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REVIEW ARTICLE

THROMBELASTOGRAPHY

S. V. MALLETT AND D. J. A. COX

In the past decade, there has been an increasing demand on transfusion services as complex surgical procedures associated with significant blood loss and coagulopathy become more common. Blood and blood products are becoming an increasingly scarce and precious resource, but their use carries some risk [24, 42]. It is mandatory, therefore, that blood component therapy is justifiable: the use of clotting factors and platelet transfusions on an empirical basis to treat real or perceived haemostatic defects is no longer acceptable.

Clotting is a dynamic process which is difficult to measure using static end-points, which provide no information about the quality of the clot or the dynamics of its formation. Conventional coagulation screens (plasma thromboplastin (PT), partial thromboplastin time (PTT), platelet count and fibrinogen concentrations) are frequently inadequate for the purpose of monitoring coagulation when there may be many potential haemostatic defects and continued blood loss may make difficult interpretation of results from samples taken previously.

Another problem with routine coagulation tests is that what is regarded as "normal" for the general population may not necessarily be "normal" for a patient who has undergone major surgery without excessive blood loss. The anaesthetist managing a bleeding patient requires a method of monitoring coagulation that is simple, sensitive and reliable and that indicates in a reasonable time scale the nature of the haemostatic defect.

Because of the limitations of standard coagulation tests, several centres have been re-examining techniques such as thrombelastography (TEG), that monitor haemostasis as a whole dynamic process, rather than as isolated end-points.

THROMBELASTOGRAPHY

Thrombelastography was developed first by Hartert in 1948 [9]. It remained largely a research tool and did not gain widespread usage in clinical practice. However, in the past few years there has been a resurgence of interest in techniques that evaluate the viscoelastic properties of whole blood during the perioperative period [16]. TEG enables a global assessment of haemostatic function to be made from a single blood sample, documenting the interreaction of platelets with the protein coagulation cascade from the time of the initial platelet–fibrin interaction, through platelet aggregation, clot strengthening and fibrin cross linkage to eventual clot lysis. The "signature" of generated tracings can give information on clotting factor activity, platelet function and any clinically significant fibrinolytic process, within 20–30 min. The Thrombelastograph (Haemoscope Corp. & Launch Diagnostics) is a small instrument that can be set up easily in the operating or anaesthetic room. By virtue of its having two separate channels, it is possible to perform serial blood coagulation profiles. This allows coagulation to be monitored directly at regular intervals.

Principles of thrombelastography

In essence, the TEG consists of two mechanical parts: a heated (37 °C) cuvette or cup, which is oscillated and a pin which is suspended freely from a torsion wire (fig. 1). The freshly drawn blood (0.35 ml) is placed in the cuvette and, whilst the sample remains liquid, the motion of the cuvette does not affect the pin. However, when clot starts to form, the fibrin strands "couple" the motion of the cup to the pin and the shear modulus and elasticity

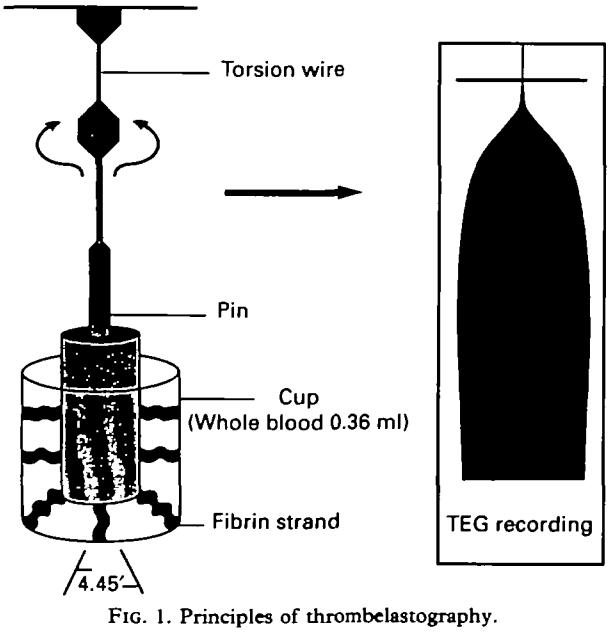

FIG. 1. Principles of thrombelastography.

