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Review Article

PREHOSPITAL COAGULATION MONITORING OF RESUSCITATION WITH POINT-OF-CARE DEVICES

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ABSTRACT—A variety of point-of-care monitors for the measurement of hematocrit, hemoglobin, blood gas with electrolytes, and lactate can be used also in the prehospital setting for optimizing and individualizing trauma resuscitation. Point-of-care coagulation testing with activated prothrombin test, prothrombin test, and activated coagulation/clotting time tests is available for prehospital use. Although robust, battery driven, and easy to handle, many devices lack documentation for use in prehospital care. Some of the devices correspond poorly to corresponding laboratory analyses in acute trauma coagulopathy and at lower hematocrits. In trauma, viscoelastic tests such as rotational thromboelastometry and thromboelastography can rapidly detect acute trauma coagulopathy and give an overall dynamic picture of the hemostatic system and the interaction between its different components: coagulation activation, fibrin polymerization, fibrin platelet interactions within the clot, and fibrinolysis. Rotational thromboelastometry is shock resistant and has the potential to be used outside the hospital setting to guide individualized coagulation factor and blood component therapies. Sonoclot and Rheorox are two small viscoelastic instruments with one-channel options, but with less documentation. The point-of-care market for coagulation tests is quickly expanding, and new devices are introduced all the time. Still they should be better adopted to prehospital conditions, small, robust, battery charged, and rapid and use small sample volumes and whole blood.

KEYWORDS—Point of care, thromboelastography, lactate, hemoglobin, coagulation, trauma

INTRODUCTION

Point-of-care (POC) blood coagulation monitors could improve resuscitation regimens, especially when used in treatment protocols (1, 2). Current POC technology has been found to be reliable, and POC tests for prothrombin time international normalized ratio (PT/INR), activated partial thromboplastin time (aPTT), fibrinogen concentration, and viscoelastic tests such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) can predict massive transfusion when performed in-hospital and would have the potential to identify patients with increased risk of massive bleeding at an early prehospital stage. Reversal of coagulopathy with hemostatic drugs and coagulation factor concentrates may be a promising concept to limit blood loss, and use of prehospital POC monitoring could be an alternative to empiric treatments. Individualizing blood component therapy, transfusion packages, or whole-blood use is also an option.

However, most whole-blood POC devices are expensive. There are several optically and plasma-based laboratory coagulometers that are cheap and reliable, but not adapted for whole blood, which contains cellular components that cause interference (3). However, whole blood will better reflect *in vivo* hemostasis than testing with platelet poor plasma.

To suit prehospital trauma resuscitation, monitors should be small and portable, robust, and battery charged; have a small built-in printer or computer; be rapid; use small sample volumes; use whole-blood analyses; be adapted to unprocessed native and/or citrated blood samples; be temperature adjustable; and use electronic quality controls. Point-of-care devices, reagents, test cartridges, test cuvettes, tests strips, and quality control materials must withstand extremes and sudden changes in humidity, temperature, altitude, and electromagnetic interference (4–6). Also, effects of operators' skills need to be addressed. Most of the present POC systems have environmental constraints. The iSTAT (Abbot, Princeton, NJ) is such a multipotent handheld POC device and has been used both in tsunami and Katrina disasters (4). It measures hemoglobin (Hb), lactate, glucose, and electrolytes including ionized calcium, blood gas data, creatinine, and coagulation with activated clotting time (ACT) and PT/INR but is adapted to only 15°C to 30°C or 59°F to 86°F. The epoc (Alere Inc, Orlando, FL) is an alternative, newly introduced handheld blood gas, electrolyte, and metabolite monitor but with no coagulation analyses. The piccolo xpress (Abaxis, Union City, CA) has an extensive metabolic test range.

There should be a clear benefit for the time spent on analysis and weighed against the cost of implementing POC testing in the prehospital setting. Short transports rarely require POC testing, but the debate whether to "scoop and run" or "stay and play" is still ongoing. With the "stay or play" approach, a POC device might improve outcome.

