FELLOW AND JUNIOR FACULTY PROGRAM

PROBLEM-BASED LEARNING DISCUSSION

“Blood Management During Cardiac Surgery”

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PRESENTERS

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LEARNING OBJECTIVES

At the conclusion of the discussion, the participants will be able to:

1. Identify the multiple factors related to increased risk of bleeding and coagulopathy in cardiovascular surgical patients, patient-related conditions, procedure-specific factors, and recognize how interactions between these factors can affect patient outcome.

2. Apply the best available evidence in order to accurately assess a patient's need for transfusion and to devise a perioperative plan to improve blood products utilization and patient outcome.
CASE PRESENTATION

The patient is a 66-year-old female presenting for elective ascending aortic and total arch replacement under deep hypothermic circulatory arrest (DHCA). The surgical indications are ascending aortic aneurysm with involvement of the aortic arch vessels. Significantly, the patient has a history of single vessel CAD which required DES placement in the RCA one-year ago. Additionally, the baseline TTE showed mild LV dysfunction (LVEF 50%) with moderate LVH and grade 1 diastolic dysfunction; normal RV systolic function, mild AR, mild MR, trivial PR, and trivial TR.

The past medical history is significant for hypertension, hypercholesterolemia / dyslipidemia, diabetes mellitus type 2, and chronic kidney disease. The patient is also an ex-smoker of 22 pack-years (with cessation 20 years ago). There is no diagnosis of lung disease. Finally, there is history of hypothyroidism and glaucoma. Prior surgical history includes a hysterectomy and a left total knee replacement.

The list of home medications includes; clopidogrel (stopped 5 days prior to surgery), aspirin, metoprolol, metformin, atorvastatin, and occasional ibuprofen and acetaminophen. The review of systems is otherwise positive for slight progressive hoarseness during the last six weeks and mildly limited physical activity due to dyspnea of exertion.

On physical examination, vital signs of relevance are arterial blood pressure: 154/65 mmHg, heart rate: 67 bpm and regular, normal respiratory rate and 100% SpO2 on room air. The anthropometrics are, weight: 68 Kg. (150 #), height: 172.7 cm. (68”), and BMI 22.8 kg/m². There is no jugular venous distention above the clavicle at 30 degrees of inclination. The chest auscultation shows normal heart sounds and clear lungs bilaterally. The rest of the physical exam is negative.

The review of laboratory values reveals that the hemoglobin is 12.5 g/dL. The platelet count is 234 x 10⁹/L. The creatinine level was 2.3 mg/dL (BUN 23 mg/dL) the day of the procedure (the creatinine was 2.2 mg/dL (BUN 30 mg/dL) twelve weeks before the procedure and it had been stable since then). The potassium serum level was stable at 4.2 mmol/L. Other laboratory values are within normal limits.
QUESTIONS

Preoperative assessment and interventions:

1. What are the specific considerations of DHCA related with the risk of bleeding and coagulopathy? What are specific pathophysiologic changes during DHCA that are related to the occurrence of coagulopathy?

The effects of anticoagulation, cardiopulmonary bypass (CPB) and DHCA on hemostasis during cardiac surgery are interrelated and difficult to separate. The combined result is a profound imbalance between coagulation and fibrinolysis.1,2

Several studies have shown that heparin administration induces a platelet function defect and prompts platelet activation even before institution of CPB.2-6 Additionally, heparin activates plasmin, which has a proteolytic action on the GPIIa platelet receptors and causes formation of D-dimers. Subsequently, D-dimers compete with fibrinogen for binding at the GPIIb/IIIa receptors.2

The use of DHCA has further impact due to the effects of profound hypothermia and blood stasis. The effects of hypothermia are multiple and complex, adding to the initial decreased platelet count due to hemodilution upon CPB initiation. Initially, even mild hypothermia causes sequestration of platelets and also a reversible decrease in enzymatic activity of platelets with further secondary platelet dysfunction.7,8 Furthermore, the effects of higher levels of hypothermia in platelet receptors include an increase glycoprotein IIb/IIIa (GPIIb/IIIa) receptor activation and its response to stimulators, as well as an increase in aggregation and fibrinogen binding.9,10 Beyond the effects of hypothermia during DHCA, the microvascular thrombus formation originated by the continued platelet aggregation has been regarded as a contributor to organ damage. The postulated mechanism is that activated GPIIb/IIIa receptors are bridged by fibrinogen with the resultant consumption causing coagulopathy.10 Additionally, hypothermia induces kinin and kallikrein activation. Another significant mechanism is hypothermia-induced coagulopathy in that blood stasis causes endothelial release of tissue plasminogen activator (t-PA) with a consequent thrombin-induced increase in protein C resulting in further fibrinolysis and anticoagulation.1 Furthermore, aortic surgery itself is a determinant in the occurrence of coagulopathy through significant vascular injury, and the use of large prosthetic vascular conduits; with massive exposure of tissue factor and endothelial activation.11