KEY WORDS

Blood: coagulation. Measurement techniques: thrombelastography.

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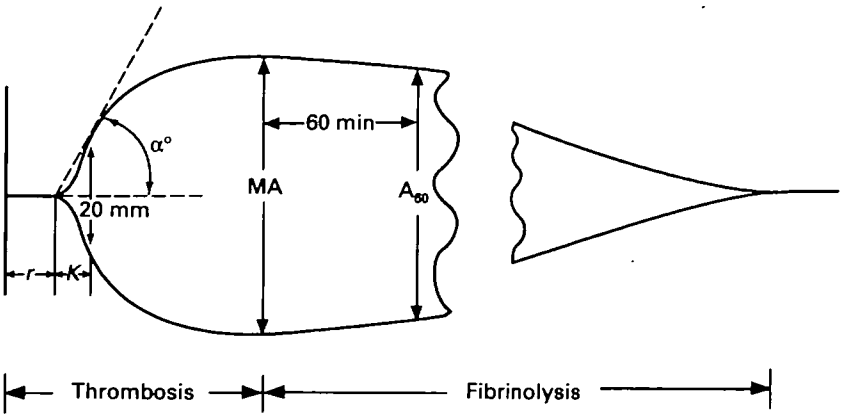

FIG. 2. Quantification of TEG variables. Analysis of the Thrombelastograph. r = Reaction time (time from sample placement in the cuvette until TEG tracing amplitude reaches 2 mm (normal range 6–8 min)). This represents the rate of initial fibrin formation and is related functionally to plasma clotting factor and circulating inhibitor activity (intrinsic coagulation). Prolongation of the r time may be a result of coagulation factor deficiencies, anticoagulation (heparin) or severe hypofibrinogenaemia. A small r value may be present in hypercoagulability syndromes. K = clot formation time (normal range 3–6 min); measured from r time to the point where the amplitude of the tracing reaches 20 mm. The coagulation time represents the time taken for a fixed degree of viscoelasticity to be achieved by the forming clot, as a result of fibrin build up and cross linking. It is effected by the activity of the intrinsic clotting factors, fibrinogen and platelets. Alpha angle (α°) (normal range 50–60°) = angle formed by the slope of the TEG tracing from the r to the K value. It denotes speed at which solid clot forms. Decreased values may occur with hypofibrinogenaemia and thrombocytopenia. Maximum amplitude (MA) (normal range 50–60 mm) = greatest amplitude on the TEG trace and is a reflection of the absolute strength of the fibrin clot. It is a direct function of the maximum dynamic properties of fibrin and platelets. Platelet abnormalities, whether *qualitative* or quantitative, substantially disturb the MA. A_{60} (normal range = MA − 5 mm) = amplitude of the tracing 60 min after MA is achieved. It is a measure of clot lysis or retraction. The clot lysis index (CLI) (normal range > 85%) is derived as $A_{60}/MA \times 100(\%)$. It measures the amplitude as a function of time and reflects loss of clot integrity as a result of lysis.

of the clot is then transmitted through the pin, and amplified to give the TEG trace, which is recorded on heat-sensitive paper moving at a rate of 2 mm min^{-1} (fig. 2).

TEG vs *conventional coagulation tests*

TEG enables a complete evaluation of the process of clot initiation and the structural characteristics of the formed clot and its stability [18]. Routine laboratory tests are generally performed on centrifuged plasma fractions and examine only isolated portions of the coagulation cascade, thereby overlooking important interactions essential to the clinical evaluation of clotting and bleeding syndromes [21].

Many of the conventional coagulation tests end with the formation of the first fibrin strands, while TEG begins at this point and continues to generate data as clotting continues through to eventual clot lysis or retraction. Although there is some correlation between TEG variables and common coagulation tests [11, 35, 44] because the TEG variables are *inter-dependent*, measuring the interaction of the clotting cascade and platelets in whole blood and not looking at isolated end-points, there is not an exact relationship between the two. Zuckerman [44] emphasized that these additional data from the TEG make it more sensitive for detecting changes in the haemostatic balance of coagulation and related systems.

