5 General Principles of Intraoperative Management of the Severe Blunt or Polytrauma Patient: The Resuscitative Phase

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Case Entry Point

A 57-year-old mailman made a delivery in a high rise office building in the financial district in New York City. As he left the building, a car going 60 miles per hour hit him and pinned him against a wall of the building. He immediately lost consciousness. Witnesses at the scene called 911 and tried to help. With a concerted effort, they tried to remove the driver as well as the mailman from the scene. The New York City Fire Department and emergency medical services arrived within 5 min. One witness was able to feel pulses in both patients, and said that both driver and mailman were breathing.

The fire department personnel towed the car backwards, enabling the rescue team to place a rigid cervical collar on the mailman and remove him from the scene on a spine board. Two large bore IV's were started and oxygen was given via facemask. The first set of vital signs was BP 66/42, pulse 110, and respirations 17. Tympanic temperature was 35.4 °C. The driver received similar treatment in a separate ambulance. All of her vital signs were stable. There was a strong smell of alcohol and vomit on her body. EMS called ahead to the nearest Level I trauma center. Two designated trauma beepers went off: one for the attending anesthesiologist on call, the second for the senior anesthesia resident on trauma.

Both patients were transported to the trauma bay, an area in the emergency department designated for a total trauma assessment by the emergency room and trauma attending physicians. It is imperative that all members of the anesthesia trauma team also attend this assessment in order to prepare for a resuscitation strategy that yields the best outcome.

The initial strategy for handling trauma has been called "damage control resuscitation" by the military. This needs to be initiated in the first or "golden" hour [1]. Damage control in the United States Navy consists of (1) control of bleeding, (2) control of contamination, and (3) restoring a survivable physiological state. The growth of trauma medicine as a unique discipline is rooted in numerous trauma specialists advocating for the development of a standardized treatment format.

The term "golden hour" has been used in several arenas of critical care, described by Tobin and Varon, and applied by R. Adams Cowley [2]. The philosophy of the "golden hour" is that the outcome of the patient resuscitated in the first hour following injury will be better than one resuscitated hours later. The evidence supporting this may not be strong, since trauma remains a difficult subject to study. Many victims of trauma have poor outcomes whether or not they are resuscitated within the

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"golden hour." Additionally, there is so much variation among severe trauma patients that it is very difficult to attain data that would yield therapeutic strategies with a high level of evidence.

In the trauma bay, a rapid assessment of the mailman was made based on his unstable condition, and the trauma attending and anesthesiologist agreed that the rapid transfusion protocol should be initiated. The focused assessment with sonography for trauma (FAST) revealed a significant amount of blood in the peritoneal and retroperitoneal spaces. There were no obvious facial fractures noted that might make intubation difficult. For intubation, a Macintosh 4 laryngoscope blade was gently placed in the patient's mouth for airway assessment. The patient bit down mildly on the blade and gagged. This "awake look" revealed that a rapid sequence intubation could be done. The cervical collar was removed and an assistant provided inline stabilization of the cervical spine. Ketamine and succinylcholine were administered and an endotracheal tube was placed atraumatically. Vital signs after intubation were essentially unchanged, with a systolic pressure in the low 70s and a pulse of 120. Rapid ultrasound of the abdomen was positive in addition for blood. Both legs had open fractures. The most outstanding finding was an open pelvic fracture, which was considered by the trauma team as a lethal injury by itself because of iliac vein bleeding.

Due to the ongoing circulatory instability and severe bleeding, a "damage control" laparotomy was chosen over any further imaging, including CT scan of the head and neck. A vasopressin bolus followed by an infusion was initiated to both increase the blood pressure and decrease the rate of bleeding. A triple lumen central line was placed into the right femoral vein and an arterial line was placed in the right radial artery. The patient was rushed to the operating room with an abdominal binder and cervical collar. This step towards the operating room is part of "overlapping care," as the patient will receive critical care after surgery and probably return later to the operating room, where he will get a hybrid of care based on both anesthesia and critical care principles.

Etomidate is often chosen for rapid sequence induction in unstable patients. However, the incidence of the complications of adrenal suppression appears to be much higher than originally thought. This may be a serious issue in the severe polytrauma patient. In trauma patients, a single dose of etomidate increased the incidence of pneumonia (56.7 vs. 25.9), prolonged ICU stay (6.3 vs. 25.9), and prolonged hospital stay (11.6 vs.6.4). Etomidate causes inhibition of 11β-hydroxylase, leading to adrenal inhibition, and results in a relative risk of death of 1.22 in 3,715 septic patients reported by de la Grandville et al. [3]. In our patient, there was a distinct possibility of a closed head injury, and the increase in intracranial pressure caused by ketamine must thus be weighed against the adrenal suppression caused by etomidate. There is a significant body of literature showing that ketamine does not elevate an already increased intracranial [4] pressure, making it a reasonable selection in the trauma patient with a possible intracranial injury. Of note, carboetomidate: an analog of etomidate that interacts weakly with 11β-hydroxylase, is in final trials and appears to have little impact on the synthesis of steroids [5]. This should make it an excellent replacement for etomidate.

There is a growing opinion among trauma experts that bypassing the operating room and going immediately to interventional radiology may be the best first step in the massively bleeding patient. The goals of the "golden hour" may be appreciated and met by measuring the time from diagnostic angiogram and embolization of essential bleeding vessels as compared to exploration and surgical control of the hemorrhage leading to control of acidosis and hypothermia. In our case, the interventional radiology suite was several floors away, and mobilizing the interventional radiology team would have taken more than 30 min.

Upon arrival in the trauma bay the driver was awake and cooperative. Rapid ultrasound assessment of her abdomen was negative. She underwent a full CT evaluation of her head and neck, and a toxicology screen was positive for alcohol and cocaine. With no definitive injury,

she was sent to the surgical ICU with a cervical collar for observation.

This chapter will discuss the possible approaches to operating room management according to a slowly developing consensus of practice. The clinical bar of excellence met in this chapter has not been attempted by all. We believe that some of these new concepts will become part of the standard of care in the severe trauma patient.

Goals and Objectives of Anesthesia Care for the Severe Trauma Patient in the Operating Room

1. Determine the clinical path that leads to damage control of bleeding, coagulopathy, acidosis, and hypothermia [6].
2. Start resuscitation by diminishing the size of the circulation with vasopressin.
3. Have a plan for increasing the blood volume if blood is not available, such as hypertonic saline solution (HSS), albumin, hemoglobin-based oxygen carriers, and standard crystalloids.
4. Have a goal for each vital sign, and determine whether the patient is a candidate for hypotensive resuscitation.
5. Use point-of-care tests to drive the resuscitation while understanding their deficiencies.
6. Determine if immunotherapy is an option.

Preparation

What is predictable about the severe trauma patient is that very little is predictable. Unlike neurosurgical or orthopedic trauma, details of blunt abdominal trauma are discovered during surgery. Level I trauma centers have a dedicated operating room always ready for the severely injured patient. A standard setup includes three pressure transducers, fluid and body warmers, and a minimum of two vasopressors ready to be administered on pumps. While there is great variability of vasopressor use from institution to institution, we usually have norepinephrine and vasopressin readily available. We tend to start norepinephrine at 0.1 μg/kg/min and vasopressin at 5 units/h after a 5 unit bolus. It is essential that the room be kept warm and fully stocked with the medications and medical devices normally used in a polytrauma case. The interventional radiology suite should be set up for trauma in the same way as the operating room.

In our institution the trauma room setup is as follows.

Rapid Infuser

We use the "Belmont" (www.belmontinstrument.com), and have had great success with his device. There are several rapid infusers on the market that differ only slightly from the Belmont. This device has a feature that we would call essential. It has a large reservoir that accommodates several liters of blood products at once. The faster blood products are infused, the greater the warming capability. The device has a line pressure monitor which stops flow and indicates an obstruction when the line pressure exceeds 300 mmHg, Internal jugular or subclavian lines provide relatively little resistance to flow and the infusion pressure is usually less than 70 mmHg. Large bore peripheral IVs (14 gauge or lower) may infiltrate when attached to the rapid infuser at high infusion rates. Air entrainment is also detected by the infuser. When air is detected, it will stop the infusion and allow the air to be removed. Blood products, with the exception of platelets, can be placed in the rapid transfuser reservoir in the ratio of the institution's rapid transfusion protocol. Since the flow is fast, warm, and turbulent, platelets cannot be poured into the reservoir without destroying them. Blood may be infused or bolused. We recommend not using the continuous infusion mode as the clinician may become distracted by another aspect of the case and only later realize that an excessive amount of blood products had been given. In bolus mode, the pump must be restarted after each unit is complete, allowing the clinician to determine if more blood products are needed. A fresh cassette is easily placed and can be primed in under a minute. Bolus rates can reach up to 500 mL/min with the Belmont and may be higher with other rapid infusers. Ideally; two rapid

infusers should be kept in the dedicated trauma room. With the advent of rapid infusers, it is rare that mortality is related to exsanguination, unless blood becomes unavailable. We do not hang fluid bags and prime lines until we are sure a trauma is coming to the operating room. Another distinct advantage of a rapid infuser is that it can be operated by one user, with an assistant to check blood products.

Ultrasound Machine

Most clinicians have been using ultrasound for central line placement, since it has been shown in several reports to aid in avoiding arterial cannulation. Our policy for placement of central lines includes the anesthesiologist scrubbing, gowning, and gloving. An assistant sterilely preps both sides of the neck and places a drape covering the body from head to toe. For our patient with an unstable cervical spine, the C-collar was removed without movement of the head. With the neck in the neutral position, the ultrasound (Sonosite, Inc.) will still show excellent anatomy [7]. We recommend the "double stick" approach to venous access. An ultrasound guide wire placed in the internal jugular is followed by a second ultrasound-guided placement of a wire next to the first wire. The longer wire accommodates a triple lumen catheter and the shorter is used to place for a 9.0 French introducer. The two wires should be almost touching at the level of the skin, as placing both catheters will otherwise require two incisions. If the two catheters are touching, they will tamponade any bleeding that may occur during dilation prior to placement of the catheters. Once the catheters are placed, their position should be reconfirmed by ultrasound. Placing a pulmonary artery (PA) catheter through the introducer may give important diagnostic information, but the utility of this information must be weighed against the use of the introducer for rapid infusion. A (PA) catheter will decrease flow and increase line pressure. If a pulmonary artery catheter is desired, we suggest preparing the other side of the neck as described above, and placing an 8.5 or 9 French introducer to accommodate the catheter.