POC hemoglobin monitoring

Admission hematocrit/Hb correlates well with signs of shock in trauma patients requiring emergency surgery secondary to

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bleeding, but also to rapid fluid shifts from the interstitial space into the vasculature (7). Optimizing Hb with blood transfusions is a vital principle in hemorrhagic shock and is also important for coagulation and primary hemostasis. Increasing Hb to more than 90 g/L can improve platelet margination (8) and primary hemostasis, but mechanisms and interactions of platelet size, leukocytes, flows, viscosity, red cell aggregability, and rigidity need to be better defined (9). Erythrocytes have several other prohemostatic mechanisms that need to be evaluated, including effects of different types of microparticles (8, 10). Hemoglobin measurements are important for guiding emergency resuscitation together with blood gases and lactate (1).

In an adult patient, Hb should increase by 7 to 10 g/L after each unit of erythrocyte concentrate transfusion (11). A smaller increase in Hb than expected may indicate continuing bleeding or overexpansion of the plasma volume. A greater increase in Hb than expected would indicate a constricted plasma volume. (One unit of erythrocyte concentrate here refers to around 40 g Hb in a volume of 250 to 300 mL, of which 7–10 mL is plasma and 100 mL is a nutrient solution.) It is difficult to assess blood loss in the emergency situation. Merlin et al. (12) compare fist size to surface area of small and large pools of blood present on the ground. They calculated with 20 mL blood per fist, and with short training, staff evaluation of real blood loss improved.

Established POC devices for whole-blood Hb are HemoCue (Angelholm, Sweden) (optical method) and iSTAT (conductivity method). Shahshahani et al. (13) found higher Hb levels measured by HemoCue than with a reference method. Furthermore, they saw a better correlation between a laboratory reference method and HemoCue for Hb levels less than 12.5 g/dL, which is of relevance in bleeding situations. The correlation was less strong for higher Hb levels and poor for Hb levels of more than 18 g/dL. Hopfer et al. (14) found lower Hb values with iSTAT as compared with HemoCue and a laboratory hematological method, and correlations decreased with plasma dilution. They therefore recommended an optical POC Hb method in patients with hypoproteinemia or substantial hemodilution, as can occur in trauma and massive transfusions.

Now there are several novel systems for continuous noninvasive blood Hb measurement such as Masimo Radical-7 Pulse Co-oximeter, Rev E ReSposable Sensor (Masimo, Irvine, CA), and Glasswing (OrSense, Petah-Tikva, Israel). Rice et al. (15) do not recommend the Masimo Radical-7 for transfusion decisions because of lack of accuracy. However, Sjöstrand et al. (16) found good agreement between invasive laboratory Hb and the noninvasive Masimo Radical-7 Pulse Co-oximeter and Rev E ReSposable Sensor Hb during crystalloid fluid resuscitation in an emergency room. These devices underestimated Hb with around 0.5 g/L. The Glasswing device is said to function also during peripheral vasoconstriction, but there are no publications registered on PubMed up to now.

Tissue Oxygenation

Pulse oximetry is routinely used to measure oxygenation in patients. The infrared light signal is decreased by skin, bone, and other organs and therefore cannot assess end-organ tissue oxygenation (StO_2). Near-infrared spectroscopy penetrates a broad range of tissues and uses reflection rather than direct transmission between an emitter and receiver pair and is therefore able to measure StO_2. This technique continues to involve in clinics and human studies. StO_2 changes preceded changes in blood pressure, heart rate, base deficit, serum lactate, and mental status (17). StO_2 also early identified trauma patients with massive transfusions or multiple organ dysfunction syndrome or those who experienced lower-extremity compartment syndrome or vascular limb injuries (17–19). StO_2 can also optimize resuscitation fluid and blood transfusion regimens (19).

POC blood gas, electrolyte, glucose, and lactate monitoring

Base deficit has been predicative of injury severity at hospital admissions; potassium level increase with onset of hemorrhagic shock and increased lactate indicate tissue hypoxia, and nonresponding to resuscitation predicts mortality (19). Triage glucose measurements can predict major injuries (19).