"Bedside" coagulation tests are now available for PT and PTT. However, these tests do not have a high predictive value for perioperative bleeding [35] and there have been no studies that directly correlate abnormal values with surgical blood loss. Indeed, because they give no information about the vital interaction between platelets and the coagulation cascade, it is theoretically possible to have normal PT and PTT values but still have active bleeding as a result of abnormal haemostasis.

Adequate *platelet function* is essential for normal haemostasis. A normal platelet count does not enable the anaesthetist to make any assumptions on platelet activity. Template bleeding times are often difficult and impractical to obtain during operation, and may be subject to inaccuracies unless performed by experienced personnel [28]. *In vitro* platelet function tests are complex and labour intensive, and are also impractical for the acute intraoperative situation. Significant correlations exist between the maximum amplitude on the TEG and platelet count and also with aggregation responses to collagen and ADP [39]. The TEG may be useful, therefore, for *in vitro* assessment of platelet function in whole blood.

Fibrinolysis is increasingly recognized as a previously underestimated cause of perioperative bleeding [12, 29]. TEG may be a more sensitive test for fibrinolysis than routine tests, including D-Dimers (fibrin degradation products) and euglobin clot lysis times [37, 43]. It has been shown to be a useful method to diagnose and guide treatment of intraoperative fibrinolysis [14, 34].

In summary, TEG gives information about fibrinolytic activity and platelet function which is not generally available from routine coagulation screens (fig. 3). It would seem, therefore, to be suited as a monitor in any type of surgery associated with haemostatic defects, either pre-existing or acquired. Both liver and cardiac surgery are frequently complicated by coagulopathies: during liver transplantation, bleeding is often the result of hyperfibrinolysis [27] and in cardiac surgery, perioperative

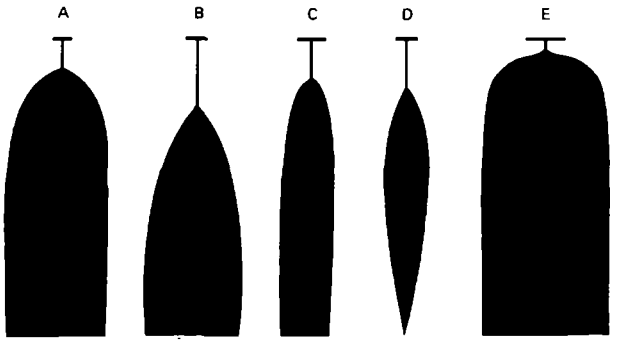

FIG. 3. Specific haemostatic defects produce characteristic TEG traces. A = Normal trace. B = Haemophilia: marked prolongation of *r* and *K* times. Decreased alpha angle. C = Thrombocytopenia: Normal *r* and *rK* times, decreased MA (< 40 mm). D = Fibrinolysis: CLI < 85%. E = Hypercoagulability: short *r* time, increased MA and steep clot formation rate.

blood loss is thought to be related to the acquired reversible defect in platelet function that follows cardiopulmonary bypass [7]. It is in these two areas that much of the recent work on the efficacy of monitoring coagulation with TEG has been undertaken.

Liver Surgery

Patients presenting for liver surgery frequently have severe derangements of coagulation and fibrinolytic systems. In cirrhotic subjects there is typically a decreased concentration of all factors (except factors I and VIII) because of malabsorption of substrate and defective hepatic synthetic function, thrombocytopenia caused by hypersplenism and defective platelet function and a 15% incidence of primary fibrinolysis [6].

The risk of bleeding following liver biopsy or during surgery cannot be evaluated easily from routine haemostatic tests [17]. In many patients it is the *qualitative* function that is disturbed, and it is well recognized that quantative blood coagulation values do not necessarily reflect *in vivo* tissue/blood clotting [5].

