronym
AKI	Acute Kidney Injury
APTT	Activated plasma thromboplastin time
A10	Amplitude after 10 mins of CT
BSH	British Society for Haematology
CABG	Coronary artery bypass graft
CCT	Conventional Coagulation tests
CI	Confidence Interval
CLD	Chronic Liver Disease
CPB	Cardio pulmonary bypass
CT	Clotting time
ECMO	Extra Corporeal Membrane Oxygenation
Xa	Activate factor X or Stuart-power factor
FiO ₂	Fraction of Inspired oxygen
FDP	Fibrin degradation products
FFP	Fresh frozen plasma
FF-MRTGG	Functional fibrinogen-maximum rate of thrombus generation
ICU	Intensive Care Unit
INR	International Normalized Ratio
K time	Speed of clot formation
k-TEG	Kaolin Thromboelastography
LMWH	Low molecular weight heparin
LT	Liver transplant
LVAD	Left Ventricular Assist Device
MA	Maximum amplitude
MCF	Maximum clot firmness
NICE	National institute for health and care excellence
OLT	Orthotopic liver transplant
PaO ₂	Partial pressure of arterial oxygen
PCC	Prothrombin Complex Concentrate
POCT	Point of Care tests
PPH	Post partum hemorrhage
PRBC	Packed red blood cell
PT	Prothrombin Time
R time	Reaction time
RCT	Randomized controlled trials
RBC	Red blood cells
ROTEM®	Rotational Thromboelastometry
SCA	Society of Cardiovascular Anesthesiologists
TEG®	Thromboelastogram
TIC	Trauma induced Coagulopathy
UFH	Unfractionated Heparin
VE	Viscoelastic
VEM	Viscoelastic measure of coagulation
VE POCT	Visco elastic point of care tests of coagulation
VKA	Vitamin K Antagonist

within a short time. This allows faster diagnosis of cause of coagulopathy and facilitates earlier administration of targeted treatment.^[2]

- VE POCTs are performed on whole blood. Time needed to separate plasma from blood sample

for performing the tests is therefore saved.^[13] Thromboelastometry results are available in 15–20 min or lesser compared with longer turnaround time of 40–60 min required for CCTs.^[7] Selective use of one or two components of ROTEM even allows relevant values available as early as within 5–10 min.^[4,5]

- CCTs often do not reflect the true clinical status. In setting of cardiac surgery using CPB, no clinically relevant differences in any of the laboratory measurements (fibrinogen, V, VII, VIII, IX, and FDP) between patients with normal postoperative blood loss and those defined as bleeders is seen, suggesting insufficiency of CCTs at diagnosing clotting defect.^[20] In setting of chronic liver disease (CLD), despite PT, APTT, and INR indicating coagulopathy, patients do not exhibit any gross bleeding tendency because hemostasis is proven to be re-balanced in stable CLD as exhibited by VE POCTs.^[11]

Limitations of VE POC tests

VE POC tests are based on use of whole blood, and are therefore likely to be different from laboratory tests in conditions such as hemodilution and platelet dysfunction (e.g., CPB).^[5] VE POC devices require calibration at regular intervals and skilled operator to run the tests. The sensitivity of the reagents differs between different manufacturers and even between different sets of reagents.^[5] These tests are expensive compared to CCTs and are not yet incorporated in different guidelines [Tables 2 and 3].^[5]

WHETHER POC TESTS OF COAGULATION INFLUENCE OUTCOME PARAMETERS?

Most of the studies and reviews have been done in context of cardiac surgeries. Weber CF *et al.* investigated and compared CCT with VE POCTs for guiding the hemostatic therapy in complex cardiac surgeries. Interim analysis of data from their study suggested significant reduction in transfusion rates of blood products in patients managed by VE POCT-based algorithm compared with CCT-based algorithm. The study was therefore aborted early because

of ethical limitations and sample size was not achieved. Also VE POCTs patients had higher ratio of partial pressure of arterial oxygen to fraction of inspired oxygen in the postoperative period, shorter postoperative ventilation time, shorter ICU stay and lower mortality during 6 months of follow-up. The authors however admitted that the study was not adequately powered to find differences in these parameters.^[21]