There are several handheld devices for blood lactate measurement on the market in addition to iSTAT and epoc mentioned above, with good correlation to laboratory methods (20).

Strategies to reduce acidosis and lactate will improve *in vitro* coagulation (21, 22). A pH of 7.1 or a base excess of −12.5 mmol/L or less significantly impairs hemostasis as most coagulation proteases function at best between pH 8 and 8.5. Acidosis impairs coagulation by depleting fibrinogen and platelets and by inhibiting clotting kinetics. However, coagulation was not improved by bicarbonate pH neutralization in a swine experimental model (23). Resuscitation regimens improving tissue perfusion and oxygenation normalized the acidotic-induced coagulation defects (24).

POC monitors for additional measurements of act, PT-INR, and aPTT

Activated clotting time, PT (PT-INR), and aPTT do not assess the whole coagulation system and use clot formation as their end point, which occurs even with minor thrombin formation, and their role in managing severe hemorrhage is questionable (25).

Activated clotting time is mainly used to monitor anticoagulation with heparin during cardiopulmonary bypass surgery, extracorporeal life support, coronary angiography, and neuro-angiography interventions. Celite, kaolin, and glass beads are the most commonly used activators to initiate contact activation with a wide range of POC devices. Activated clotting time is usually prolonged with hemodilution, but varies with different POC tests (26). The storage lesion in erythrocyte concentrates can be detected as a prolonged iSTAT-ACT after 3 to 5 weeks as compared with 1 and less than 3 weeks' erythrocyte concentrate storage (27).

Point-of-care devices for performing PT/INR on capillary blood samples are being increasingly used to monitor patients receiving anticoagulation therapy. The iSTAT also measures PT (PT/INR) (28, 29). Other small coagulation PT/INR monitors are Coaguchek^{XS} (Roche, Basel, Switzerland) (25),

Hemochron-Jr (ITC, Edison, NJ) (30), Coagu-Sense PT/INR Monitoring System (CoaguSense, Fremont, CA), Gem PCL Plus (Instrumentation Laboratory, Brussels, Belgium), and ProTime Microcoagulation System (ITC). However, outside warfarin monitoring and its reversal with prothrombin complex concentrates, plasma, and vitamin K, these POC PT and aPTT whole-blood tests correlate poorly with laboratory methods (31, 32).

The Coaguchek^{XS} PT-INR shows a higher variability of test results than laboratory analyses at hematocrits lower than 30% and higher than 55%, but it is not affected by platelet count or fibrinogen concentration (25). The Coaguchek^{XS} also shows less agreement with laboratory analyses in acute trauma coagulopathy (25). Hemochron-Jr can use both native and citrated whole blood and measures ACT and aPTT. Hemochron-Jr is affected by hemodilution, hypothermia, platelet dysfunction, hypofibrinogenemia (<0.5 g/L), and clotted or partially clotted blood. It failed to detect reversal of an *in vitro* albumin-induced dilutional coagulopathy with high doses of fibrinogen and factor XIII concentrates using Hemochron-aPTT and -PT cuvettes (33). Abaxis VSPro (Abaxis) and CoaguCheck Plus (Roche) are POC analyzers that also measure both PT and aPTT.

A more advanced PT/aPTT/ACT monitor is the Hemochron Response (ITC), which also analyzes whole-blood thrombin time. Plasma-based thrombin time can be used to optimize fibrinogen blood levels (34). An alternative microchip method for measuring plasma fibrinogen has been described by Dudek et al. (35), but has not been commercialized. Whole-blood thrombin generation tests (36) may also be of value because one such plasma-based test appears to be superior to PT-INR for monitoring the reversal of warfarin with prothrombin complex coagulation factor concentrates (37).