Liver transplantation

The procedure of orthotopic liver transplantation (OLT) exemplifies the difficulties of monitoring coagulation when the haemostatic system is subjected to multiple and rapidly changing insults. Baseline coagulation is disturbed, the degree varying with the underlying disease process—being worst in patients with hepatocellular disease. In the anhepatic phase, no coagulation factors are produced and reduced clearance of inhibitors and activators increase susceptibility to a fibrinolysis. Massive blood loss can result in a dilutional coagulopathy being superimposed on a deranged clotting profile. After reperfusion of the grafted liver there is frequently further deterioration in coagulation (both clinically and on the TEG). Conventional coagulation tests do not substantially alter at this point and it is likely that this deterioration is primarily a functional or qualitative problem caused, for example, by hypothermia, acidosis and substances released from the donor liver [13].

Generally, after the newly grafted liver resumes its synthetic function, coagulation returns towards normal in 1–2 h after reperfusion. However, with a poorly functioning graft the coagulopathy may continue, resulting in substantial and sometimes uncontrollable blood loss. In this setting, it is readily apparent that routine coagulation screens are inadequate to deal with the rapidly changing circumstances (fig. 4).

Kang and colleagues [16] pioneered the use of thrombelastography to monitor coagulation during OLT. Therapy is guided by the various TEG variables: fresh frozen plasma 2–4 units is given if the "*r*" time exceeds 15 min, platelets 1 u/10 kg are given if the maximum amplitude (MA) is less than 40 mm (*even if the platelet count is normal*) and cryoprecipitate 6–12 u is given for persistent poor clot formation (alpha angle < 40°) with normal MA. Kang's group found that total red cell and fresh frozen transfusions decreased in the TEG monitored group and attributed this to improved coagulation as a result of more intensive monitoring.

Fibrinolysis

Fibrinolysis is a major component of the haemostatic disorders that contribute to perioperative bleeding during hepatic surgery [27]. Patients under-

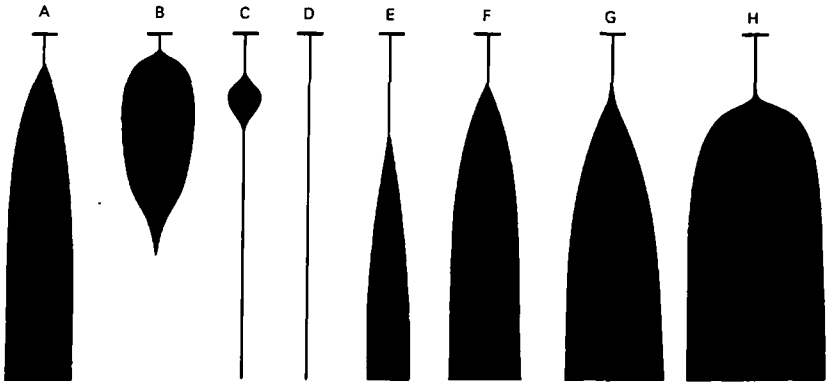

FIG. 4. Typical sequence of TEG traces during orthotopic liver transplant (OLT). A = Baseline TEG: low in clotting factors and platelets. B = Anhepatic + 10 min: fibrinolysis developing. C = Anhepatic + 45 min: severe fibrinolysis. D = Reperfusion + 5 min: straight line TEG—no clot formation. E = Reperfusion + 15 min: after tranexamic acid. F = Reperfusion + 30 min: some spontaneous correction in coagulation. G = Reperfusion + 90 min: additional FFP and platelets given. H = Reperfusion + 120 min: normal TEG apart from prolonged *r* time (International Normalized Ratio = 2.3).

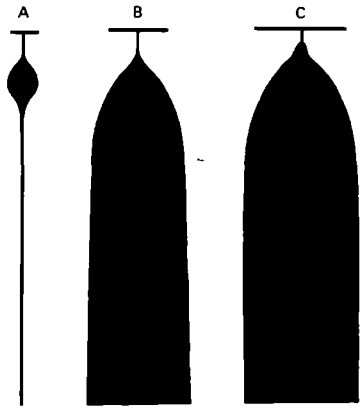

FIG. 5. *In vitro* assessment of antifibrinolytic therapy. A = Severe fibrinolysis in a patient undergoing OLT. B = Tranexamic acid *in vitro*: demonstrates successful reversal of fibrinolysis. C = Tranexamic acid 500 mg given *in vivo*.