In non-trauma patients who require central venous access, strict protocols for aseptic technique have become the standard of care. If the decision is made to take the trauma patient to the operating room as soon as possible, it is impractical to follow this standard as the surgeons are rushing to control the bleeding in an unstable patient. The goal is "clean" central venous access. Classically defined anatomic landmarks cannot be relied upon in a trauma patient, therefore ultrasound is extremely useful. While safety is always dependent on the operator, the "straight neck" or neutral position should not impair central line placement [8]. The volume status of the patient may create difficulty in identifying the internal jugulars. An "empty" patient may have an intermittently identifiable internal jugular vein, which may disappear depending on the mode of ventilation. There are three steps one can perform to assure cannulation of a vein and not an artery. The first is ultrasound visualization of the needle or plastic catheter in the vein. The second involves attaching a length of pressure tubing to the catheter. Once attached, the open end of the tubing is raised above the patient. If the catheter is in a vein, the level of blood in the tubing will fluctuate with ventilation and may empty into the patient. If the catheter is in an artery, the blood in the tubing will pulse continually and not return to the patient. The third is performed by attaching an angiocatheter to a pressure transducer and viewing a distinct venous pressure tracing as opposed to the arterial line tracing consistent with carotid artery placement.

Underbody Forced Air Warmer

Hypothermia a significant factor in morbidity and mortality [9]. In many polytrauma cases the abdomen, chest, and extremities are exposed for the surgical procedure. Heat loss is inevitable; therefore every effort should be made to create a neutral thermal environment. Underbody forced air devices tend to work well. In addition, the room temperature should be kept above 70 °F at

all times, as warming the room, when the patient arrives in the OR rarely, achieves the goal of preventing further cooling. All fluids should be warmed. The rapid infuser works well to warm fluids at high flow rates.

Additional Essential Equipment

Three transducers are set up for arterial and any other necessary pressure measurements, including intracranial pressure and tissue pressures for compartment syndromes. In addition, a BIS monitor, cerebral co-oximetry, pulse pressure variation monitor, HSS, multiple infusion pumps, blood filters, large bore introducer kits, single and triple lumen central line kits, ACT monitor, and defibrillation pads are essential. The "crash cart" must be brought into the room at the inception of the case.

Goal-Directed Tests and Therapy for the Trauma Patient

Thromboelastography

Conventional tests for coagulation are generally of little value in trauma, particularly in the severely injured patient, since their results may be normal in the face of coagulopathy. Fibrinolysis, clot instability and breakdown, which may commonly occur in liver transplantation and open cardiac operations, are not detected by conventional testing. TEG, and more recently thromboelastometry, are goal-directed point-of-care tests that indicate clot stability [10]. While thromboelastography was first described in 1948 by Hartert, there remains some resistance in many institutions to make it part of point-of-care testing. TEG and thromboelastometry are not routinely taught to most medical students or residents, and even many of our trauma surgeons are unfamiliar with these tests. However, the concepts of TEG and examples of TEG printouts are now part of the American Board of Anesthesiology Certification exam. Thromboelastography (2012 Haemonetics Corporation) measures the life of a clot, including clot retraction or fibrinolysis, from 0.36 mL of blood. Thromboelastography is performed by taking a sample of blood and placing it in a small cup called a cuvette. Moving the cuvette back and forth in a 4° arc mimics sluggish venous flow, which is a main extrinsic component of clot formation (Fig. 5.1a). A sensor (torsion wire) attached to a computer is placed in the cuvette. When fibrinogen and platelets interact, a clot begins to form, and the computer senses the ongoing forces that develop from the bonds forming in the clot, and thus creates a trace of clot formation and dissolution (Fig. 5.1b).

Figure 5.2 is a computer generated diagram of the TEG. The "torsion wire" is the sensor. The top of the image "R" is the beginning of clot formation and the bottom is the end of the computer trace. In general, the time from top to bottom in a normal patient is about 45 min.

If R exceeds the limits of normal, the patient needs clotting factors. The management of clotting factor deficiency is evolving, with the production of procoagulants like recombinant factor VII. For the most part, a prolonged R time is treated with fresh frozen plasma. There is no exact correlation of the R time with how many units of FFP are needed. While a full TEG takes 45 min, evaluating the R time takes only a few minutes after the trace begins (Fig. 5.3).

MA stands for maximum amplitude. If the MA exceeds normal reference values, the patient is hypercoaguable. If the MA is narrow, the patient is deficient in platelets, platelet function, and/or fibrinogen. To sort out a narrow MA, monoclonal antibodies targeted at platelets can be administered prior to running the TEG. The MA would then be representative of only fibrinogen. This trial can also be done by adding heparinase in the cuvette in the heparnized cardiac patient. The image in Fig. 5.1 is a computerized generated TEG with the reference points added.

K is the time from beginning of clot formation until the amplitude of the thromboelastogram is 20 mm. A prolonged k-time is ominous and therapy should be initiated before complete TEG results are available.

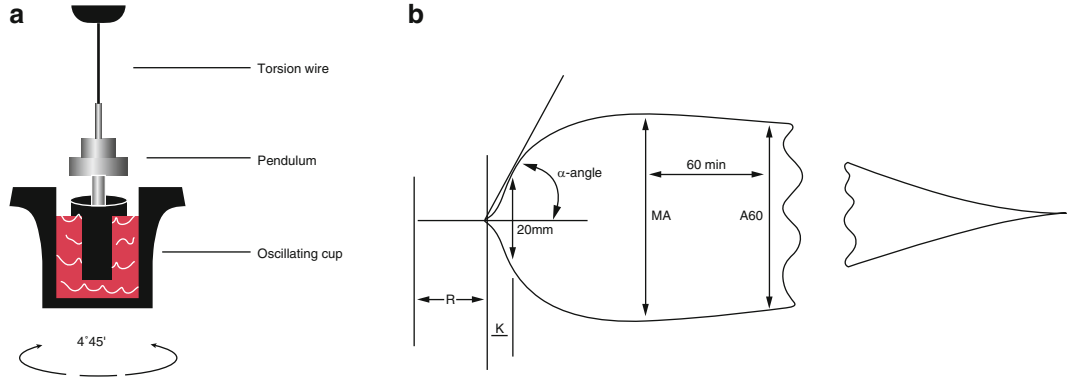


Fig. 5.1 The technology of thromboelastography. (**a**) The thromboelastograph cup (cuvette) rotates through an arc. Blood is placed in an oscillating cuvette. As the blood begins to clot, the cup slows down and transmits a force to the torsion wire that generates an image drawn by a computer. Different rates of slowing lead to different forces on the torsion wire and different images (With permission from Hemologix.) (**b**) R represents clotting factors. If the R is very long and exceeds the limits of a normal R time, the patient needs clotting factors. MA stands for maximum amplitude. If the MA exceeds the normal reference values, the patient is hypercoaguable. If the MA is narrow, the patient is deficient in platelets, platelet function, and/or fibrinogen. K is the time from beginning of clot formation until the amplitude of the thromboelastogram is 20 mm. A prolonged k is very ominous and is a sign that therapy should be initiated while waiting for complete TEG results. Alpha angle is the angle between the line in the middle of the TEG(r) tracing and the line tangential to the evolving "body" of the TEG(r). The angle represents the speeding up process of fibrin build-up and cross-linking (TEG® tracing and parameters are used by permission of Haemonetics. TEG® and Thromboelastograph® are registered trademarks of Haemonetics Corporation in the USA, other countries, or both.)

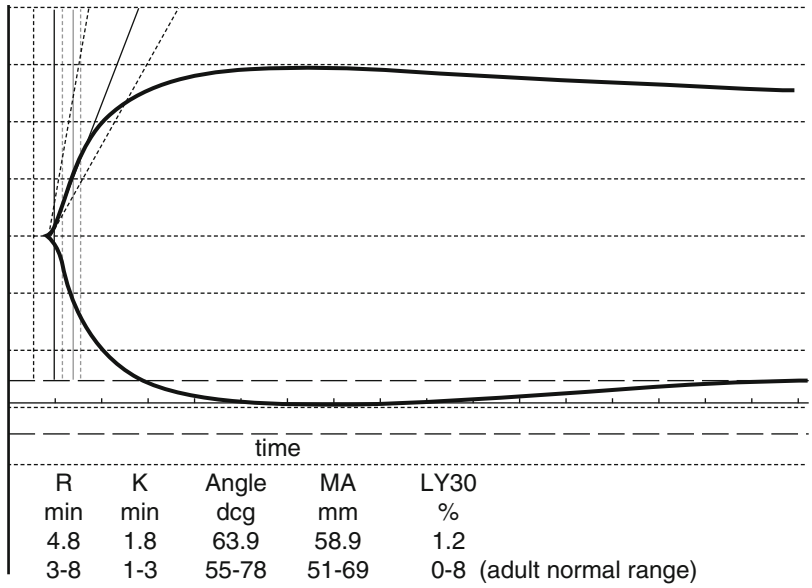


Fig. 5.2 The final computerized generated thromboelastogram. The top set of numbers represents normal values and the bottom number represents the patient. All of this patient's numbers are normal and the image looks perfectly normal (With kind permission from Springer Science + Business Media: Pediatr Cardiol, Thromboelastography of patients after fontan compared with healthy children, 2009;30(6):771–6, Raffini L, Schwed A, Zheng XL, Tanzer M, Nicolson S, Gaynor JW, Jobes D.)