Intraoperative management:

General anesthesia is induced and tracheal intubation occurs uneventfully. The surgical procedure proceeds without incident. After CPB is initiated via cannulation of femoral vessels,
the patient is systemically cooled to 16°C. DHCA is initiated when EEG is isoelectric confirming no cerebral electrical activity. The aortic arch is repaired with a Hemashield graft where the bypass arterial cannula is transferred to, and CPB is reinitiated while the ascending aorta is repaired. Thereafter, rewarming is initiated. The core temperature is 32°C, and the current hemoglobin is 8.8 g/dL. At this point, the surgeon requests prophylactic administration of packed red blood cells (PRBCs) with the goal to maintain hemoglobin level \( \geq 10 \) g/dL.

1. How do you respond to the surgeon’s request?

The issue of a specific hemoglobin level (“trigger”) as an indication for PRBCs transfusion has been the subject of extensive debate and research during the last decades in both cardiac and non-cardiac surgical settings. There is little high-level evidence-based data to support particular hemoglobin or hematocrit levels as transfusion triggers.

From a physiologic perspective, the critical level of oxygen delivery (at which delivery is unable to meet the demands) for all mammalian species is 333 mL O\(_2\)/min/m\(^2\).\(^{12}\) Likewise, it has been established that the critical values of oxygen delivery that cause a dependent decrease in oxygen consumption are a hemoglobin level of 3-4 g/dL, a mixed venous oxygen saturation (S\(_{\text{vO}_2}\)) of 56%, an oxygen extraction ratio of 0.44, and a mixed venous oxygen of 34 mmHg.\(^{13}\) The above information comes from experimental settings. From a clinical point of view, there is little data regarding critical oxygen delivery and utilization in diseased cardiac surgical patients. However, it has been determined that normovolemic dilution to hemoglobin levels of 6 – 7 g/dL maintain tissue oxygenation in CABG surgery patients.\(^{14,15}\) Similarly, there is a delay in cardiac metabolic recovery in patients with a high-risk of perioperative myocardial ischemia with hemoglobin level below 6 g/dL.\(^{13}\) Several observational studies, mostly assessing data from Jehovah’s Witness populations have shown increased mortality among cardiac surgical patients when hemoglobin is less than 5 g/dL.\(^{16-19}\) In terms of patient outcomes, several large single- and multicenter prospective studies have shown an association between the lowest hematocrit (ranging from 14 to 22% depending on the study and patient population) during CPB and worse outcomes including mortality, stroke, acute kidney injury, myocardial infarction, pulmonary edema, sepsis, as well as increased hospital and ICU-length of stay.\(^{16,20-23}\) From an opposite point of view, a prospective observational study has shown that the incidence of postoperative myocardial infarction was higher in patients who had hematocrit greater than 34% and more severe LV dysfunction after CABG.\(^{24}\) These results add to the evidence questioning the application of arbitrary transfusion triggers in cardiac surgical patients.\(^{25,26}\)

The lack of high level evidence and the multiplicity of expert opinions prompted the combined Society of Thoracic Surgeons (STS) and the Society of Cardiovascular Anesthesiologists (SCA) taskforce to publish The Perioperative Blood Transfusion and Blood Conservation in Cardiac Surgery Clinical Practice Guidelines in 2007.\(^{25}\) Regarding the issue of transfusion triggers, the consensus asserts: “Transfusion is unlikely to improve oxygen transport when the hemoglobin concentration is greater than 10 g/dL and is not recommended (class III, level of evidence C). It is not unreasonable to transfuse red cells in certain patients with critical noncardiac end-organ ischemia whose hemoglobin levels are as high as 10 g/dL, but more evidence to support this
recommendation is required (class IIb, level of evidence C).\textsuperscript{25} The guidelines provide indications for transfusions during CPB to keep hemoglobin level at least 6 g/dL, but higher levels are justified in patients at risk of decreased cerebral oxygen delivery (class IIa, level of evidence C).\textsuperscript{25} Otherwise, it is not unreasonable to keep the hemoglobin level at 7 g/dL or greater in patients with risk of critical end-organ ischemia/injury (class IIb, level of evidence C).\textsuperscript{25} The recommendations emphasize that the decision to transfuse PRBCs should be based on multiple factors including patient’s clinical situation and surgical setting, as well as available monitoring and laboratory information. The 2011 update to the STS/SCA blood conservation clinical practice guidelines maintained the recommendations from the 2007 document regarding hematocrit during CPB.\textsuperscript{27} Other similar recommendations have been produced by similar international professional groups.\textsuperscript{26}

2. A few minutes later, before any discussion or transfusion has taken place, the surgeon informs you about the presence of diffuse microvascular bleeding. What is the significance of this clinical observation?