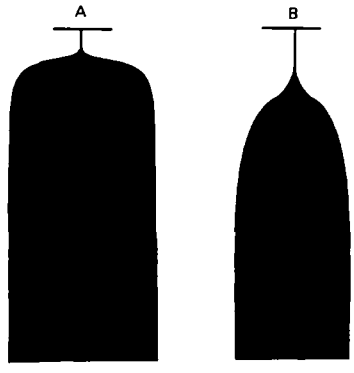

FIG. 6. TEG "hypercoagulability" during the anhepatic phase of OLT in a patient with primary biliary cirrhosis. A = TEG in anhepatic phase: hypercoagulable, short *r* time and abnormally wide MA. B = After reperfusion of grafted liver: increased *r* time and normal MA.

going hepatic resections may develop fibrinolysis because of activated factors released by extensive liver resection that are not adequately cleared by the liver remnant or because of hepatic ischaemia from intermittent occlusion of hepatic blood flow. During OLT there is an imbalance between activators and inhibitors of the fibrinolytic system. In particular, increased concentrations of tissue-type plasminogen activator (tPA) occur, peaking at the end of the anhepatic period and immediately after graft reperfusion. At the same time, concentrations of inhibitors (plasminogen activator inhibitor (PAI) and alpha 2 antiplasmin) are almost unrecordable, often resulting in "explosive" fibrinolysis [4, 13].

The degree of fibrinolysis that occurs during any liver surgery, but specifically during OLT, correlates significantly with intraoperative blood loss [19, 27]. Before the use of TEG, antifibrinolytic therapy was, to a large extent, empirical and the indications for its use were ill defined, as monitoring of fibrinolysis is generally inadequate. Measurement of the clot lysis index (CLI) from the TEG gives useful information about fibrinolytic activity and serial traces enable therapy to be monitored. This is of obvious importance as antifibrinolytic therapy used inappropriately can have potentially disastrous consequences for the patient. In addition, TEG can be used for *in vitro* assessment of the effects of any antifibrinolytic therapy [14]. This technique offers a unique method to test coagulation therapy before its administration to the patient (fig. 5).

Hypercoagulation

All the hepatic diseases that present for liver transplantation do not result in major coagulopathies with clotting factor deficiencies and thrombocytopenia. Patients with primary hepatocellular carcinomas and those with cholestatic disease (primary biliary cirrhosis and sclerosing cholangitis) often have only minimally deranged coagulation profiles. Indeed, a proportion of patients with these underlying diagnoses may be *hypercoagulable* [10, 26], as indeed are many patients with Budd–Chiari syndrome.

Hypercoagulability is difficult to detect on routine coagulation tests unless the platelet count or fibrinogen concentration is increased markedly. It is diagnosed readily with the TEG by the presence of a short *r* time, a rapidly increasing and broad alpha angle and an MA that exceeds 70 mm. Diagnosis of a hypercoagulable state prevents the unnecessary and possibly dangerous use of clotting factor and platelet support (fig. 6).

Hypercoagulability has also been documented in patients undergoing hepatic resections. In carefully selected patients, administration of heparin 1000–3000 u may reverse TEG signs of hypercoagulability and potentially decrease the incidence of thrombotic complications [10].

One of the most serious complications of liver transplantation is vascular thrombosis, especially of the hepatic arterial anastomosis [36]. It is well documented that deficiencies in antithrombin III and protein C occur in a proportion of patients for some days after transplantation [8] and may create a prothrombotic state that contributes to the risk of thrombosis. Detection of this hypercoagulable state by regular thrombelastography is obviously of major clinical importance.