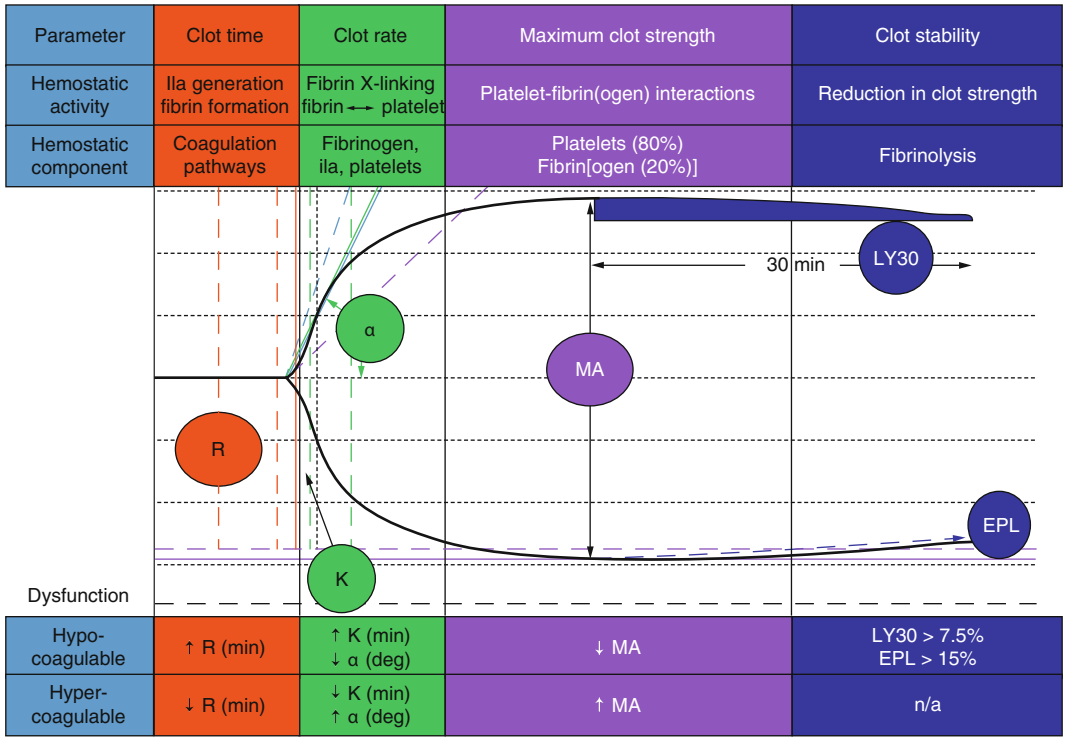


Fig. 5.3 The integration of the TEG and the components of the coagulation cascade (With permission from TEM Systems, Inc.)

The α-angle is the angle between the middle line of the TEG(r) tracing and the line tangential to the evolving "body" of the TEG(r). It represents the acceleration of fibrin build-up and cross-linking. Like the k-time, a narrow angle represents poor acceleration and is likely that the patient has become coagulopathic.

Figure 5.4 demonstrates what standard coagulation tests do not show. The patient is bleeding and the R-time is normal. We can deduce that we do not need factors. The TEG starts out looking normal, but then the MA narrows.

This demonstrates loss of clot stability and the onset of fibrinolysis, which is very difficult to treat. [11]. There are currently two antifibrinolytic agents available to the clinician: ε-aminocaproic acid and tranxemic acid. Much of what we know about them comes from the cardiac literature where they are used prophylactically from the start of each procedure. The efficacy of these drugs is highest when administered before fibrinolyis occurs. There is growing evidence for the use of these medications in trauma. It is common that patients become hypercoaguable during major surgery. There is an argument against aiming for a normal coagulation state during many operations as hypercoagulation and the threat of pulmonary emboli may develop with an overzealous attempt at perfection. We give antifibrinolytics prophylactically when the rapid transfusion protocol is activated. Our team cannot state at this time if this fairly benign treatment is actually effective. Figure 5.4 demonstrates the TEG changes in other pathologic states. Treatments are suggested for each illustration.

The TEG permits goal-directed transfusion of blood products. While manufactured procoagulants and synthetic blood are in development, thromboelastography and thromboelastometry are essential for guiding the resuscitation of the hemorrhaging patient in the operating room. Recently the sensitivity of TEG and TEM has been disputed in the literature. In Raza et al. [11], blood was drawn on arrival for TEM and

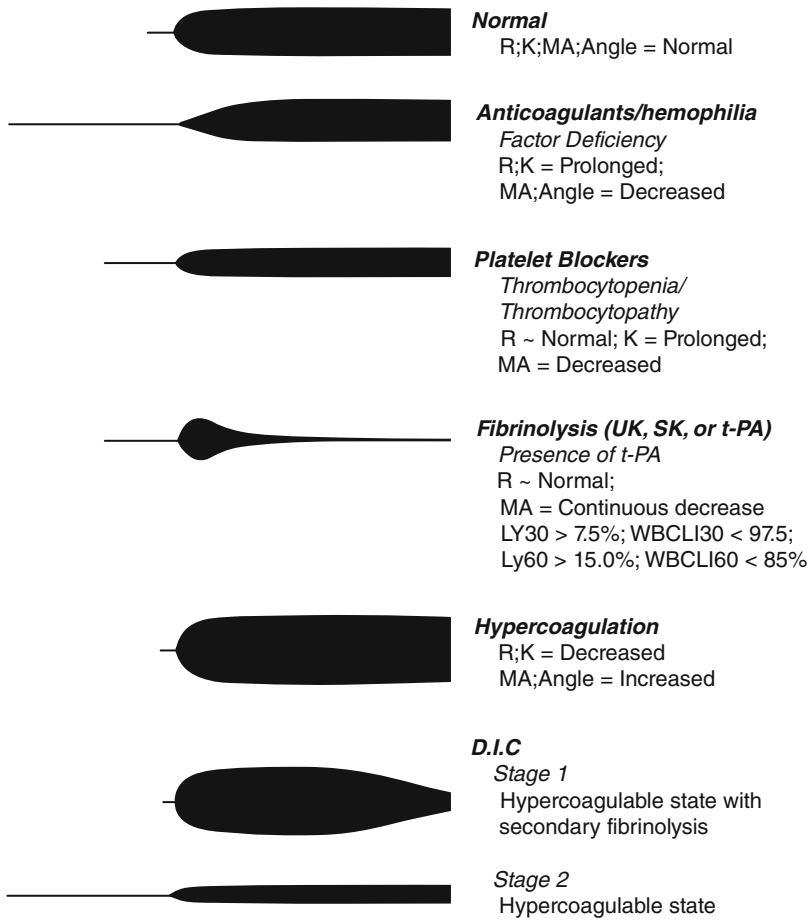


Fig. 5.4 Examples of goal-directed TEGs. These TEGs are typical for the disorders that are shown here

coagulation assays. TEM hyperfibrinolysis was defined as maximum clot lysis of >15 %. Fibrinolytic activation (FA) was determined according to plasmin–antiplasmin (PAP) complex and d-dimer levels. Only 5 % of patients had severe fibrinolysis on TEM, but 57 % showed evidence of "moderate" fibrinolysis, with PAP complex levels elevated to over twice normal (>1,500 μg/L) while no lysis was seen on TEM. TEM detected clot lysis only when PAP complex levels were increased to 30 times normal ($p < 0.001$) and antiplasmin levels were <75 % of normal. This one study has led investigators to determine actual procoagulant factors and inhibitors, and to compare them to TEG/TEM and clinical events. Many clinicians do not follow the thromboelastogram, since many trauma thromboelastograms appear the same as each other and institutional standard treatment is given irrespective of the TEG.

Thromboelastometry

Rotational thromboelastometry is another technique that determines clot stability [12]. As in TEG, the test is performed by placing blood in a cuvette. A sensor fixed on the tip of a rotating axis is placed in the cuvette. It is important to note that in the TEG, the cuvette is moving and in thromboelastometry the sensor is moving (Rotem.de). The shaft of the sensor is rotated back and forth over an arc of 4.75°, mimicking low venous flow. As a clot begins to form, the

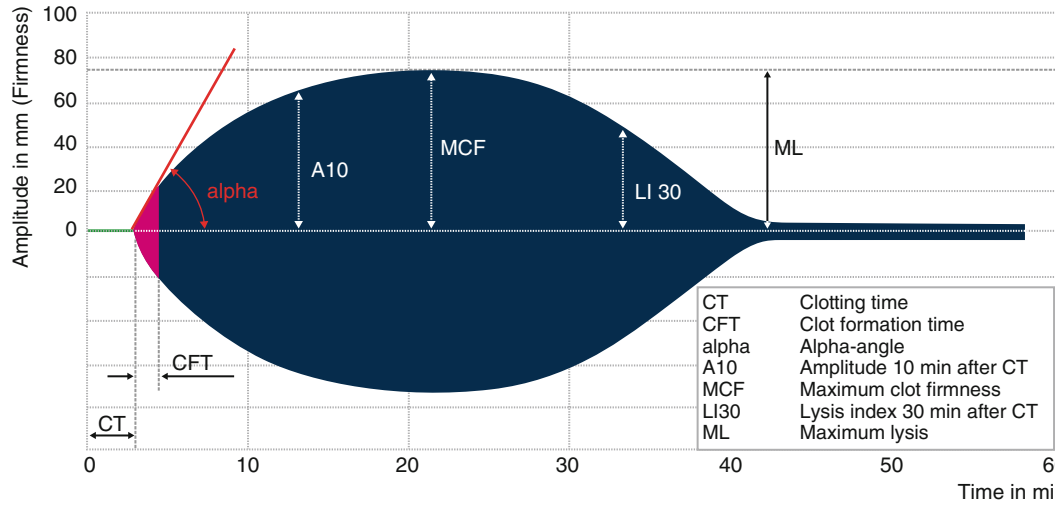


Fig. 5.5 Terms and explanations of Rotem components (With permission from TEM Systems, Inc.)

shaft movement slows. The shaft is connected to a spring that measures elasticity. The exact position of the shaft is determined by light reflection from a small mirror on the shaft. Data from the detected light is processed by computer that generates a graph similar to the one created by the TEG, with related parameters including clotting time (CT) and maximum clot firmness (MCF) (Fig. 5.5). Similar to TEG, there are specific reagents that can be added to the blood sample to help define the exact etiology of a clotting disorder.

The ROTEM permits several tests at different points in the coagulation cascade that cannot be done with the TEG (Fig 5.6a–e). Essentially, thromoboelastometry indicates more specific disorders. The following are some of the tests offered by ROTEM:

INTEM	Contains phospholipid and ellagic acid as activators and provides information similar to that of the APTT
EXTEM	Contains Tissue Factor as an activator and provides information similar to that of the PT
HEPTEM	Contains lyophilised heparinase for neutralizing heparin
APTEM	Contains aprotinin for inhibiting fibrinolysis
IBTEM	Utilizes cytochalasin D, a platelet inhibitor which blocks the platelet contribution to clot formation, allowing qualitative analysis of the functional fibrinogen component.

There are cases when TEG results are different from those obtained by the TEM, even when samples are taken concurrently [13]. It is believed the mismatch is related to the differences in the technologies that generate the clot. Until this variance is better understood, we recommend developing different treatment algorithms based on specific results [14].