Whiting P *et al.* performed a systematic review in setting of cardiac surgery and found that there was significant reduction in transfusion of blood and blood products in the group whose bleeding was managed with VE POCT compared to the group managed with CCTs. None of the RCTs evaluated sonoclot. The authors concluded that VE POCTs proved cost saving in setting of cardiac surgery.^[22]

In another systemic review of VE POCT in cardiac surgeries, authors concluded that TEG[®]/ROTEM[®] guided algorithms for management of coagulopathic hemorrhage reduced the number of patients requiring transfusion of blood products, but had no effect on mortality, stroke, prolonged intubation, emergency reoperation for bleeding, or length of ICU and hospital stay. Significant reduction in the frequency of severe acute kidney injury (AKI) was also seen in four trials that used VE POCT.^[2]

A Cochrane database review compared transfusion guided by clinical judgment, standard laboratory tests or a combination of two with VE POCTs. The review suggested reduced mortality (7.4% vs, 3.9%; Risk ratio 0.52, 95% CI 0.28–0.95) with use of VE POCTs compared to others.^[23] Fewer participants managed with VE POCTs developed AKI needing dialysis. The review also concluded positive effect of VE POCTs compared to other methods on the number of patients receiving PRBC, FFP, and platelets. No difference was seen in the proportion of postoperative patients needing surgical re-intervention, had excessive bleeding or requiring massive transfusion. The authors opined that the application of VE POCT guided transfusion strategies may reduce the need for blood products and improve morbidity in patients with bleeding, primarily in setting of elective cardiac surgery but cautioned that the quality of evidence to support the findings was low.^[23]

Another study involving cardiac surgery patients compared blood management in two cohorts—one by CCT-guided algorithm and the other by ROTEM-guided algorithm.^[4] Authors reported significantly lower blood loss, absolute risk for transfusion of RBCs (17%) and FFP (12%) in the ROTEM-guided algorithm patient group and also significant reduction in length of hospital stay but found

no difference in transfusion of thrombocyte concentrate and in the rate of re-thoracotomies or mortality. The expenses and cost saved per patient in ROTEM-guided algorithm patient group was calculated to be substantial. Authors also claimed that ROTEM guidance allowed 25 times earlier initiation of treatment of perioperative bleeding than using CCTs, thus less blood was lost, and less crystalloids and colloids needed to be transfused to maintain normovolemia, thereby avoiding hemodilution while awaiting CCT results.^[4]

Caie L *et al.* (2019) performed a systematic review and meta-analysis to assess the effects of TEG/ROTEM-guided transfusion algorithm versus CCTs in adult cardiac surgical patients undergoing combined CABG and valve replacement with CPB. Authors did not find significant difference in incidences of surgical re-exploration, massive bleeding, massive transfusion, length of ICU or hospital stay, or mortality between the two groups. However, the frequencies of transfusion of blood products were significantly higher in control group. The authors also failed to find any association between reduced transfusion requirements and improvement of long-term prognosis despite the potential benefits of TEG/ROTEM in the management of bleeding after cardiac surgery.^[8] Several factors could be attributed for the observations with regards to long-term prognosis, other than blood loss and transfusion, like surgical skills, duration of surgery and of CPB and aortic cross-clamp time, presence of co-morbidities, complexity of surgery, hematocrit level, platelet count, temperature on arrival to ICU, etc.^[8]

Haensig M *et al.* in a retrospective analysis compared cardiac surgical patients who had more than expected bleeding in the postoperative period (>200 ml/h) into two groups. Bleeding in one group was managed by algorithm based on four chamber ROTEM-guided blood component transfusion protocol and the other group was managed by algorithm-based on CCTs. They found that there was no significant difference between the study groups in transfusion requirement of any of the blood product or incidence of repeat thoracotomies, time spent on mechanical ventilation, need of dialysis because for AKI, 30 days and 5 years mortality. The 24 h drainage was though lesser in the ROTEM group, but difference was statistically not significant.^[3]

There could be ambiguity regarding evidence of VE POCTs to improve morbidity and mortality because it is not the devices and assays, rather clinicians' interpretation of these tests and the consequent treatment decisions which influence outcome.^[24]

WHAT GUIDELINES SAY

National Institute for Health and Care Excellence (NICE) recommends using POCTs like ROTEM and TEG to monitor and manage hemostasis during and after cardiac surgery. Sonoclot is being advocated for research purpose only. NICE guidelines have refrained from suggesting routine use of VE POCTs for emergency control of bleeding following trauma and during PPH, citing inadequate evidence and have instead advised further research to delve into the clinical benefits and cost-effectiveness of these POCTs.^[25]