Viscoelastic and platelet function POC monitors

In a trauma setting, bleeding is often associated with a derangement of the coagulation system; early diagnosis of acute traumatic coagulopathy is essential as it is a known predictor of mortality (38). Viscoelastic tests can be performed to monitor coagulation parameters and obtain information on clot properties. These tests can be run with whole-blood samples, and various parameters are displayed in real time during clot formation, which is initiated either naturally or by the addition of activating factors. Single-channel, small viscoelastic POC devices, such as the Sonoclot analyzer (Sienco, Arvada, CO) and the ReoRox (MediRox, Nykoping, Sweden) rheometer, are suitable for coagulation monitoring in prehospital conditions but are less well documented (39, 40) compared with the two leading viscoelastic POC systems: TEG and thromboelastometry (ROTEM) (41, 42). These devices are routinely used to guide hemostatic therapy in various clinical settings (43–45) and can also be handled in prehospital conditions (46). Moreover, modified self-contained ROTEM systems, which can easily be transported in the field, are being developed (47).

The TEG and ROTEM devices can be used to simultaneously run multiple coagulation assays showing different aspects of coagulation. This is allows goal-directed haemostatic therapy because various conditions can lead to a coagulopathic state. For example, hyperfibrinolysis (enhanced clot destabilization) is a common coagulopathy associated with increased mortality in trauma patients and can be diagnosed with a combination of TEG- or ROTEM-based assays (48–50). Similarly, hypofibrinogenemia is often observed in coagulopathic trauma patients and is also associated with an increased mortality risk (51–53). Specific assays can be used to guide fibrinogen replacement therapy, for example, the TEG Functional Fibrinogen and ROTEM FIBTEM assays, which contain platelet inhibitors and provide an indication of fibrins contribution to the clot (52).

Defects in platelet function or contribution to coagulation should also be considered in acute traumatic coagulopathy. This is becoming increasingly important because the proportion of individuals on antiplatelet therapy is increasing, and such patients must be identified rapidly as they are at a high risk of bleeding after injury. Measurement of platelet function is evolving in trauma care. Several platelet aggregometry POC systems are available; most used so far are Multiplate (Roche), VerifyNOW (Accumetrics, San Diego, CA), and Plateletworks (Helena Laboratories, Beaumont, TX). Currently, the Platelet Mapping assay on the TEG device allows for the detection of antiplatelet medication effects. Rotational thromboelastometry with Platelet Mapping has previously been described, and a new ROTEM version is being made available with a built-in platelet aggregometer. Finally, the newly developed T2HemoStat (T2Biosystems, Lexington, MA) system combines coagulation and platelet function tests and requires as little as 5 to 40 μL of blood; this device is available only as a research tool but might prove to be useful in diagnostic procedures in the future.

Recently, flow-dependent automated microchip techniques have been introduced and can monitor coagulation at both high and low shear rates/stresses, corresponding to arteriolar and venous circulation. These monitors can detect von Willebrand defects and give other results upon correcting a dilutive coagulopathy with fibrinogen and prothrombin complex concentrate than TEG (54).

In conclusion, with prehospital POC testing of coagulation, Hb, lactate, blood gases with electrolytes, and glucose together with noninvasive techniques for Hb and local tissue oxygenation, there is an opportunity to improve patient outcomes. Manufacturers need to improve and adapt POC devices for prehospital conditions, and researchers test these systems early in trauma to improve resuscitation regimens and outcome.

REFERENCES

1. Asimos AW, Gibbs MA, Marx JA, Jacobs DG, Erwin RJ, Norton HJ, Thomason M: Value of point-of-care blood testing in emergent trauma management. *J Trauma* 48(6):1101–1108, 2000.
2. Schöchl H, Schlimp CJ, Voelckel W: Potential value of pharmacological protocols in trauma. *Curr Opin Anaesthesiol* 26(2):221–229, 2013.
3. Yang CL, Huang SJ, Chou CW, Chiou YC, Lin KP, Tsai MS, Young KC: Design and evaluation of a portable optical-based biosensor for testing whole blood prothrombin time. *Talanta* 15(116):704–711, 2013.
4. Kost GJ, Tran NK, Tuntideelert M, Kulrattanamaneeporn S, Peungposop N: Katrina, the tsunami, and point-of-care testing: optimizing rapid response diagnosis in disasters. *Am J Clin Pathol* 126(4):513–520, 2006.
5. Fermann GJ, Suyama J: Point of care testing in the emergency department. *J Emerg Med* 22(4):393–404, 2002.