PFA-Platelet Function Analyzer

PFA-platelet function analyzer determines the total platelet count and the percentage of platelets that are actually functioning [15]. A system for the detection of platelet dysfunction, the PFA-100 is widely used in centers that perform cardiac, liver transplantation, and trauma surgery. There is rarely a major trauma case in which platelet function does not come into question. The PFA-100 (Siemens Healthcare Diagnostics) measures platelet function in citrated whole blood in a few minutes. The instrument aspirates blood from a reservoir through a capillary and a microscopic aperture in a membrane which is coated with collagen and epinephrine, or collagen and adenosine 5′-diphosphate. The presence of these coatings combined with high shear rates, results in platelet

activation, adhesion, and aggregation, and thus builds a stable platelet plug at the aperture. The time to occlusion of the aperture and cessation of blood flow is called closure time. Abnormal closure times may indicate impairment of platelet enhancers like Von Willebrand's factor, low platelet numbers, or medications like clopidogrel.

Goal-Directed Ventilation of the Severe Trauma Patient

Other than during exceptional circumstances, when jet ventilation or oscillators are needed, modern anesthesia machines do an acceptable job of ventilating patients. Trauma patients are at high risk for developing acute respiratory distress syndrome [16]. In a pig model, Roy et al. [16] determined that early airway pressure release ventilation stabilized alveoli, reduced pulmonary edema, and prevented ARDS. This "pig model" has interesting significance for the human trauma patient, as ARDS carries significant mortality. Simply stated, early treatment of the patient who is at high risk for ARDS with ARDS paradigm for ventilation, may prevent the development of the syndrome. Low tidal volumes and fluid-conservative management comprise the essentials of management of the ARDS patient [17]. Arguments against low tidal volume ventilation include the risk of bilateral atelectasis that might occur if tidal volumes fall below 6 cm^3/kg/breath. Without recruitment maneuvers, atelectasis may lead to ARDS and pneumonia in the postoperative period. This can be avoided with manual distention of the lungs every 30 min.

The evidence that clinicians should change from high volume to low volume ventilation first appeared in the ARMA clinical trial, which was followed by numerous papers praising the non-volutrauma approach to ARDS patients [18]. While the science in many of these studies may be flawed, the conclusions of these studies have been proven by a high number of good clinical outcomes. Trials suggest that a strategy of low tidal volume ventilation (6–8 mL/kg ideal body weight) reduced absolute mortality from 42.5 % in the control group receiving 10 cm^3/kg to 34 % in the low tidal volume group. On the other hand, high tidal volumes have historically been recommended for mechanically ventilated patients during general anesthesia [19]. As a result, a protective ventilation strategy is underutilized, even in patients with ARDS. However, recent data support LTVV for almost all mechanically ventilated patients beginning immediately after intubation [17].

The Strategy of Mechanical Ventilation in ARDS: 2012 Update (From ARDSNet.org).

1. Start in any ventilator mode with initial tidal volumes of 8 mL/kg predicted body weight in kg, calculated by: [2.3 (height in inches—60) +45.5 for women or +50 for men].
2. Set the respiratory rate to 35 breaths/min to deliver the expected minute ventilation requirement (generally, 7–9 L/min).
3. Set positive end-expiratory pressure (PEEP) to at least 5 cm H_2O (higher is better), and FiO_2 to maintain an arterial oxygen saturation (SaO_2) of 88–95 % (paO_2 55–80 mmHg). Maintain FiO_2 below 70 % when feasible.
4. Over a period of less than 4 h, reduce tidal volumes to 7 mL/kg, and then 6 mL/kg. Ventilator settings are adjusted to keep the plateau pressure (measured during an inspiratory hold of 0.5 s) less than 30 cmH_2O (preferably as low as possible), while maintaining reasonable blood gas parameters. Hypercapnea is usually well tolerated. An elevated pCO_2 should be accepted, as elevated plateau pressures may worsen alveolar damage and contribute to mortality. If the plateau pressure remains elevated, one can employ several techniques to reduce it. Tidal volume may be reduced to as low as 4 mL/kg in 1 mL/kg steps. Heavy sedation to minimize fighting the ventilator should be considered. Other factors unrelated to the lungs that can increase plateau pressures, such as a pneumoperitoneum from a laparoscopic procedure, or lack of muscle relaxation should also be considered.

Using this strategy, arterial blood gases will demonstrate respiratory acidosis. Treatment of respiratory acidosis with sodium bicarbonate or

THAM is often employed by clinicians with minimal evidence of positive outcome. There are scenarios in trauma when prophylactic ARDS ventilation is not acceptable, such as traumatic brain injury, when there is evidence of elevated intracranial pressure. Permitting a pCO_2 greater than 50 may further increase ICP. In this scenario, the brain takes preference over the lungs. The same holds true in cases of severe hypovolemia and coronary artery disease.

Intraoperative Fluid Monitoring and Treatment with Pulse Pressure Variation

Whether administering crystalloids or colloids, the formulas normally used to calculate fluid administration are inaccurate and potentially dangerous in the severely injured patient. Even in the non-trauma patient the standard formula for maintenance fluids often leads to over-resuscitation. Giving crystalloids to increase hemodynamic stability often results in transfer of 2/3 of the administered fluid into the extravascular space within minutes. Thus each liter of crystalloid contributes only one-third of a liter to increasing the blood pressure and should not be counted on to correct hypotension.

The goal of fluid management in the trauma patient is to optimize stroke volume. Monitoring pulse pressure variation has been proven effective in guiding fluid resuscitation [20]. Pulse pressure is the difference between the systolic and diastolic pressures.

Low or narrow pulse pressure: Pulse pressure is considered low if it is less than 25 % of the systolic value. The most common cause of a low pulse pressure is a decrease in ventricular stroke volume. In trauma, a narrow pulse pressure suggests significant blood loss. By increasing pleural pressure, mechanical ventilation induces cyclic variations in cardiac preload that result in cyclic changes in left ventricular stroke volume and arterial pulse pressure. The variation in arterial pulse pressure (ΔPP) induced by mechanical ventilation is an accurate predictor of fluid responsiveness during resuscitation. Simply stated, if the height of arterial systole varies with each positive pressure breath, the patient does not have an optimal stroke volume. When patients are hypovolemic, they are on the steep portion of the Frank-Starling curve in terms of the preload/stroke volume relationship. Patients who are on the flat portion of the curve are insensitive to cyclic changes in preload induced by mechanical ventilation, and thus ΔPP is low: increasing circulating volume will not cause a significant increase in stroke volume (GE Healthcare).

By increasing cardiac preload, volume loading induces a rightward shift on the preload/stroke volume relationship and causes a decrease in ΔPP. The goal of maximizing stroke volume can therefore be achieved simply by minimizing ΔPP [20].

Positive pressure ventilation causes vascular pressure changes in the thoracic cavity. Inspiration increases and expiration decreases pressures. Systolic pressure variation (SPV) and pulse pressure variation (dPP) reflect these respiratory changes. The magnitude of change depends on the fluid status of the patient. In our hypovolemic trauma patient, the degree of pressure change was greater than in those who are normovolemic or hypervolemic [21] (Fig. 5.6a,b).

SPV and dPP are calculated from the invasive arterial blood pressure using the following equations:

$$\mathrm{SPV}\ [\mathrm{mmHg}] = \mathrm{SBP}_{\max} - \mathrm{SBP}_{\min}$$

$$\mathrm{dPP}\ [\%] = \frac{(\mathrm{PP}_{\max} - \mathrm{PP}_{\min})}{[(\mathrm{PP}_{\max} + \mathrm{PP}_{\min})/2]} \times 100$$

$\mathrm{SBP}_{\max}$ and $\mathrm{SBP}_{\min}$ represent the highest and lowest values of the systolic blood pressure over the measurement period. We measure SPV/dPP to determine fluid responsiveness. Will the patient's stroke volume and cardiac output improve with fluid resuscitation? It is important to note that dPP is given as a percentage and SPV as mmHg (Fig. 5.7).

Monitoring arterial pressure variation, i.e., SPV/dPP, helps to answer the question of fluid responsiveness and can be used to guide fluid