Diffuse microvascular bleeding refers to the clinical presence of continuous oozing and bleeding in the operative field and in vascular points of puncture that occurs suddenly. This clinical sign is associated with severe abnormalities of coagulation and provides clinical diagnosis of coagulopathy. The presence of diffuse microvascular bleeding has been found to be consistently associated with a fibrinogen level less than 0.5 g/L or coagulation factor levels less than 20%. The clotting factor activities less than 20% are reliably reflected by marked prolongations of the prothrombin time (PT) and partial thromboplastin time (PTT) with values greater than 1.8 times control.\textsuperscript{28,29} Thus, in any surgical setting the presence of diffuse microvascular bleeding signals the presence of severe coagulopathy, which requires prompt and effective intervention.

3. Following this, the surgeon asks if you would start transfusing blood products to the patient according to the algorithm. What is a transfusion algorithm? Which of these algorithms are you aware of? What is the evidence regarding these protocols? Do they help to improve patient outcomes?

The effort to reduce the amount of inappropriately transfused blood products includes the development of multiple strategies such as clinical guidelines/recommendations, retrospective audits/peer review of practice, and educational interventions. Most of these efforts have been insufficient to substantially reduce the amount of unnecessary transfusions. There are many reasons contributing to these findings including unfamiliarity and/or skepticism towards guidelines. Also, educational interventions are usually targeted to areas or individuals identified principally by retrospective review and therefore limited range of action. Many difficulties are related to inadequate documentation and the challenges of applying pre-existing guidelines during clinical situations of active or massive bleeding. Due to the aforementioned limitations, transfusion algorithms are an alternative to retrospective audits and quality reviews.
The transfusion of actively bleeding cardiac surgical patients involves multiple and complex therapeutic decisions due to the multifactorial nature of the hemostatic disorder and the scarcity of laboratory data. Therefore, the intent of transfusion algorithms is to proactively assist the clinical decision-making process by combining relevant evidence-based clinical information, point-of-care laboratory values, and patient specific data. These tools can assist stratification of patients at risk and in standardizing blood products administration.

Several of these algorithms have been developed and tested mostly at an institutional level. There is prospective evidence of their efficacy in the reduction of the amount of blood products utilization, the amount of intra- or postoperative bleeding, and the need for surgical exploration. The criteria used by early developed algorithms include; evidence of microvascular bleeding and other clinical parameters in conjunction with standard PT/PTT, fibrinogen level, and platelet counts. The later availability of point-of-care testing allowed the design of other algorithms. The most recent and widely used ones include thromboelastography showing similar results. At present, it is clear that use of transfusion algorithms decreases the number of patients transfused and the amount of products utilized, limiting exposure to the known associated risks of transfusion. It has not been elucidated whether or not any or all of the following contributes to the reduction in transfusions: the use of an algorithm, point-of-care testing, or the behavior derived from them.

The 2011 update to the STS/SCA Blood Conservation Clinical Practice Guidelines recommended the use of enforceable transfusion algorithms supplemented with point-of-care testing as part of a multidisciplinary approach for management of blood resources, for limiting blood transfusions and providing optimal blood conservation for cardiac operations (class I, level of evidence A).

4. During rewarming, the surgeon informs you that achieving hemostasis is challenging, and the procedure is going to be more prolonged than usual. The duration of CPB at this point is 182 minutes. What are the hematologic implications of prolonged CPB course?

Several studies have aimed to elucidate the possible risk factors for significant bleeding and transfusion in cardiac surgery. Those studies have been developed in an effort to identify and optimize the management of patients at risk, as well as rationalize and allocate the use of scarce resources. Multiple studies identified diverse variables associated with excessive blood loss and transfusion. Most of these studies consistently found longer CPB duration to be a significant single predictor for PRBCs transfusions and excessive blood loss in cardiac surgical patients. In 2006, Karkouti et al. published a risk prediction model and simplified risk score for massive blood transfusion in cardiac surgery. They found a linear relationship between the duration of CPB and massive blood transfusion. The duration of CPB > 180 minutes provided the highest score in the modified risk classification (CPB < 120 minutes was considered low-risk, and > 150 minutes moderate-risk). Similarly, CPB duration was the most important factor amongst the variables associated with platelet-related coagulopathy. A more recent study published in 2011 found similar predictors of massive transfusion in thoracic aortic surgery under DHCA.
Particularly, the duration of CPB was an independent predictor of massive transfusion as well as of the total amount of blood products transfused in that patient population.