6. Zielinski MD, Smoot DL, Stubbs JR, Jenkins DH, Park MS, Zietlow SP: The development and feasibility of a remote damage control resuscitation prehospital plasma transfusion protocol for warfarin reversal for patients with traumatic brain injury. *Transfusion* 53(Suppl 1):59–64, 2013.
7. Ryan ML, Thorson CM, Otero CA, Vu T, Schulman CI, Livingstone AS, Proctor KG: Initial hematocrit in trauma: a paradigm shift? *J Trauma Acute Care Surg* 72(1):54–59, 2012.
8. Hardy JF, de Moerloose P, Samama CM: Members of the Groupe d'Intérêt en Hémostase Périopératoire: massive transfusion and coagulopathy: pathophysiology and implications for clinical management. *Can J Anaesth* 53(Suppl 6): 40–58, 2006.
9. Reasor DA Jr, Mehrabadi M, Ku DN, Aidun CK: Determination of critical parameters in platelet margination. *Ann Biomed Eng* 41(2):238–249, 2013.
10. Kriebardis A, Antonelou M, Stamoulis K, Papassideri I: Cell-derived microparticles in stored blood products: innocent-bystanders or effective mediators of post-transfusion reactions? *Blood Transfus* 10(Suppl 2):25–38, 2012.
11. Liumbruno G, Bennardello F, Lattanzio A, Piccoli P, Rossetti G: Recommendations for the transfusion of red blood cells. *Blood Transfus* 7(1):49–64, 2009.
12. Merlin MA, Alter SM, Raffel B, Pryor PW 2nd: External blood loss estimation using the MAR method. *Am J Emerg Med* 27(9):1085–1090, 2009.
13. Shahshahani HJ, Meraat N, Mansouri F. Evaluation of the validity of a rapid method for measuring high and low haemoglobin levels in whole blood donors. *Blood Transfus* 11(3):385–390, 2013.
14. Hopfer SM, Nadeau FL, Sundra M, Makowski GS: Effect of protein on hemoglobin and hematocrit assays with a conductivity-based point-of-care testing device: comparison with optical methods. *Ann Clin Lab Sci* 34(1):75–82, 2004.
15. Rice MJ, Gravenstein N, Morey TE: Noninvasive hemoglobin monitoring: how accurate is enough? *Anesth Analg* 117(4):902–907, 2013.
16. Sjöstrand F, Rodhe P, Berglund E, Lundström N, Svensen C: The use of a noninvasive hemoglobin monitor for volume kinetic analysis in an emergency room setting. *Anesth Analg* 116(2):337–342, 2013.
17. Kotanen CN, Guiseppi-Elie A: Monitoring systems and quantitative measurement of biomolecules for the management of Trauma. *Biomed Microdevices* 15(3):561–577, 2013.
18. van Haren RM, Ryan ML, Thorson CM, Namias N, Livingstone AS, Proctor KG: Bilateral near-infrared spectroscopy for detecting traumatic vascular injury. *J Surg Res* 184(1):526–532, 2013.
19. Hampton DA, Schreiber MA. Near infrared spectroscopy: clinical and research uses. *Transfusion* 53(Suppl 1):52–58, 2013.
20. Gaieski DF, Drumheller BC, Goyal M, Fuchs BD, Shofer FS, Zogby K: Accuracy of handheld point-of-care fingertip lactate measurement in the emergency department. *West J Emerg Med* 14(1):58–62, 2013.
21. Engström M, Schött U, Romner B, Reinstrup P: Acidosis impairs the coagulation system. A thromboelastographic study. *J Trauma* 61(3):624–628, 2006.
22. Engström M, Schött U, Romner B, Reinstrup P: Increased lactate levels impair the coagulation system - a potential contributing factor to progressive hemorrhage after traumatic brain injury. *J Neurosurg Anesthesiol* 18(3): 200–204, 2006.