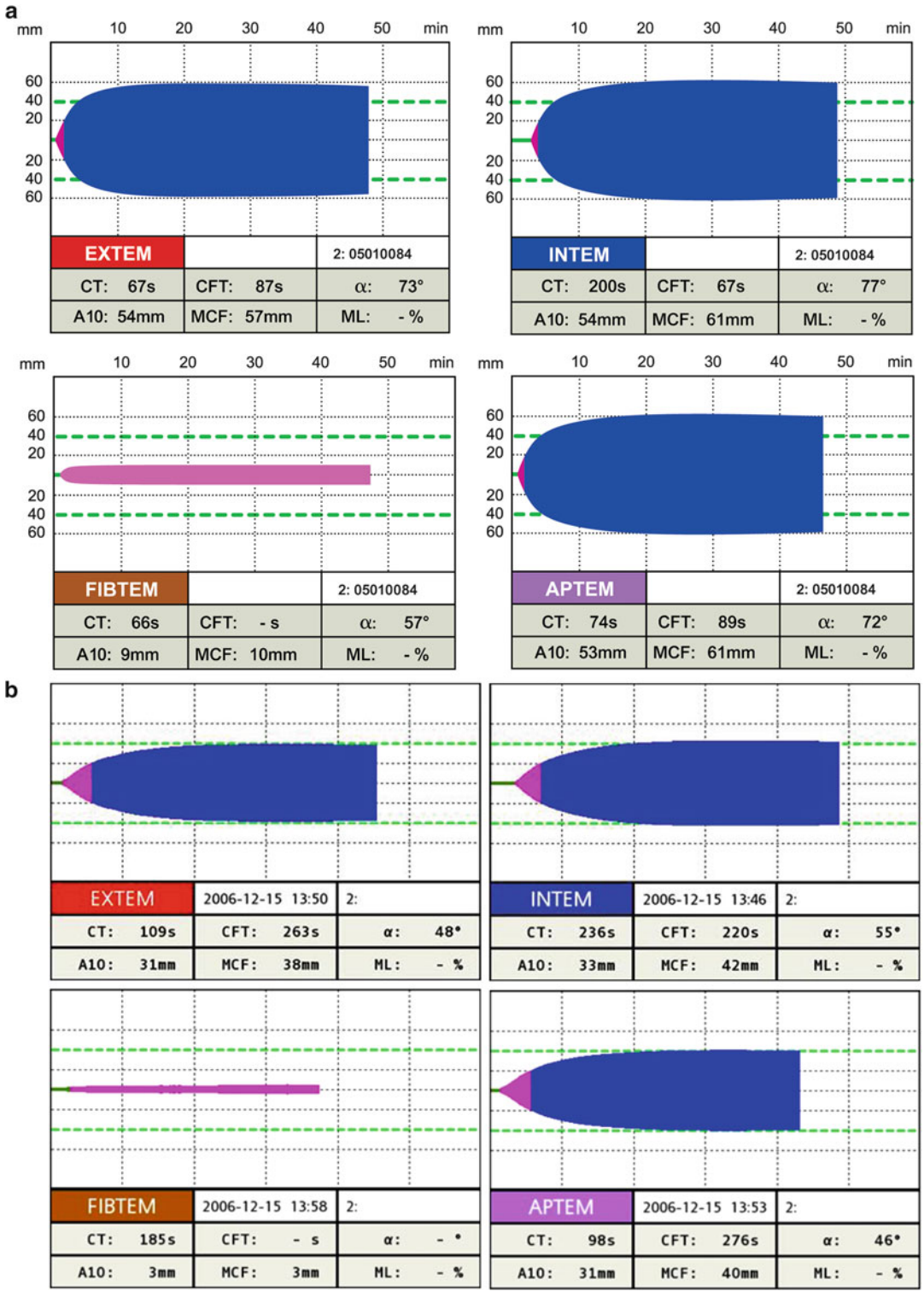
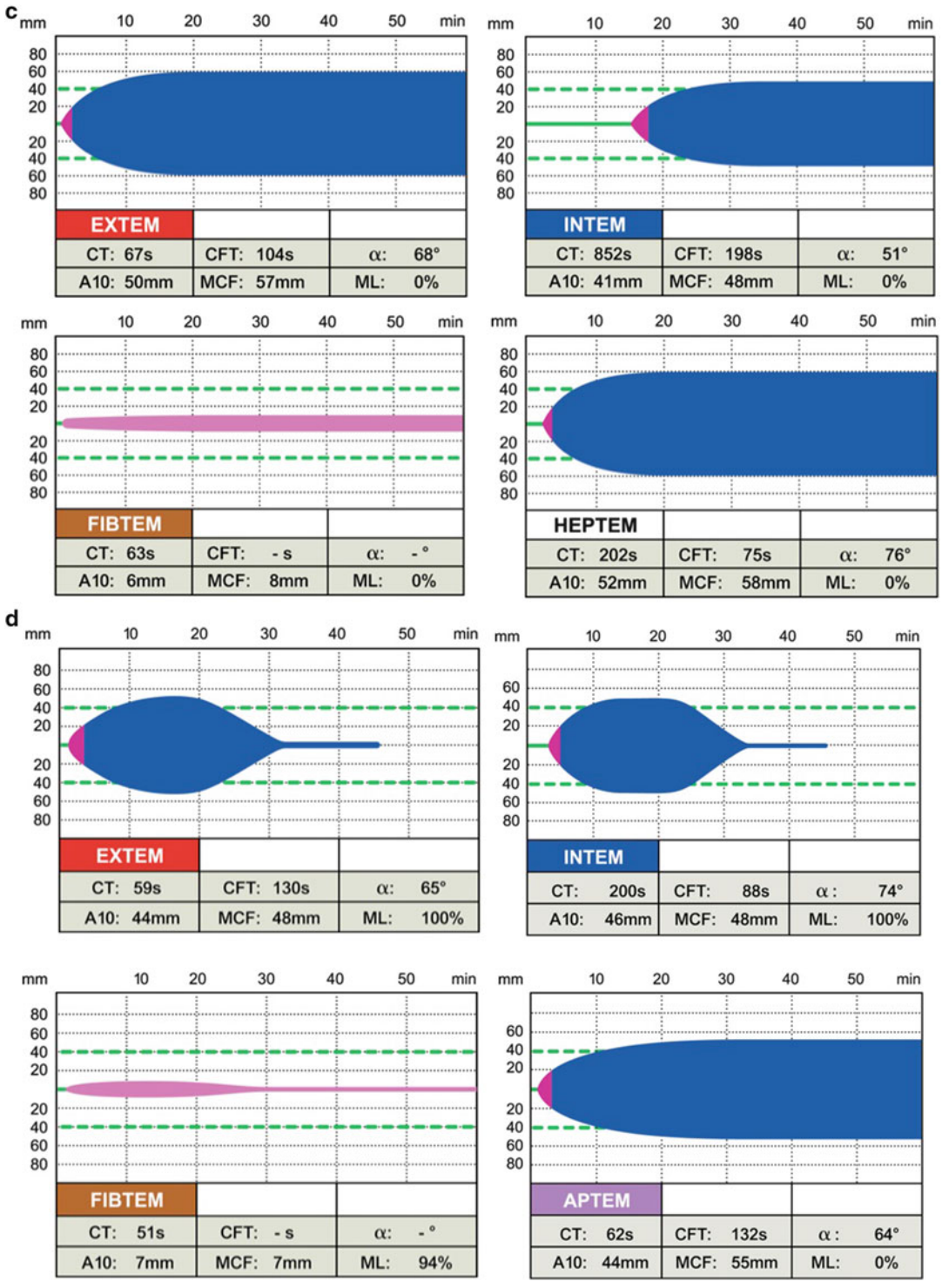


Fig. 5.6 (Continued)



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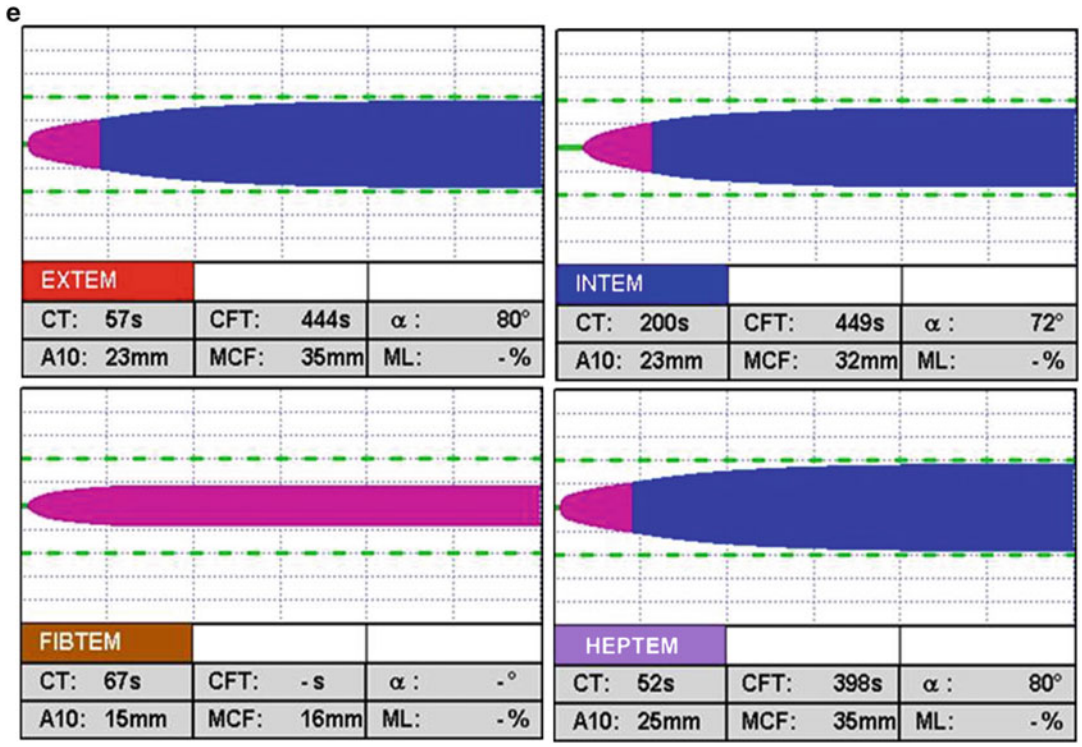

Fig. 5.6 ROTEM and coagulation disorders from Rotem. de with permission, mixing various reagents to help make a coagulation disorder diagnosis (**a**) Normal ROTEM images, (**b**) Fibrinogen deficiency (**c**) Heparin influence (**d**) Hyperfibrinolysis, and (**e**) Platelet deficiency. EXTEM, contains tissue factor as an activator and provides information similar to that of the PT; INTEM, contains phospholipid and ellagic acid as activators and provides information similar to that of the APTT; FIBTEM, utilizes cytochalasin D, a platelet inhibitor which blocks the platelet contribution to clot formation, allowing qualitative analysis of the functional fibrinogen component; APTEM, contains aprotinin for inhibiting fibrinolysis; HEPTEM, contains lyophilized heparinase for neutralizing heparin (With permission from TEM Systems, Inc.)

therapy. While it seems logical that a colloid would contribute more to decreasing pulse pressure variation, this remains controversial and unproven. The dPP values that indicate fluid responsiveness have been shown to range from 10 to 15 %. In the diagram above, the dPP is 27 %, which suggests that the patient may be extremely responsive to fluid. Fluids would be given until the value decreases to 10–15 % [20] Hydrating to a dPP below this could result in overhydration.

Limitations: The values of dPP and SPV are only reliable when the patient is intubated and ventilated, and only in patients without cardiac arrhythmias. Since SPV and dPP values are calculated from an invasive arterial blood pressure waveform, they are reliable only if the readings of the arterial line are reliable. The pressure transducer needs to be at mid-heart level, zeroed, and without air in the transducer or in the catheter line.

Monitors

Placing standard ASA monitors on a trauma patient can be a significant challenge. If the chest and back are sites of injury, standard EKG leads will not work. Eighteen or nineteen gauge needles can be inserted into the skin where EKG leads are normally placed and then attached to alligator clips that fit into the ECG cable to monitor the EKG. Two sets of these vital substitutes should be available. They are particularly useful for the burn patient. Some injuries may also preclude proper placement of a noninvasive blood pressure cuff;

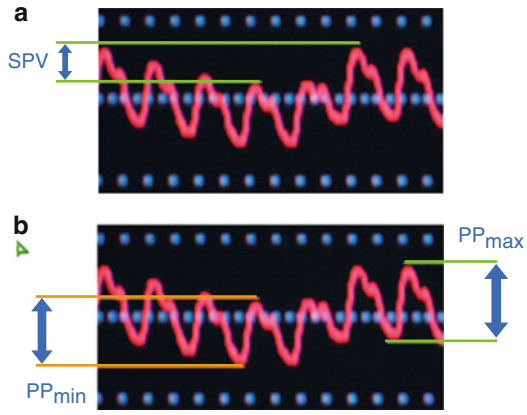

Fig. 5.7 (**a**) Systolic pressure variation; (**b**) pulse pressure variation (Used with permission of GE Healthcare.)