A fact of major significance is that the duration of CPB is influenced by other factors found to be of predictive value such as reoperative status (or previous sternotomy), type of procedure (higher complexity), and the use of DHCA. In this regard, duration of CPB is increased during DHCA in order to achieve appropriate temperature targets. Otherwise, the duration of CPB is also increased during more complex procedures, reoperations and in patients with previous sternotomy. The pathophysiology of coagulopathy during cardiac surgery on CPB includes foreign surface contact, consumption of clotting factors, activation of coagulation, activation of platelets, platelet dysfunction, and increased fibrinolysis. Upon the course of CPB, the coagulation system is activated via both intrinsic and extrinsic pathways. The final result is the generation of thrombin, which causes further activation of platelets, the coagulation cascade, and the endothelium. Thereafter, the activation of platelets creates a positive feedback loop that generates more thrombin. Therefore, the course of CPB causes a progressive impairment in platelet function.

5. After the decision to transfuse PRBCs is made, you notice that there are varying expiration dates on the PRBCs bags. Which units should be transfused first? What are the implications of PRBCs’ age at the time of transfusion for patient outcomes? Are long-term outcomes specifically adverse in cardiac surgical patients?

The effect of PRBCs storage duration has been a topic of intense debate and controversy. It is known that the so-called “storage lesion” comprises a group of reversible and irreversible functional and structural changes that start after 2 – 3 weeks of storage and progress with the duration of storage. Those changes are characterized by the loss of nitric oxide bioavailability, decreased red cell deformability with increased adhesiveness and consequent alterations in microvascular flow, depletion of adenosine triphosphate (ATP) in the erythrocytes, and the accumulation of phospholipids and proinflammatory mediators. There is also depletion of 2,3-diphosphoglycerate (2,3-DPG) which shifts the oxyhemoglobin curve to the left causing a reduction in oxygen delivery. A significant impairment results from the activation of the Neutrophil NADPH oxidase system by oxidized /proinflammatory lipids. Interestingly, there is a slow restoration of 2,3-DPG with partial reversibility of some functional and biochemical changes. However, the 2,3-DPG remains at only 50 – 70% of the normal range 24 hours after transfusion.

Some studies have not shown an association between PRBCs storage duration and adverse outcomes. Other research has suggested that the risk of adverse effects and poor outcomes related with transfusions is increased if blood had been stored for prolonged periods of time. In both cases, many studies have included small sample sizes, heterogeneous populations, and a diversity of end-points. Nonetheless, most protocols seem to agree that given the present knowledge about storage lesion, “old” blood can be defined as that which has been stored for more than 14 days, whereas blood stored for 14 days or less, when storage lesion is still not apparent, is considered “young” blood. Several studies in diverse populations and different
clinical settings have demonstrated an association between “old” blood and increased infectious complications, regional ischemia, multi-organ system failure and mortality.\textsuperscript{54-57}

In the specific setting of cardiac surgical patients, the studies have conflicting results with most of them demonstrating an association between duration of PRBCs storage and adverse outcomes. The study by Koch \textit{et al.} in 2008 analyzed data in large homogeneous population of cardiac surgical patients, showing that patients who received “old” PRBCs have a significant reduction in both short-term (particularly in the first six months) and long-term survival.\textsuperscript{51} There was also a significantly increased risk of in-hospital death, prolonged intubation, acute kidney injury, sepsis, and multi-organ system failure.\textsuperscript{51} A smaller and more recent study conducted in the United Kingdom by McKenny \textit{et al.} published in 2011 did not demonstrate an association between red cells storage duration and adverse outcomes.\textsuperscript{58} However, they found an association between the number of units transfused and major postoperative complications.\textsuperscript{58} Of relevance, the transfusion of leuko-reduced blood products is a universal practice in the United Kingdom, and is reflected in the study by McKenny \textit{et al.;}\textsuperscript{58} which is a major difference with the study by Koch \textit{et al.}\textsuperscript{51} Another recent study performed in the United Kingdom, corroborated an association between transfusion of any “old” PRBCs and an increased hospital length of stay.\textsuperscript{52} This group also demonstrated that when compared with patients receiving exclusively “young” blood, patients receiving any “old” blood had a higher incidence of new renal complications. Each day of additional storage was associated with a 7% increase in risk of new renal complications.\textsuperscript{52} Alternatives to this issue include modification in storage duration limits or in the storage methods/techniques.\textsuperscript{26}

6. The perfusionist asks whether you would like a hemofilter to be placed in the circuit. What does this achieve? Are there any perfusion-related strategies that could decrease the incidence of coagulopathy or the use of blood products?