Cardiac Surgery

Cardiopulmonary bypass (CPB) induces several complex disturbances in the coagulation and fibrinolytic systems. In particular, multiple qualitative defects in platelet function have been reported, including decreased aggregation and adhesion, reduced binding of fibrinogen and depletion of alpha granules [1, 7]. Routine coagulation tests are unable to assess the major haemostatic disturbance resulting from CPB—that is, the alteration of the interaction between the coagulation cascade and platelet surface, caused by altered platelet function. Coagulation function and heparin activity during CPB are monitored routinely using activated clotting times (ACT). ACT, although rapid and easy to use, assesses coagulation only up to the time of initial fibrin formation and gives no information on platelet–fibrin interactions, clot retraction or clot lysis; CPB affects all these aspects of coagulation.

Spiess and colleagues [35] recently assessed the usefulness of TEG as an indicator of post-bypass coagulopathies. They found that TEG was a sig-

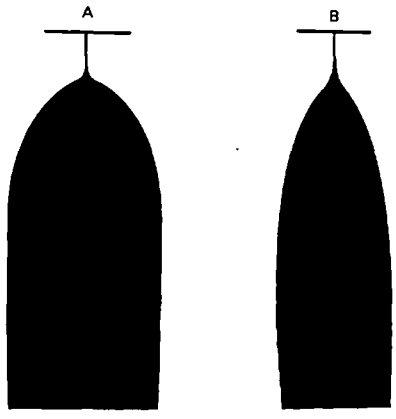

FIG. 7. Characteristic changes in the TEG before (A) and after (B) cardiopulmonary bypass. The most significant difference between the TEG before and after bypass is the change in the MA: the degree of change varies, but in most cases there is a reduction in MA. A marked deterioration in MA is indicative of platelet dysfunction. The alpha angle also decreases, indicating reduced platelet activity and fibrinogen concentrations. The *r* time is generally unchanged after bypass; a very important finding that stresses that a deficiency in clotting factors is uncommon, and that *fresh frozen plasma is usually NOT required.*

nificantly better predictor (87% accuracy) of postoperative haemorrhage and need for reoperation than either ACT (30% accuracy) or conventional coagulation tests (PT, PTT, platelet count and fibrinogen: 51% accuracy).

Kang and colleagues also have examined the use of TEG monitoring in cardiac surgery [15]. In a group of 34 patients undergoing routine CABG or valve replacements, post-bypass bleeding was managed on the basis of clinical judgement, conventional clotting screens, or both. On this basis, 92% of the patients received fresh frozen plasma (FFP) and 30% also received platelet transfusions. However, on reviewing the TEG tracings in these same patients, there was no evidence to indicate the need for FFP in any patient, and 60% of the platelet transfusions were unnecessary. Kang and colleagues concluded that TEG-guided therapy would decrease the use of empirical therapy and excessive transfusions (fig. 7).

Platelet dysfunction and aspirin therapy

Patients treated with low-dose aspirin therapy are well known to have bleeding problems sometimes, as a result of the effects of aspirin on platelet function. Template bleeding time is the only routinely available test that is available currently to assess platelet function, but this is not always practical for use in the operating room. It would appear that the TEG is unable to demonstrate the platelet dysfunction that may result from low-dose aspirin therapy [3, 20, 25]. This lack of effect on the TEG is not entirely surprising, as platelet aggregation by thrombin is relatively unaffected by aspirin and the TEG is not able to measure platelet adhesion/release actions. Similarly, investigators have had difficulty interpreting TEG changes in patients with chronic renal failure [31]. The failure to demonstrate a reduction in MA may be because the primary abnormality of platelet function is a result of impaired adhesion to the vessel wall, rather than impairment of the aggregation mechanism [2]. In contrast, the TEG is an extremely useful tool to evaluate agents that affect platelet aggregation [33, 41].