Fig. 5.8 Pulse pressure variation monitor. The dPP represents the difference in pulse pressure on the Arterial line tracing before and after a positive pressure is given by mechanical ventilation. It is recommended that volume is administered to a dPP of 15 %. At 15 %, patients will have an optimal stroke volume (Used with permission of GE Healthcare.)

an arterial line should be used instead. In severe trauma cases at least two anesthesiologists should be placing lines. Femoral and axillary catheters may be considered, but they must be inserted with caution. Arterial lines that require repeated manual flushing are suboptimal. The dorsalis pedis artery is not optimal for blood pressure monitoring, as it typically does not represent central arterial pressure. A small gauge brachial arterial catheter with vigilant monitoring of the insertion site and the hand (for perfusion), may have to be an alternative.

In addition to standard ASA monitors, there is growing evidence that cerebral oximetry may be useful in the prevention of neurologic injury. If hypotensive technique is chosen, they may be essential in preventing brain injury. A low pressure may result in a low saturation.

Transcranial Doppler differs from cerebral oximetry in that it looks at larger arteries (middle cerebral) and is helpful for major embolic phenomena. It has lost popularity since data from this monitor are difficult to interpret. Perioperative neurologic injury may often be related to an imbalance in regional cerebral microcirculation, which may be monitored by the cerebral oximeter. In a prospective study of over 11,000 patients, Likosky and colleagues [22] found that 75 % of strokes occur among the 90 % of patients with low to intermediate risk undergoing coronary artery bypass grafting (CABG) surgery. These neurologic insults often occur despite well-maintained blood pressure and cardiac output. The leads of the cerebral oximeter are placed symmetrically on the forehead (Fig. 5.8) and estimate regional tissue oxygenation by transcutaneous measurement of areas most vulnerable to changes in oxygen supply and demand (frontal cerebral cortex). Light from the oximeter penetrates the skull and is used to determine hemoglobin oxygenation according to the amount of infrared light absorbed by hemoglobin. Cerebral oximetry differs from pulse oximetry by utilizing two photodetectors with each light source, allowing sampling of tissue within a specified depth. Near-field (scalp and skull) detection is subtracted from the far-field (scalp, skull, and brain) reading to provide a measurement of brain oxygenation beyond a predefined depth (Fig. 5.9a).

Cerebral oximetry also differs from pulse oximetry in that the results represent primarily (70–75 %) venous, rather than (20–25 %) arterial blood. Monitoring is not dependent upon pulsatile flow. Normal saturations are ~70 % (Fig. 5.9b). A saturation below 50 % is a call for clinical action either by increasing cerebral circulation or by increasing oxygen carrying capacity. The target mean arterial pressure for the young trauma patient is 50–60 mmHg. This MAP is associated with a more rapid improvement of trauma-induced coagulopathy and significantly less blood product administration (Fig. 5.7). To treat patients with the goal of a systemic MAP of 50 compels the clinician to use the cerebral oximeter. A mean pressure of 50

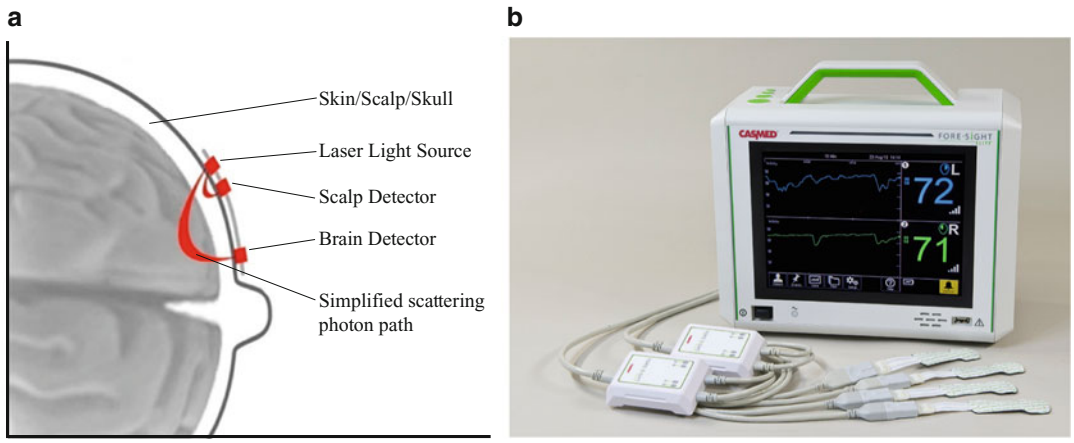

Fig. 5.9 Cerebral oximetry. (**a**) Cerebral oximetry differs from pulse oximetry by utilizing two photodetectors with each light source, thereby allowing sampling of tissue beyond a specified depth beneath the skin. Near-field photodetection is subtracted from far-field photodetection to provide tissue oxygenation measurement beyond a predefined depth. (**b**) A state-of-the-art oximeter with the two numbers representing the oxygen saturation of the right and left side of the brains (FORE-SIGHT Elite™ Absolute Tissue Oximeter. Courtesy of CASMED, Inc.)

with a low cerebral O_2 saturation, necessitates raising the pressure despite the possible clinical disadvantages of doing so. The frontal cortex is most common region of neurologic damage in a trauma patient. While cerebral oximetry has been used in cardiac surgery for years, evidence to support its use in other settings has grown. Several recent articles have demonstrated an association between decreased cerebral oximetric values and neurocognitive decline, increased major organ morbidity, and increased hospital length of stay (LOS) after major surgery [23]. Monitoring cerebral oxygenation has helped guide clinicians in the operating room, although its utility has yet to be determined fully in severe trauma. It may be of great value during surgery, especially in patients with multiple comorbidities. There are many possible therapeutic interventions for a fall in cerebral saturation, including increasing blood pressure, cardiac output and/or FiO_2; increasing $PaCO_2$ to >40 mmHg by decreasing minute ventilation; administering anesthesia and/or muscle relaxants as indicated; and finally, red blood cell transfusion if the patient's hematocrit is <20 %. Patients with cerebral desaturation during non-cardiac surgery have been shown to demonstrate decreases in their Mini Mental State Examination (MMSE) scores.

Casati and colleagues [23] studied 122 patients older than 65 years scheduled for major abdominal, nonvascular surgery under general anesthesia, with an expected duration of surgery greater than two hours. Patients were randomly assigned to an intervention group (the monitor was visible and rSO_2 maintained at >75 % of preinduction values) or a control group (the monitor was blinded and anesthesia was managed routinely). There was a significant correlation between the area under the curve of $rSO_2 < 75$ % of baseline and postoperative decrease in MMSE score from preoperative values. Control group patients with intraoperative cerebral desaturation also experienced a longer time to post-anesthesia care unit (PACU) discharge compared with patients in the treatment group.

Another useful area for the cerebral co-oximeter is in patients positioned in the sitting or "beach chair" position, for instance in shoulder surgery. Cerebral co-oximetry has identified cerebral hypoperfusion when blood pressure is measured in the nonoperated arm positioned well below the level of the brain. The physiologic and anatomic changes that occur with the beach chair position may include decreased venous return, vasodilation, and head flexion, which may impede jugular venous flow and thus decrease cerebral perfusion. Providing deliberate hypotension

along with these physiologic changes requires enhanced vigilance. The use of a cerebral oximeter in this setting provides a tool to assess adequate oxygen delivery to vulnerable cerebral tissue.

The clinical studies described above demonstrate the potential benefits of cerebral oximetric monitoring in a variety of clinical situations. Although the majority of studies have been conducted during cardiac surgery, the application of cerebral oximetry to non-cardiac patients is compelling in certain clinical situations. The previously described work by Casati demonstrated the benefits of using cerebral oximetry among elderly patients undergoing major abdominal surgery. In our trauma patient, intubated and brought to the OR without any brain imaging, the cerebral oximeter could be a vital monitor for ICP management.

Temperature monitors: Trentsch et al. [24] determined that hypothermia is a powerful independent predictor of death in the severely injured blunt trauma patient, based on data from the Trauma Registry of the German Society for Trauma Surgery (TR-DGU). The investigators utilized the Revised Injury Classification Score (RISC score). Data from 5,197 severe trauma patients were reviewed. Hypothermia was defined as a temperature of 35 °C or less. Statistical analysis revealed that hypothermic patients were more severely injured and had higher rates of shock, organ failure, and sepsis. Hypothermia was also shown to correlate with hemorrhage and coagulopathy.

While Foley catheters with temperature probes are ideal for measuring temperature in trauma patients, not all centers have them. For patients with facial fractures or significant neck or chest trauma, often an esophageal temperature probe cannot be used. Temperature reading from the axilla or skin using esophageal temperature probes is often inaccurate. Recent advances in NASA's telemetry and miniaturizing technologies have led to the development of a CorTemp [25].

Ingestible Temperature Sensor, or "pill" (HQ, Inc.). If the pill cannot be ingested by the patient, it can be placed inside a surgically exposed body cavity. The pill is a small electronic device that senses the body's temperature and transmits it via a radio signal to an external receiver. The advantage of the pill over other temperature measurement devices is that it enables core temperature measurement for many hours without the need for wired connections. This is an ideal tool for temperature measurement in or out of the hospital location, or for continuous monitoring of ambulatory patients over long periods. The pill temperature values usually fall between the (higher) rectal and the (lower) esophageal values, considered the gold standard for core temperature measurement. Core body temperature is normally tightly regulated. All general anesthetics produce a profound dose-dependent reduction in the core temperature, triggering responses including arteriovenous shunt, vasoconstriction, and shivering. The primary cause of hypothermia in most patients in the operating room is anesthetic-induced impairment of normal thermoregulatory control, and the resulting core-to-peripheral redistribution of body heat.

Key Management Concerns in Our Patient

In the operating room for "damage control laparotomy," our patient presented dilemmas inherent to many major trauma cases. He had a penetrating abdominal wound, bilateral pelvic fractures, disruption of both iliac arteries, and lacerations of the spleen, liver, and stomach. His abdominal and vascular injuries, combined with dilutional coagulopathy, hypothermia, and acidosis precluded completion of the laparotomy. "Damage control" (DC), defined as initial control of hemorrhage and contamination followed by intraperitoneal packing and rapid closure, allows resuscitation to normal physiology in the intensive care unit and subsequent definitive reexploration and repair.

Although the Massive Transfusion Protocol was activated for our patient, no blood was available in the operating room on arrival. The patient was receiving normal saline. There has been an ongoing debate among anesthesiologists and surgeons about fluid administration in hemorrhagic shock when blood is not available. Hemoglobin-based oxygen carriers and

hypertonic saline, although not ideal, have advantages over other fluids in this circumstance. Hemoglobin-based oxygen carriers have been approved for use in Russia and South Africa, while phase III trials are ongoing in the USA.