The American Society of Anesthesiologists Task Force on perioperative blood management released the practice guidelines in 2015. The task force agreed that TEG/ROTEM-guided algorithms reduced the blood transfusion requirements in presence of coagulopathy, but had still advised to use platelet count and CCTs or VE POCTs, based on availability, without giving preference to any of them.^[26]

The Task Force on Patient Blood Management for Adult Cardiac Surgery of the European Association for Cardio-Thoracic Surgery and the European Association of Cardiothoracic Anesthesiology in 2018 did not recommend routine use of viscoelastic and platelet function testing to predict bleeding in patients who were not on any antithrombotic treatment (Class 3 Level C). These task forces, however, did suggest that perioperative treatment algorithms for the bleeding patient should be based on VE POCTs to reduce the number of transfusions.^[27]

The British Society for Hematology (BSH) in 2018 published guidelines for using VE POCTs for management of major bleeding in four common scenarios, namely obstetric hemorrhage, liver disease, cardiac surgery, and trauma hemorrhage which are mentioned in appropriate places.^[28]

The fifth edition of the European guideline on management of major bleeding and coagulopathy following trauma (2019) recommended that routine practice should include early and repeated monitoring of hemostasis with CCTs and/or a viscoelastic method, (Grade 1C) without giving preference to any set of methods. The resuscitation measures should be continued using a goal-directed strategy, guided by CCTs or VE POCTs (Grade 1B). When transfusion of FFP is contemplated, it should be guided by standard laboratory coagulation screening parameters (PT and/or APTT > 1.5 times normal and/or viscoelastic evidence of a coagulation factor deficiency) (Grade 1C). Regarding use of coagulation factor concentrate

for treatment of coagulopathy, CCTs or POCTs should be used to establish evidence of functional coagulation factor deficiency (Grade 1C). In instances of bleeding with normal fibrinogen level, it is suggested that platelet concentrate be transfused based on delayed coagulation initiation using VE POCTs (Grade 2C). For establishing bleeding because of hypofibrinogenemia too, it is suggested to employ either viscoelastic signs of functional fibrinogen deficit or a plasma Clauss fibrinogen assay, before initiating administration of cryoprecipitate.^[9]

The society of Cardiovascular Anesthesiologists (SCA) issued clinical practice improvement advisory for management of perioperative bleeding and hemostasis in cardiac surgery patients in 2019. It recommended the application of transfusion algorithms incorporating predefined intervention triggers based on POC coagulation monitoring assays to guide hemostatic intervention. The SCA also suggested implementation of transfusion and coagulation management algorithms (based on ROTEM/TEG) can reduce transfusion associated adverse events and that the goal-directed therapy with coagulation factor concentrates (fibrinogen and/or PCC) may reduce transfusion associated adverse events.^[10] The SCA advisory also emphasizes on measures to prevent bleeding like correction of hypothermia, hypocalcemia, anemia, and acidosis and they are concise, offers algorithms for management of bleeding post-cardiac surgery based on POCTs as well as CCTs.

WAY FORWARD: ROUTINE TO RATIONAL

Cardiac surgery

In the study by Haensig M *et al.* in the sub group of patients whose CPB time was prolonged (>115 mins), ROTEM-guided management of bleeding resulted in significantly lower 24 h drainage.^[3] VE POCT for coagulation therefore might be more useful in selected sub group of patients, for example, prolonged CPB time and routine use may not offer any advantage over CCT but has definite cost implications.^[4]

ROTEM has a negative predictive value of 82% for excluding diffuse coagulopathy as the cause of bleeding and instead suggest surgical reasons for bleeding^[29,30] CCT, whereas are not good for the purpose as suggested by a Cochrane database review which reported negative predictive accuracy of only 50% for diagnosis of coagulopathy.^[23]

While making cost-benefit analysis using ROTEM, studies used entire set of assays (EXTEM, INTEM, FIBTEM, APTTEM) available in ROTEM which made it a costly choice.^[5] The selection of specific ROTEM assay may instead be made, based on the understanding of the

pathophysiology of any given clinical scenario and would thus save cost while still allowing diagnosis of the cause for coagulopathy.^[31] The three most important causes of coagulopathy in cardiac surgery are thrombocytopenia/platelet dysfunction, hypofibrinogenemia, and impaired thrombin generation.^[32] and using only two components of ROTEM, namely EXTEM (A10) and FIBTEM (A10) could reduce transfusions.^[14]