Coagulation changes during cardiopulmonary bypass

Monitoring of coagulation on bypass is complicated by heparinization and a blood sample at this stage gives only a straight line TEG. Recent pilot studies have shown that the TEG may be used to follow coagulopathy development during bypass in the fully heparinized patient, by adequately activating blood samples with celite before adding them to the TEG [32]. Celite shortens coagulation time because it acts as a contact surface which activates Factor XII and platelets and stimulates the reserve clotting ability of a blood sample. By mixing the blood in the ACT tube in the recommended manner and then placing a sample in the TEG cup for analysis, a complete TEG profile may be obtained starting with the *r* time which is equivalent to the ACT time.

Optimum therapeutic interventions

The possibility of *in vitro* assessments of the effects of pharmacological management of coagulation [14] raises interesting possibilities with regard to the use of antifibrinolytic agents such as epsilon-aminocaproic acid, tranexamic acid and aprotinin. Where abnormalities such as fibrinolysis are demonstrated on the TEG during cardiopulmonary bypass, the efficacy of using a particular pharmacological agent can be assessed *in vitro*, before administering it to the patient. In the same way, dose regimens for individual patients can be calculated, by using, for example, *in vitro* titrations of increasing concentrations of antifibrinolytic therapy [30].

Massive Blood Loss: Dilutional Coagulopathy

After major haemorrhage, the replacement of red cell loss with banked blood is known to create the potential for dilutional coagulopathy, as old blood is deficient in both active clotting factors and functional platelets. To deal with this potential problem, many centres use procedures for replacement therapy that are empirical and in some cases inappropriate. New studies have questioned the recommendations and, indeed, the need to use FFP supplementation or platelet transfusions after massive transfusions in all patients unless deficiencies are first demonstrated [22, 23, 38].

Tuman and colleagues studied the effects of progressive blood loss on coagulation as measured by TEG [40]. Analysis of the TEG demonstrated a trend towards *increased* coagulability with progressive blood loss, even though losses were replaced only with crystalloid and packed red blood cells. It was only when blood losses exceeded 80% of the estimated blood volume that some patients began to show clinical and TEG evidence of coagulopathy. The mechanisms that maintain or even enhance coagulation during progressive blood loss are uncertain. It may well be that normal individuals have a "coagulation reserve" and that this, together with the hormonal changes associated with surgery (increased concentrations of renin, angiotensin, cate-

cholamines etc.), and the release of tissue thromboplastin from tissue trauma offsets any tendency to hypocoagulation associated with haemodilution.

The authors concluded that, in patients without factors known to influence coagulation (underlying haematological disease, hepatic dysfunction, sepsis or hypothermia), there is no justification for the routine use of FFP or platelet supplementation during moderate to massive blood loss. Use of blood product support has to be justified on haematological and clinical grounds, rather than on the basis of empirical procedures [38].

The varied response to massive normovolaemic haemodilution (blood loss exceeding 80% EBV) emphasizes the need to monitor coagulation regularly throughout surgery in such patients, in order that platelet and clotting factor support is given when indicated on an *individual* basis, rather than according to a generalized format.

CONCLUSION

There is still a "monitoring gap" in our ability to assess coagulation adequately in the operating theatre and a need to improve our management and understanding of haemostasis during the perioperative period. There are many sophisticated haematological tests available to assist in the diagnosis of haemostatic failure, but these are not generally available on an immediate or "on call" basis. In the operating theatre, faced with a bleeding patient and perhaps complex and rapidly changing alterations in the haemostatic system, the anaesthetist requires rapid and accurate information on which to base decisions for intervention.

TEG offers a unique method of monitoring coagulation that is practical for use in the operating theatre. It simplifies the diagnosis of coagulopathy during operation by providing clinically relevant information and identifies changes for which therapy is available. Information about the whole clotting process is provided rapidly and can be monitored serially. In addition, it may be used to determine the effect of haemostatic drugs *in vitro* before administration in the patient.

The use of the TEG facilitates the early detection of abnormalities in the haemostatic process and allows the anaesthetist to carry out remedial measures with confidence before there is progression to severe coagulopathy and uncontrolled blood loss. Accurate diagnosis of the current coagulation status enables rationalization of the use of clotting factors and platelet transfusions and eliminates the need for empirical therapy in patients undergoing surgery.

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