A Cochrane database review in 2003 [26] explored the "continuing uncertainty" about the timing of fluid resuscitation in the bleeding patient. Large volume fluid infusions (blood products, colloids, crystalloids) have been linked to multiorgan failure (MOF), coagulopathy, acute lung injury, compartment syndrome, edema, immune suppression, promotion of further blood loss, and hypothermia. In addition, the 1:1:1 ratio of FFP, PRBCs, and platelets in the massive transfusion protocol supplies a mean hematocrit of 29 %, a hematocrit upon equilibration may be too low.

Volume Replacement While Waiting for Blood

The goals of the early resuscitative stage are: (1) to restore an effective blood volume, (2) to optimize tissue perfusion (early initiation of vasopressin infusion), and (3) to limit ischemic and reperfusion injury (antioxidants, complement inactivators). By establishing adequate blood pressure through appropriate volume resuscitation, it is possible to lessen reperfusion injury. Although the colloid vs. crystalloid debate may never be resolved, there is increasing evidence suggesting that lactated ringers is proinflammatory and contributes to end organ damage [27]. Resuscitation with large volumes of crystalloids has also been linked to abdominal compartment syndrome [28]. These findings have led to the use of hypertonic saline 7.5 % in initial volume resuscitation.

In 1980, a critically ill, hypotensive Brazilian man inadvertently received 100 cm^3 of 7.5 % hypertonic saline. His rapid and remarkable recovery stimulated much interest in hypertonic solutions for resuscitation. Many investigators have established a recommended dose of 4 cm^3/kg of 7.5 % saline [29], which correlates to large volume resuscitation with respect to cardiac output and organ perfusion. Theoretical, practical, and physiological advantages of HSS over all other crystalloids for hemorrhagic shock have been reported in the literature. HSS promotes rapid mobilization of fluids from intracellular to extracellular space by creating an osmotic gradient [30]. The increased oncotic pressure expands the vascular space and increases mean arterial blood pressure. Transcapillary refill is restored or increased, with fluid movement into the vascular space, resulting in increased blood flow to the tissues. Dextran 70, a high molecular weight colloid, can be given with HSS. Dextran helps to maintain the oncotic gradient and thus the intravascular volume for a longer period of time than HSS alone [31]. Other attributes of HSS include reduction of pulmonary and systemic vascular resistance, expansion of the interstitial and plasma volumes, increased cardiac output, natriuresis, restoration of membrane potentials, prevention of cellular edema, improved microcirculation, and a smaller overall volume of solution needed for resuscitation. Animal models have shown that HSS has several immune and inflammation modulating effects. Additionally, HSS has been shown to impede oxidative stress, apoptosis, and degranulation of neutrophils, and to lower the rate of bacterial translocation.

However, HSS has not been shown to have any survival advantage over other crystalloids. In traumatic or hemorrhagic shock, the nature of the injury is usually the most important factor determining survival. In clinical trials, boluses of 250 mL of 5, 6, or 7.5 % HSS with dextran 70 have been studied. The most commonly used formulation studied in humans has been 7.5 % with 6 % dextran 70. When HSS is used alone, 3–5 % HSS in a dose of 4–6 cm^3/kg is infused, and repeated as needed. When administering HSS, serum sodium, potassium, and creatinine should be measured at least every 6–8 h. HSS should not be infused through a peripheral IV, as it has been associated with regional vascular complications.

The main concerning side effect of HSS is theoretical: osmotic demyelination syndrome (ODS). There has been only one reported case of ODS when HSS was used for resuscitation. Repeated doses of HSS more commonly may lead to hypernatremia, hypokalemia, and

metabolic acidosis. Dextran may cause anaphylaxis and dextran-induced renal failure.

Hemoglobin-Based Oxygen Carriers

The oxygen carrying solutions are blood, cell free hemoglobin-based oxygen carriers (HEBOC), cell free hemoglobin encapsulated in artificial cells, and perfluorocarbon solutions. Only the HEBOC solutions are devoid of antigenicity issues and can carry a high concentration of oxygen. HEBOC fluids do not have cellular rheology, making them ideal in the massively bleeding patient. They have a shelf life of 3 months, which permits stockpiling in areas of shortage. HEBOC carries universal donor status due to its lack of red blood cell antigens. It appears to be an ideal resuscitation fluid [31]. Clinicians have been waiting for decades for these products to be released in the USA, but lingering issues remain before FDA approval.

There are currently two HEBOCs that have undergone phase three clinical trials. Hemopure (HBOC-21) (Bio-Pure Products, Inc.) has been approved for human use in South Africa and Russia. It has been used in over 800 humans in clinical trials, and in over 70 people for compassionate use. It has not received FDA approval and has been given the status of available under the Code of Federal Regulations, Title 21, Parts 312 and 316. (Expanded access to investigational drugs for treatment use.) The FDA noted several deficiencies when HEBOC-21 was used in humans. In compromised elderly patients with multiple comorbidities, clinical mismanagement occurred, ranging from congestive heart failure to failure to maintain adequate hemoglobin levels because of its brief (19 h) half-life compared to the 22–33 day half-life of PRBCs. It also has vasoconstrictive properties; therefore patients must be closely monitored for hypertension during infusion of the agent. When infusing HEBOC, the total hemoglobin includes the patient's hemoglobin plus that from HEBOC. As HEBOCs are acellular, the hematocrit level is not useful. The dosing schedule of HEBOC is targeted at keeping the hemoglobin level above 5 g/dL by a continuous infusion over 2–6 h. The infusion should be repeated in 12–18 h.

HBOC is not a substitute for blood. The hemoglobin content of PRBCs is 32–36 g/dL while HBOC-201 has a hemoglobin level of 13 g/dL. The significant difference in hemoglobin content between HEBOC and blood is another reason why HEBOC has not yet been FDA approved.

Blood Pressure Management in Our Patient

Our patient entered the operating room hypotensive and bleeding. There are several studies that suggest that permissive hypotension during initial resuscitation may improve trauma outcomes [32]. This strategy, while long standing, remains controversial. It should never be used for a patient with traumatic brain injury, as poor neurologic outcomes have been reported after hypotension in those patients.

Morrison, et al. reported that hypotensive resuscitation reduces transfusion requirements and severe postoperative coagulopathy in trauma patients with hemorrhagic shock [32]. In their randomized controlled trial, once a patient had a systolic pressure of 90 mmhg, they were randomized to a target mean pressure of 50 or 65. The mean arterial pressures were kept at 50 or 65 by means at the discretion of the anesthesiologists. If the patient's pressure responded to treatment, their pressures were allowed to drift up to a level that the patient could sustain without support.

Patients in the lower mean arterial pressure group received significantly less blood products and intravenous fluids than those patients targeted to a mean of 65. The most important outcomes of the study were that postoperative coagulopathy was decreased in the low pressure group, and early postoperative mortality was significantly lower. However, there was no difference between the two groups in late mortality (>24 h), duration of mechanical ventilator support, organ failure, infection, or LOS in the ICU or hospital.

With high volume resuscitation, the lethal triad of acidemia, coagulopathy, and hypothermia are almost always exacerbated. While the INR was elevated in both groups, the average INR was drastically higher in the higher MAP group. Of note, more patients died from bleeding and coagulopathy within the first 24 h in the higher MAP group than in the lower MAP group, despite the fact that patients with higher MAP received more FFP. The smaller doses of FFP did not result in increased coagulopathy in the lower MAP group, and mortality from coagulopathy was significantly reduced.

Both groups had nearly equal hemoglobin levels in the early postoperative period, as well as similar platelet counts. The fact that significantly less blood products are used with the hypotensive resuscitation strategy has great implications for cost and blood use.

It is important to note that the study randomized more blunt trauma patients to the higher MAP group, and thus it is possible that the results may have been confounded by the severity of the injuries in that group. In summary, the evidence supports maintaining a MAP of 50 for trauma patients in hemorrhagic shock, without the use of hypotensive agents. Control of blood pressure during resuscitation for hemorrhagic shock affects morbidity and mortality, and permissive hypotension may be beneficial. Among the likely reasons, lower MAP was tolerated, was that trauma patients tend to be young and healthy, with a mean age of 29.

This study provides evidence to modify the current standard of care for trauma patients, which includes massive transfusion of blood and fluids [33]. The massive transfusion protocol, with an equal ratio of factors and red cells, suffers from a lack of strong evidence of improved survival [33, 34]. In many severe trauma cases, the nature of the injury is the greatest predictor of survival.

The design of Morison's study of hypotensive resuscitation is worthy of discussion as it brings out many issues related to trauma care and research. When a new approach to a clinical situation arises, it is customary that multiple clinical trials revealing strong evidence for the new approach are done before it becomes acceptable, if not the standard of care. In the trauma arena, investigators try to obtain a waiver of consent for research, as trauma patients are not usually capable of understanding the research study, nor are they able to sign consent.

According to federal law, trauma or emergency medicine researchers seeking a waiver of consent must first consult with "representatives of the communities in which the research will be conducted" who are willing to move forward with the trial. The community in Morrison's trial was defined as patients who used the emergency room at the study institution for their own care. The community gave consent before the initiation of the trial. In addition, the institutional IRB and the Center for Medical Ethics and Health Policy at Baylor College of Medicine approved the study, which was also registered with the National Institutes of Health. This approach was successful in obtaining a waiver of consent from trauma patients. The study was accomplished by including the community, ethical board, IRB, and the United States government. This trial serves as an excellent model for others who would like to study new strategies for trauma treatment.

Vasopressors in Our Patient

Arginine vasopressin (AVP), also known as vasopressin or antidiuretic hormone (ADH), is a neural hormone derived from a precursor made in the hypothalamus and secreted by the posterior pituitary gland. Its two primary functions are to constrict blood vessels and to regulate the body's water by increasing water absorption from the collecting ducts of the kidney [34]. It also increases peripheral vascular resistance, which in turn increases arterial blood pressure. It plays a key role in homeostasis by regulation of water, glucose, and electrolyte concentrations in the blood.

During hemorrhagic stress, blood levels of AVP fall. An infusion of vasopressin can restore blood pressure. In both animal and limited human investigations, the use of AVP for

circulatory support has been linked to improved outcomes. Part of AVP's efficacy lies in its ability to increase the sensitivity of vascular smooth muscle to calcium in an acidotic environment. Vasopressin is also associated with a "steal" phenomenon in which blood is shunted from the periphery to the vital organs.