23. Martini WZ, Dubick MA, Pusateri AE, Park MS, Ryan KL, Holcomb JB: Does bicarbonate correct coagulation function impaired by acidosis in swine? *J Trauma* 61(1):99–106, 2006.
24. Sharrock AE, Midwinter M: Damage control—trauma care in the first hour and beyond: a clinical review of relevant developments in the field of trauma care. *Ann R Coll Surg Engl* 95(3):177–183, 2013.
25. Davenport R, Manson J, De'Ath H, Platton S, Coates A, Allard S, Hart D, Pearse R, Pasi KJ, MacCallum P, et al.: Functional definition and characterization of acute traumatic coagulopathy. *Crit Care Med* 39(12):2652–2658, 2011.
26. Horton S, Augustin S: Activated clotting time (ACT). *Methods Mol Biol* 992:155–167, 2013.
27. Aucar JA, Sheth M: The storage lesion of packed red blood cells affects coagulation. *Surgery* 152(4):697–702, 2012.
28. Thomas FO, Hoffman TL, Handrahan DL, Crapo RO, Snow G: The measure of treatment agreement between portable and laboratory blood gas measurements in guiding protocol-driven ventilator management. *J Trauma* 67(2): 303–313, 2009.
29. Peña JA, Lewandrowski KB, Lewandrowski EL, Gregory K, Baron JM, van Cott EM: Evaluation of the i-STAT point-of-care capillary whole blood prothrombin time and international normalized ratio: comparison to the Tcoag MDAII coagulation analyzer in the central laboratory. *Clin Chim Acta* 413(11–12):955–959, 2012.
30. Thomas O, Schött U: Bedside point of care coagulation testing for individual AVK reversal in emergency surgery. *JCvD* 1(1):8–12, 2013.
31. Zalunardo MP, Zollinger A, Seifert B, Patti M, Pasch T: Perioperative reliability of an on-site prothrombin time assay under different haemostatic conditions. *Br J Anaesth* 81(4):533–536, 1998.
32. Ferring M, Reber G, de Moerloose P, Merlani P, Diby M, Ricou B: Point of care and central laboratory determinations of the aPTT are not interchangeable in surgical intensive care patients. *Can J Anaesth* 48(11):1155–1160, 2001.
33. Hanna J, Winstedt D, Schött U: Dose-response of fibrinogen and factor XIII concentrate for correcting albumin induced coagulopathy. *Scan J Clin Lab Invest* 73(7):553–562, 2013.
34. Kreuz W, Meili E, Peter-Salonen K, Haertel S, Devay J, Krzensk U, Egbring R: Efficacy and tolerability of a pasteurised human fibrinogen concentrate in patients with congenital fibrinogen deficiency. *Transfus Apher Sci* 32(3): 247–253, 2005.
35. Dudek MM, Lindahl TL, Killard AJ: Development of a point of care lateral flow device for measuring human plasma fibrinogen. *Anal Chem* 82(5): 2029–2035, 2010.
36. Ninivaggi M, Apitz-Castro R, Dargaud Y, de Laat B, Hemker HC, Lindhout T: Whole-blood thrombin generation monitored with a calibrated automated thrombogram-based assay. *Clin Chem* 58(8):1252–1259, 2012.
37. Ogawa S, Szlam F, Ohnishi T, Molinaro RJ, Hosokawa K, Tanaka KA: A comparative study of prothrombin complex concentrates and fresh-frozen plasma for warfarin reversal under static and flow conditions. *Thromb Haemost* 106(6):1215–1223, 2011.
38. Brohi K, Singh J, Heron M, Coats T: Acute traumatic coagulopathy. *J Trauma* 54(6):1127–1130, 2003.