The development of whole blood ultrafiltration techniques intends to be part of a blood conservation strategy.\textsuperscript{59} Ultrafiltration conserves blood by filtrating water and low-molecular substances from the CPB circuit, producing protein-rich concentrated whole blood that is reinfused to the patient. Therefore, available ultrafiltration devices are assembled into the CPB as an option to limit hemodilution during CPB.\textsuperscript{27} There are three ultrafiltration procedure variants available. First, \textit{conventional ultrafiltration} is performed exclusively during the course of CPB. \textit{Modified ultrafiltration} is conducted after termination of the CPB course using the existing cannulae. Lastly, \textit{zero balance ultrafiltration} is performed in a similar fashion to conventional ultrafiltration but with replacement of lost volume with crystalloid solution.

In this regard, a meta-analysis by Boodhwani showed evidence favoring the use of \textit{modified ultrafiltration} \textsuperscript{60} and also demonstrated no advantage with \textit{conventional ultrafiltration}. A recent randomized clinical trial also concluded a significant reduction in blood loss at 24 hours and in PRBCs, FFP and platelet transfusion in patients treated with \textit{modified ultrafiltration}.\textsuperscript{61} Otherwise, patients may benefit by removal of inflammatory mediators via \textit{zero balance ultrafiltration} rather than as a result of fluid removal.\textsuperscript{62}
Upon review of the available literature, the 2011 update to the STS/SCA Blood Conservation Clinical Practice Guidelines provided the following recommendations regarding those techniques. “The use of modified ultrafiltration is indicated for blood conservation and reducing postoperative blood loss in adult cardiac operations using CPB (class I, level of evidence A).” “Benefit of the use of conventional or zero balance ultrafiltration is not well established for blood conservation and reducing blood loss in adult operations (class IIb, level of evidence A).”

Another widely used technique that aims to reduce the use of crystalloid prime in the CPB circuit is the so-called retrograde autologous priming (RAP). This method described in 1998 involves the displacement of pump prime volume with the patient blood. Once the patient is heparinized and cannulated, a shunt in the CPB circuit is opened, and the patient’s volume is allowed to drain back toward the circuit and to displace the prime, which is being redirected to a bag or separate holding reservoir. Several studies have shown RAP to work independent of other prime reduction techniques by reducing allogenic blood transfusions, as well as by providing a synergistic effect with other blood management strategies. Careful attention should be placed with pharmacological support of patient hemodynamics while the blood volume is reduced. A recent randomized controlled trial published in 2011 demonstrated the efficacy of RAP in decreasing both hemodilution and the volume of PRBCs transfused. However, a meta-analysis in 2009 could not provide definitive evidence regarding the ability of RAP in reducing the number of intraoperative PRBC transfusions due to small size of the eligible studies. Nonetheless, the analysis showed a reduction in the total hospital stay transfusions. The STS / SCA Perioperative Blood Transfusion and Blood Conservation in Cardiac Surgery Clinical Practice Guidelines in 2007 recommended that RAP may be considered for blood conservation (class IIb, level of evidence B).

The 2011 update to the STS/SCA Blood Conservation Clinical Practice Guidelines recommended other perfusion techniques including: microplegia (class IIb, level of evidence B), minicircuits (reducing priming volume in minimized CPB circuits; class I, level of evidence A), vacuum-assisted drainage (in conjunction with minicircuits; class IIb, level of evidence C), and biocompatible CPB circuits (class IIb, level of evidence A).

7. How do you assess the coagulation status in the operating room? What are the possible tests that can be used to direct your transfusion strategies?