In the massively hemorrhaging patient, administration of vasopressin is essential as an early, if not first-line, treatment [35]. Vasopressin supports vascular tone by binding to the V1 receptors responsible for vascular smooth muscle constriction, and modulates nitric oxide and ATP sensitive K-channels, as well as potentiating adrenergic agents [36]. Vasopressin also binds to V2 (renal) receptors which are located in the distal renal tubules to increase free water absorption. By binding to both V1 and V2 receptors, vasopressin increases volume retention and increases blood pressure, commonly producing an adequate perfusion pressure. Endogenous vasopressin blood levels increase dramatically in the bleeding patient, stimulated by increased osmolarity and decreased circulating volume. Volume loss is a greater stimulus to increased output of vasopressin than is osmolarity. These levels decline in 24 h, coinciding with the refractory hypotension seen in some patients [36].

In hemorrhagic shock, 10–20 % of AVP stores are released from the pituitary, and as the shock state continues, the supply of endogenous vasopressin becomes exhausted, resulting in worsening of the shock state. In a low perfusion state, lactic acidosis develops, resulting in an acidic environment. Acidosis hyperpolarizes calcium-sensitive potassium channels. This decreased sensitivity to calcium leads to poor vascular tone, decreased perfusion pressure and persistence of shock. Therefore, exogenous vasopressin should be started early when hemorrhage is present. There is strong evidence that in hemorrhagic shock vasopressin works more physiologically than catacholamines, since epinephrine and norepinephrine are not as effective as vasopressin for increasing blood pressure in the severely hemorrhaging patient.

The usual starting dose of AVP is a bolus of 2–4 units followed by an infusion of 0.04 units/min, which is then titrated to effect. As with all vasopressors, there may be adverse effects depending on the dose and the physiological state of the patient. Doses of vasopressin that elevate liver enzymes also decrease blood flow to abdominal organs. At therapeutic doses, perfusion to abdominal organs is usually not dangerously impaired.

The delivery of oxygen to the liver is carried out by the hepatic artery and portal vein. Fifty percent of oxygen is carried by the portal vein and 50 % by the hepatic artery. When the flow is decreased in one vessel, a hepatic flow buffering mechanism takes over and increases flow in the other vessel. Vasopressin is unique in that its effect on the portal vein is temporary, while the hepatic artery flow remains high. With vasopressin, the microcirculation of the liver usually remains unchanged. Elevated bilirubin and liver enzymes associated with vasopressin administration have not been shown to be related to patient mortality [36].

In summary, by increasing the circulatory volume, vasopressin enables the clinician to decrease the amount of blood products and fluids given. Although the adverse effects of a unit of blood are extremely low, morbidity quickly becomes an issue when multiple and various blood products are administered.

Antimicrobial Therapy in Our Patient

Broad spectrum antibiotics are initially administered to blunt trauma patients. If a single area is contaminated, more specific antibiotic coverage is used. Facial fractures involving the sinuses often contain different microbes from a fractured hip. The bacterial contamination in polytrauma cases can be extensive, with multiple large lacerations, open fractures, and violation of the abdominal or thoracic cavity. Anesthesiologists play a significant role in both selection and administration of antimicrobial therapy. In a large meta-analysis by Shiu et al. comparing intermittent vs. continuous infusion of antibiotics [37], no difference was found in mortality, infection recurrence, clinical cure, superinfection post

therapy, and safety outcomes between the two methods.

The Surgical Care Improvement Project (SCIP) established antibiotic prophylaxis guidelines for surgical patients. These guidelines did not include trauma patients. The guidelines include (1) prophylactic antibiotic administration, (2) antibiotic received within one hour of incision, (3) correct antibiotic selection, and (4) discontinuation of antibiotics 24 h after surgery. In a sentinel retrospective review of severe trauma patients, those who received antibiotics according to the four SCIP guidelines did not have a higher infection rate than normal surgical patients irrespective of severity or location of trauma. Trauma patients treated by SCIP guidelines had less than half the infections than those not treated by the guidelines [38].

The Anesthesiologist and the Immune System: The New Frontier

The trauma literature refers to the initial immunological response in the injured patient the "first hit." Until recently there was poor understanding of the "second hit," which consists of the subsequent immunological reactions that make the victim vulnerable to further injury. The activation of the immune system within the first hours after the traumatic event is the early phase of hyperinflammation, which may occur locally in isolated injuries, or may manifest as massive systemic immune activation in the polytrauma patient [39]. The endogenous triggers of trauma-associated inflammation have been recently elucidated. The very early stage of trauma is characterized by activation of complement [40] and neutrophils. The complement system is the critical effector of immune responses; it functions in the elimination of invading pathogens by opsonization for phagocytosis, chemotaxis of leukocytes, and by direct lysis of pathogens through the membrane attack complex. The complement system "complements" the ability of antibodies and phagocytic cells to clear pathogens. The complement system consists of small proteins in the blood, synthesized by the liver. They normally circulate as inactive pro-proteins. When triggered, proteases in the system cleave specific proteins to release cytokines and start an amplifying cascade of further cleavages. The end result of this activation cascade is massive augmentation of the response and activation of the cell-killing membrane attack complex. Three biochemical pathways activate the complement system: the classical complement pathway, the alternative complement pathway, and the lectin pathway [41].

Anaphylatoxins C3a and C5a are chemoattractants for phagocytes and neutrophils and recruit immune cells to a site of injury. In addition degranulation occurs in mast cells, basophils, and eosinophils. Many studies have demonstrated that trauma activates complement locally at the site of injury as well as systemically. The complement cascade is activated at the level of C3, and the extent of activation correlates with the severity of injury.

As the complement system is the humoral response to injury, neutrophil activation is the cellular response. Within minutes of injury and up to several days, neutrophils mount an immunologic response, and are essential to the debridement of injured or devitalized tissue. Neutrophils release cytokines, chemokines, reactive oxygen species, and tissue-toxic enzymes such as myeloperoxidase and elastase, all of which contribute to the massive inflammatory response [42]. which involves not only the site of injury but also healthy tissues. This reaction is not completely understood. Shortly after the inflammatory response is initiated, a significant failure of components of the innate immune system follows, including reduced proliferation of T lymphocytes [43]. Simply stated, all patients suffer from an impairment of lymphocytes and monocytes.

The majority of polytrauma patients receive blood; a therapy that ignites the immune system. Other than issues related to blood storage injury, transfusion has a negative impact on the patient's immune system and hyperinflammatory response. Proinflammatory cytokines (Interleukins) IL-8, IL-6, and counterregulatory cytokines (IL-10) are markedly elevated in patients resuscitated

with PRBCs [44]. It is unlikely that such high levels came from the donated cells. More likely, the elevated cytokines are the host's response to the transfusion. These isolated cytokines are now being evaluated to determine if they are involved in MOF [44].

Over the years, a large body of scientific evidence has accumulated from evaluating over 100 monoclonal antibodies, antiendotoxins, and antioxidants. Testing of these agents on severely injured patients has become infrequent, since attempts to control the immune response have not been successful [45]. Timing and treatment of inflammatory changes is essential in preventing MOF. IL-1 and TNF were the first to be elucidated in the inflammatory response; however, antibodies to them worked well in animal models but not at all in humans. In the 1980s, antibodies to endotoxin component lipid and HA-1 proved to be both neuro- and hepatotoxic. Protein C and corticosteroids did not give meaningful results. Clearly, full understanding of the proinflammatory response and immunomodulation needs further research.

The most significant trials to halt the massive immunological response to trauma are targeted at the complement system, in attempts to moderate or avoid the multiorgan failure associated with severe trauma. Recombinant C1 inhibitor concentrates (C1-INH) and the anti-C5 Ab eculizumab (Alexion pharmaceuticals) are the first anticomplement drugs to be approved and utilized [46]. These agents prevent complement initiation at the classical and lecithin pathways. Clinical trials have begun for the attenuation of thromboinflammatory responses in trauma (ClinicalTrials.gov identifier NCT01275976). In contrast to C1-INH, eculizumab is complement-specific. It works at the C5 level, preventing the generation of C5a which attacks cell membranes [46]. Countless other substances that attack various levels of the complement system are under investigation and are likely to be available to anesthesiologists for trauma cases as well as for a host of other areas like transplants and medical diseases.

This brief introduction to proinflammatory/immunosuppression and catabolism (PICS) reactions is important for the anesthesiologist, as these responses are the basis of multiorgan failure. This complex inflammatory response is likely responsible for the dysphoria and exhaustion those patients feel after surgery. Prevention of MOF by controlling the immune system and the hyperinflammatory response will be a new challenge for clinicians.

Case Summary

The patient arrived in the operating room at 8:00 PM, with a blood pressure of 55/35. 100 cm^3 of HSS were administered while the anesthesia team was waiting for blood. A total bolus of 10 units of vasopressin was given followed by an infusion of 10 units/h. The blood pressure responded to both therapies. Two radial arterial lines were placed and the pulse pressure showed a 35 % variation with respiration. Packed red blood cells were alternated with fresh frozen plasma and platelets until the pulse pressure variation was 12 %. The hematocrit at that time was 27. The infusion of vasopressin was decreased until a mean pressure of 50 mmHg was sustained. A bolus of 5 g of ε-aminocaproic acid was administered upon arrival and an infusion was maintained at 1 g/h. The TEG demonstrated a significant decrease in the MA, which proved to be related to low fibrinogen as the platelet function analyzer showed 90,000 platelets with 80 % function. Cryoprecipitate was administered to address the fibrinogen deficit.

During the damage control laparotomy, the left iliac vein was traumatized and could not be repaired, and therefore had to be ligated. The abdomen was packed and the patient was sent to the ICU. The patient was stable for only a short period of time as both coagulopathy and overt bleeding were worse. The patient was transferred to the interventional radiology suite and the anesthesiologists resumed their resuscitation plan while the interventional radiologists coiled every bleeding vessel they could find. It was discovered that the other iliac had become aneurysmal and after much discussion among the surgeons, anesthesiologists, and radiologists, it

was embolized. With both iliacs "down," the patient's legs, rectum, bladder, and perineum began to "die." The patient was not eligible for a hemicorpectomy both because of his medical condition as well as the wishes of the family. When he arrived back in the ICU, "comfort" care was started. The patient was extubated and morphine sulfate was administered each time the patient had a respiratory rate greater than 20 and when he appeared to be uncomfortable. Death was pronounced 5 h after extubation.

Many of the concepts presented here are not "mainstream" clinical practice. It is essential to note that the consensus of practice for the severe trauma patient is evolving. There is an ongoing explosion in investigations related to blood transfusion, immunology, oxidative stress, and MOF. Of equal importance, there is evolution in the ethics of dealing with these complex cases. In all of these areas, anesthesiologists will be playing a vital role.

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