Role in extra corporeal membrane oxygenation and left ventricular assist devices

ECMO and LVAD provide critical support to patients with life threatening cardiac or pulmonary failure.^[33] Management of anticoagulation in patients with ECMO or LVAD is a tight rope walk as both bleeding (5-81%) and thrombotic (about 18%) complications are common.^[34] Unfractionated heparin (UFH) is the most common anticoagulant in circuits.^[33] In patients with LVAD, antiplatelet agents are also part of therapeutic regime.^[33] Patients on LVADs used as destination therapy are frequently managed with LMWH or vitamin K antagonist (VKA).^[33] As of now, the standard practice in most of the centres managing LVADs is to use of APTT to monitor UFH, anti-Xa assay to monitor action of LMWH and INR to monitor VKA.

Petricivic M *et al.* (2015) in their review of use of VE POCTs for management of bleeding in such patients, although favored the use of personalized management of bleeding based on VE POCTs also advocated the need for prospective trials focussed on bleeding and thromboembolic events as primary endpoints, with the aim of elucidating cutoff values or reference ranges according to which hemostatic management may be accomplished.^[34] Laine A *et al.* (2016) reported that in patients on ECMO or LVAD, hypocoagulation suggested by low MCF values on FIBTEM or EXTEM was associated with increased bleeding, whereas hypercoagulability could not predict thromboembolic disorders.^[35] Shen L *et al.* (2017) reported that in patients with VAD, shortened CT or increased MCF on ROTEM may predict thromboembolic complications. They also found that low MCF values were associated with episodes of bleeding. Use of VE POCTs was associated with less mortality and was more cost-effective.^[36] To date, there have been no randomized multi-institutional trials comparing TEG or ROTEM with APTT, PT/INR, or anti-Xa levels for monitoring and dose adjustment of anticoagulation and antiplatelet medications in such patients.^[33] Colman E *et al.* (2019) retrospectively compared patients on ECMO whose bleeding was managed either with APTT alone or in combination with TEG. They reported that incidence of major bleeding did not differ between the two groups, whereas the mortality

and incidences of retroperitoneal bleeding were less in the group managed with TEG.^[37] Thus, there are no unequivocal cutoff values for the various parameters which could discriminate between patients at increased risk of bleeding or thrombotic events nor robust evidence to suggest use of VE POCTs in patients with ECMO or LVADs.^[34]

Vascular surgery

Bleeding in vascular surgery is multifactorial—patient factors include commonly aged population, usually on antiplatelet and anti-thrombotic medications, intraoperative heparinization, and renal impairment.^[38] Acute coagulopathy during vascular surgery is deemed to be similar to trauma induced coagulopathy (TIC), with the severity correlated directly to the severity of shock and tissue hypoperfusion. It is precipitated by tissue injury and hypotension which in turn lead to dilutional coagulopathy, metabolic acidosis, hypothermia, hyperfibrinolysis, and systemic inflammatory response.^[38]

Chee YE *et al.* (2016) in a review article lamented that acquired coagulopathy in vascular procedures has not been well studied and evidence on the management of major bleeding during vascular surgery was largely derived from trauma or cardiac surgery.^[38] The guidelines on trauma do recommend early and repeated monitoring of coagulation following trauma with either CCTs or VE POCTs (Grade 1C).^[9]

As in other situations, in spite of the seeming advantage of VE POCTs over CCTs in TIC, a Cochrane review failed to throw adequate evidence to support the use of VE POCTs for accurate diagnosis of reason of coagulopathy.^[39] Another review which studied the role of TEG or ROTEM for diagnosis of coagulopathy, transfusion guidance, and mortality noted that although the VE POCTs decreased need for blood product transfusion but failed to make any difference in mortality or other important outcomes.^[40]