The difficulty in obtaining timely and accurate information about the platelet and coagulation status of patients in the operating room is one of the main reasons for the failure of guidelines to drive a change in transfusion practices. This particular situation prompted the development and prospective evaluation of transfusion algorithms derived from institutional practices, combined with accurate point-of-care testing to guide the management of bleeding and transfusion decision-making. Most studies showed how the combination transfusion algorithms guided by point-of-care laboratory testing were effective in providing adequate hemostasis and reduction of blood products transfusion. Several randomized controlled trials support the use of point-of-care testing as part of transfusion algorithms. All of these trials demonstrated cost effectiveness of their interventions in reducing blood products transfusion.
Multiple point-of-care tests were used in the interventions evaluated in the earlier performed studies including, platelet count, fibrinogen level, PT/INR, and PTT. Most recent studies also included reagent modified thromboelastography (i.e., heparinase after rewarming during CPB), and other platelet function tests (such as platelet function analyzer-100). A recent study evaluated their protocol exclusively in aortic surgery patients under DHCA. Therefore, the contribution of individual tests and the effects of a particular combination of them are difficult to discern. Moreover, it is unclear if the algorithmic and multidisciplinary approach is more important than the specific point-of-care testing used. Most likely, the implementation and consistent application of a multimodal approach to blood management is more important and efficacious than the individual parts of the protocol. As such, it is difficult to assign particular value to specific components of point-of-care testing.

The STS / SCA Perioperative Blood Transfusion and Blood Conservation in Cardiac Surgery Clinical Practice Guidelines in 2007 supports the use of transfusion algorithms and point-of-care tests to guide transfusion practices and enhance blood conservation (class I, level of evidence A).

8. The medical student assisting for the day remembers that in a prior case PRBCs and fresh frozen plasma (FFP) units were transfused at a fixed ratio. The medical student asks if you would like to transfuse one unit of FFP for each unit of PRBCs? How do you respond?

The modalities of transfusion of FFP are also a matter of intensive study and debate. The use of FFP intends to decrease the morbidity and mortality associated with the coagulopathy present during massive hemorrhage. In this setting, several studies of trauma patients requiring massive transfusion have suggested that early use of FFP and high FFP to PRBC ratios may decrease morbidity and improve survival. Moreover, in circumstances of major trauma and massive active hemorrhage with multiple coagulation factor deficiencies, patient management may be delayed while awaiting test results, justifying such use of FFP for prevention of further dilutional coagulopathy. It is now accepted that patients with multiple trauma with massive hemorrhagic shock are likely to derive benefit from a one-to-one FFP to PRBC transfusion strategy. Therefore, FFP transfusion should be initiated early with a high FFP to PRBC ratio in those circumstances due to the multiple hemostatic abnormalities. However, at present, it is not clear if that recommendation can be extended to the correction of high blood loss and/or coagulopathy in other settings such as elective surgery.

More importantly, it is known that use of FFP in massive transfusions can also lead to an increased incidence of transfusion-related acute lung injury (TRALI), acute respiratory distress syndrome (ARDS), and multi-organ system failure. Other adverse effects of FFP transfusion include febrile and allergic reactions and transfusion-associated circulatory overload. In most clinical settings, the administration of FFP should be used to correct a clinically relevant coagulopathy, and as such, driven by appropriate coagulation tests avoiding unnecessary exposure to the risks of FFP.
Regarding the use of FFP in cardiac surgery, a meta-analysis of randomized controlled trials published in 2004 showed no evidence that prophylactic use of FFP affected perioperative blood loss in cardiac surgical patients. The same meta-analysis was updated in 2011 with more recent trials showing similar results and no consistent clinical benefit of prophylactic use of FFP in cardiac surgical patients.

According to the existing evidence, the 2011 update to the STS / SCA Blood Conservation Clinical Practice Guidelines recommended that: “Prophylactic use of plasma in cardiac operations in the absence of coagulopathy is not indicated, does not reduce blood loss and exposes patients to unnecessary risks and complications of allogeneic blood component transfusion (class III, level of evidence A). Transfusion of plasma may be considered as part of a massive transfusion algorithm in bleeding patients requiring substantial amount of red blood cells (class IIb, level of evidence B)”

9. You decide to send a tromboelastogram (TEG)? What is a TEG? What are the applications of TEG in cardiac surgery?

Thromboelastography (TEG) is a laboratory method that provides a global assessment of hemostatic function. This test records and displays a graphical representation of the continuous profiles of whole blood coagulation in vitro by measurement of the viscoelastic changes that are associated with the fibrin polymerization process. TEG assesses such changes in clotting of whole blood under low shear conditions after adding a specific coagulation activator such as Caolin. The basic principle behind TEG is the dynamic tensile force resulting from the interaction between activated platelets and polymerizing fibrin during endogenous thrombin generation and fibrin degradation by fibrinolysis.