39. Lidgard E, Frigyesi A, Schött U: Effects of high dose fibrinogen on *in vitro* haemodilution with different therapeutic fluids. *J Blood Disord Transfus* 2(1):1–5, 2011.
40. Winstedt D, Tynngaard N, Olanders K, Schött U: Free oscillation rheometry monitoring of haemodilution and hypothermia and correction with fibrinogen and factor XIII concentrates. *Scand J Trauma Resusc Emerg Med* 21:20, 2013.
41. Whiting D, Dinardo JA. TEG and ROTEM: Technology and clinical applications. *Am J Hematol* 89(2):228–232, 2014.
42. da Luz LT, Nascimento B, Rizoli S: Thrombelastography (TEG(R)): practical considerations on its clinical use in trauma resuscitation. *Scand J Trauma Resusc Emerg Med* 21:29, 2013.
43. Solomon C, Cadamuro J, Ziegler B, Schöchl H, Varvenne M, Sørensen B, Hochleitner G, Rahe-Meyer N: A comparison of fibrinogen measurement methods with fibrin clot elasticity assessed by thromboelastometry, before and after administration of fibrinogen concentrate in cardiac surgery patients. *Transfusion* 51(8):1695–1706, 2011.
44. Roullet S, Pillot J, Freyburger G, Biais M, Quinart A, Rault A, Revel P, Sztark F: Rotation thromboelastometry detects thrombocytopenia and hypofibrinogenaemia during orthotopic liver transplantation. *Br J Anaesth* 104(4):422–428, 2010.
45. Huissoud C, Carrabin N, Benchaib M, Fontaine O, Levrat A, Massignon D, Touzet S, Rudigoz RC, Berland M: Coagulation assessment by rotation thrombelastometry in normal pregnancy. *Thromb Haemost* 101(4):755–761, 2009.
46. Schobersberger W, Fries D, Mittermayr M, Innerhofer P, Sumann G, Schobersberger B, Klingler A, Stöllnberger V, Fischbach U, Gunga HC: Changes of biochemical markers and functional tests for clot formation during long-haul flights. *Thromb Res* 108(1):19–24, 2002.
47. Doran C, Midwinter M. Dealing with trauma coagulopathy on deployment. *MCIF* 4:34–36, 2009.
48. Schochl H, Frietsch T, Pavelka M, Jambor C: Hyperfibrinolysis after major trauma: differential diagnosis of lysis patterns and prognostic value of thrombelastometry. *J Trauma* 67(1):125–131, 2009.
49. Kashuk JL, Moore EE, Sawyer M, Wohlauer M, Pezold M, Barnett C, Biffl WL, Burlew CC, Johnson JL, Sauaia A: Primary fibrinolysis is integral in the pathogenesis of the acute coagulopathy of trauma. *Ann Surg* 252(3):434–442; discussion 443–444, 2010.
50. Theusinger OM, Wanner GA, Emmert MY, Billeter A, Eismon J, Seifert B, Simmen HP, Spahn DR, Baulig W: Hyperfibrinolysis diagnosed by rotational thromboelastometry (ROTEM) is associated with higher mortality in patients with severe trauma. *Anesth Analg* 113(5):1003–1012, 2011.
51. Chambers LA, Chow SJ, Shaffer LE: Frequency and characteristics of coagulopathy in trauma patients treated with a low- or high-plasma-content massive transfusion protocol. Am *J Clin Pathol* 136(3):364–370, 2011.
52. Fries D, Martini WZ: Role of fibrinogen in trauma-induced coagulopathy. *Br J Anaesth* 105(2):116–121, 2010.
53. Rourke C, Curry N, Khan S, Taylor R, Raza I, Davenport R, Stanworth S, Brohi K: Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes. *J Thromb Haemos* 10(7): 1342–1351, 2012.
54. Schött U, Johansson PI: Editorial. Bringing flow into haemostatis diagnostics. *Br J Anaesth* 111(6):864–867, 2013.