Role in trauma

TIC is seen in about a quarter of patients with polytrauma (INR>1.5) and is associated with death because of hemorrhagic shock, venous thromboembolism, and multiple organ failure.^[41] It is recognized that TIC is characterized by hypofibrinogenemia and increased fibrinolytic activity. Fifth edition of “Management of major bleeding and coagulopathy following trauma” recommends early and repeated monitoring of hemostasis using either CCT (Gr 1A) or VE POCT methods (GR 1C).^[9] A Cochrane review and meta-analysis in 2016 demonstrated that the utilization of ROTEM and TEG to monitor

coagulation and to guide treatment translated into improved survival and reduction of blood transfusions in bleeding patients with and without trauma and TIC.^[23] VE POCTs may be preferred because of faster diagnosis and early initiation of treatment. ROTEM assays, FIBTEM-MCF and EXTEM-CT, and TEG functional fibrinogen should provide early and sufficient information to guide the therapy. Wahleen BM *et al.* reported that implementation of VE POCT, viz TEG-guided management of bleeding in major trauma is feasible and promising.^[42] Similar finding was expressed by Gratz J *et al.* among patients with traumatic brain injury.^[43] Thus, all bleeding patients of trauma must receive tranexamic acid 1 g within 3 h of injury and another 1 g as infusion over next 8 h. If available two assays of ROTEM, that is, FIBTEM and EXTEM or TEG, preferably FF TEG may be employed.

Other major areas of use of VE pocts

Role in liver transplants

Changes in coagulation status in patients undergoing LT is dynamic because of bleeding, hemodilution, and hyperfibrinolysis. Hyperfibrinolysis being the commonest cause of non-surgical bleeding during LT, a prospective observational study compared TEG and ROTEM in detection of hyperfibrinolysis. In the ROTEM assay, FIBTEM had the highest sensitivity (94%) compared to EXTEM (46%) and k-TEG (23%) in detecting hyperfibrinolysis.^[44] In another study by Hashir A *et al.* in patients of orthotopic liver transplant, MCF (maximum clot firmness) could be reliably predicted as early as 5–10 min after CT from A5 and A10 values of EXTEM and FIBTEM. Thus, early ROTEM variables A5 and A10 values of EXTEM and FIBTEM can effectively predict thrombocytopenia and hypofibrinogenemia.^[5] In the study, EXTEM A5 of 18 mm and A10 of 25 mm predicted a platelet count of $<50,000/\text{mm}^3$ with good specificity and sensitivity. EXTEM A5 of 21 mm and A10 of 30 mm also predicted a fibrinogen level of $<100 \text{ mg/dl}$ with good specificity and sensitivity.^[5] BSH guidelines also advocates use of VE POCTs in LT surgery to reduce overall need for transfusion.^{(Grade IC).}^[28]

Role in PPH

Coagulation defects account for about 1% of cases of PPH.^[45] Within 1 h of child birth, serum concentration of tissue plasminogen activator doubles because of tissue damage causing early activation of fibrinolysis after delivery.^[46] Hypofibrinogenemia ($<2 \text{ gm/L}$) is the strongest predictor of PPH progressing to severe one with PPV of 100%.^[15]

Ondondo BO *et al.* (2018) reported that in patients with PPH, FIBTEM (A5) assays correlate well with fibrinogen

level and can be used to guide fibrinogen therapy. EXTEM assay, which measures the contribution of platelets to coagulation, correlates well with platelet count in this group of patients.^[13] TEG provides a rapid and reliable estimate of hypofibrinogenemia ($\leq 2 \text{ gm/dl}$) and/or thrombocytopenia $\leq 80,000/\text{dl}$. Among the various parameters assessed, functional fibrinogen-maximum rate of thrombus generation (FF-MRTGG) has an edge over other parameters as its value is available within $\leq 5 \text{ min}$.^[15] While using ROTEM, only one component, that is, FIBTEM is recommended. If FIBTEM A5 $<7 \text{ mm}$ or less than 12 mm with ongoing bleeding, fibrinogen replacement may improve clinical hemostasis. (Grade 2C).^[28]

CONCLUSION

It is still unclear whether VE POCTs-based management of bleeding makes any difference in objective measures of surgical outcome like mortality, incidences of emergency re-sternotomy, stroke, ventilation time, ICU, and hospital length of stay when compared to CCTs. Guidelines do not strongly favor use of VE POCTs over CCTs. There is definite role of VE POCTs in selected high risk cases. A particular component of VE POCTs should be chosen based on unique pathophysiology of particular scenario to get the information earlier and be cost-effective.

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Conflicts of interest

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