The TEG principles are based on the known changes occurring during the coagulation process. A whole blood sample, with or without citrate, is incubated in a cup at 37°C. A stationary pin attached to a wire which can monitor movements is immersed into the sample. The cup oscillates back and forth six times per minute. Caolin is added to activate the coagulation cascade, leading to thrombin formation, and subsequently fibrinogen is converted to fibrin. Finally, a stable clot is formed as fibrin polymers are stabilized by factor VIII and activated platelets, which also is an effect of thrombin formation. The clot strength will influence the oscillation of the pin, and these dynamic changes are converted to a curve. The curve reflects the different phases of the clotting process and enables qualitative evaluation of the individual steps involved. These steps are defined as follows:

**Reaction/clotting time (R-time):** the period from the initiation of test until the beginning of the clot formation.

**K-time (K):** the period from the start of the clot formation to when the curve reaches amplitude of 20 mm; thus indicating clot kinetics.

**α-Angle:** the angle between the baseline and the tangent to the TEG curve through the starting point of coagulation, after the end point of the R-time. The α- angle assesses the acceleration and the kinetics of fibrin formation and cross-linking.
Maximal amplitude (MA): a direct measure of the highest point on the TEG curve and represents clot strength. MA is dependent of platelet concentration, platelet function, and platelet–fibrin interaction.

Lysis at 30 minutes (Ly30): the estimation of the fibrinolytic activity during the first 30 minutes after MA. The amplitude after 30 minutes (A30) is also measured, and the difference between MA and A30 reflects the degree of fibrinolysis. Ly30 is calculated on the basis of the reduction in the area under the curve.

Clot Lysis Index (CLI): the ratio between the amplitude at a given time point, and MA given as percent of MA. Thus, CLI is a measurement of fibrinolysis at a given time.

Clot Index (CI): Represents the hemostasis profile and is calculated based on R, K, α-angle, and MA parameters.

The use of TEG allows assessment of complex coagulopathy present in the intraoperative period. Unfortunately, it cannot detect the in vivo contribution of endothelial cells or blood flow shear forces on clot formation and fibrinolysis. Of major importance is the fact that TEG is particularly sensitive to changes in fibrin polymerization and platelet count. Therefore, the greatest benefit is early detection of dilutional coagulopathy occurring due to trauma and during surgery, in which fibrinogen and platelets fall rapidly. In addition, TEG has proven valuable in guiding platelet and cryoprecipitate transfusion. Moreover, it has been suggested that the inclusion of TEG in transfusion algorithms optimizes targeted transfusion therapies reducing the empiric administration of multiple components.

Currently, TEG is used only in conjunction with standard coagulation tests to decrease the risk for bleeding and reduce homologous blood transfusion in cardiac surgery. More importantly, the use of transfusion algorithms that include TEG has been shown to reduce both transfusion requirements and blood loss in cardiac surgery. Several randomized controlled trials have been performed that demonstrated reduced component therapy use when a TEG-based decision-making algorithm was used without clinical detriment. One of these studies performed in aortic surgery under DHCA showed that the TEG-guided algorithm significantly decreased the need for massive perioperative transfusion. Of note, it is likely in those studies that the use of TEG allowed earlier intervention that may have resulted in better efficacy of blood products transfusion.

10. The following are the results of the TEG you recently sent:

- **R-Time:** 7.4 min. (4.0 - 8.0)
- **K-Time:** 1.9 min. (1.0 - 4.0)
- **α-Angle:** 60.4 degrees (47 - 74)
- **Maximum Amplitude:** 50.2 mm. (55 - 73)
- **Lysis at 30 minutes:** 14.3 % (0 – 8.0)

How can the TEG results be interpreted? After interpreting the above results, what are the coagulation abnormalities present in the patient? Which products are you going to transfuse and why?
Performing TEG tests has technical particularities, and many methodological variations can affect the results. First, the use of citrated blood requires reinforcing a strict time post sampling for testing. Second, even when performing TEG under all manufacturer specifications, it is advisable to determine a local normal range. Otherwise, it is important to remember that reference values for TEG are based on unspecified surgical patient samples of limited size.

As mentioned earlier, TEG differs from the standard coagulation tests in that it provides a global view of the coagulation process. As such it may detect dynamic interactions between platelets and coagulation factors not assessable by other tests. This is the major clinical advantage of TEG testing. Oppositely, standard coagulation tests analyze factors in plasma and isolated components or fractions of the whole system. Despite advantages, TEG has limitations, and subsequently the results must be interpreted carefully. In this regard, the most important considerations are:

1. A normal TEG curve DOES NOT exclude defects in the hemostatic process.
2. TEG testing DOES NOT detect the presence of surgical bleeding.
3. Adhesion defects are not identifiable by TEG.
4. TEG is not sensitive to Factor VII deficiency and is not suitable for monitoring vitamin K antagonist treatment.
5. The standard TEG test does not diagnose increased bleeding risk due to treatment with acetyl salicylic acid or ADP receptor inhibitors (i.e., clopidogrel or ticlopidin).

In particular, regarding the use of TEG during the course of CPB, heparin effects are easily demonstrated using the same procedure and parameters by testing a plain cup and a heparinase cup in parallel runs. This enzyme reverses the effects of heparin present in the whole blood sample. In this case, prolonged R-time may be caused by heparin effects as well as by hemodilution or other causes of coagulation factors deficiency.

Due to the fact that different TEG parameters reflect different phases of coagulation, the intervention may be tailored. Additionally, repeated testing after treatment will enable evaluation of the effects of intervention. The possible alterations can be summarized as follows:

1. Prolonged R-time will indicate decreased coagulation factors, and if this is not due to heparin therapy, transfusion of plasma will replete the deficient coagulation factors reversing the pathology. If heparin effect is present, protamine administration will be able to normalize a prolonged R-time.
2. Reduced α-angle indicates shortage of fibrinogen, which may be corrected by fibrinogen concentrate or plasma. The final decision should be made according to the clinical context in conjunction with standard coagulation studies.
3. Low MA indicates reduced platelet function. Depending on the particular patient situation, DDAVP and/or platelet administration may be indicated.
4. Ly30 and CI: Evaluation of both Ly30 and CI, in conjunction with the morphology of the TEG trace, will assess the fibrinolytic activity. Associated with different TEG curves, elevated Ly30 combined with low CI indicates primary fibrinolysis, whereas elevated Ly30 and elevated CI points towards secondary fibrinolysis. If primary fibrinolysis
is present, the patient would need antifibrinolytic medication, whereas a patient with secondary fibrinolysis could benefit from anticoagulation.

(5) Importantly, the abnormalities related to fibrinogen or platelets may be both qualitative and quantitative. Additional measurement of fibrinogen concentration or platelet count is mandatory.

(6) TEG may not be able to detect abnormalities in primary hemostasis defects, such as the bleeding tendency related to von Willebrand’s disease.

(7) TEG is not able to detect changes in the natural anticoagulants, limiting its use in the evaluation of thromboembolic events.

In summary, an increased clotting time is associated with the need for plasma component replacement, whereas decreased clot strength is associated with the need for either platelet transfusion or fibrinogen supplementation. Otherwise, the influence of these two factors on the clot strength, can be differentiated by studying the results in the presence and absence of platelet inhibitors.75

Post-CPB course:

After completion of the surgical repair, the patient is separated from CPB with no difficulty but continues to show signs of active diffuse bleeding. The surgeon asks you to proceed with reversal of heparin anticoagulation after test dose of protamine is uneventful.

1. After completion of an estimated dose of protamine, the result of the activated clotting time (ACT) test is significantly elevated (149 seconds for a baseline of 99)? What is the most appropriate next step?

Protamine administration is used to neutralize the effects of unfractionated heparin. The neutralization process results from the covalent binding of the abundant polycationic arginine residues present in the protamine (alkaline) molecule to the polyanionic glycosaminoglycan residues of heparin (acidic).

Traditionally, fixed protamine dosing schemes are the most widely used method for quantitative calculation of protamine doses at the end of CPB. Such dosing regimens are developed according to a heparin dose – response curve analysis based on activated clotting time (ACT) in order to determine the quantity of circulating heparin remaining. The initial study that validated such approach was performed by Bull et al. in 1975.79 The initial recommended dosing schemes overestimated the amounts of protamine required. Further studies determined that lower doses of protamine were required due to progressive decreases of heparin plasma levels over time.80
Although, protamine is useful due to its heparin antagonism properties, it has multiple adverse effects on coagulation, particularly on platelet function. Most significantly, protamine causes platelet degranulation with reduced activation, as well as decreased platelet activation. Additionally, protamine causes a large release of t-PA which is one of the main activators of fibrinolysis. In this regard, there is evidence that administration of lower doses of protamine per unit of heparin is associated with reduced blood loss and transfusion requirements. These effects are likely related to reduced protamine-related platelet inhibition and reduced complement levels.

Unfortunately, there are multiple other factors that complicate use of protamine for heparin reversal after CPB. Most of those factors are related to monitoring of heparin plasma levels and subsequent calculation of protamine dosing. Significantly, during extreme hemodilution or hypothermia below 30°C, there is a marked discrepancy between ACT response and actual heparin levels. In this setting, heparin level monitoring and automated protamine titration are preferred. The clinical advantages obtained with the use of these devices are that higher heparin levels can be achieved, and lower protamine doses are used at the end of CPB. The presence of high plasmatic levels of heparin have been associated with reduced activation of the clotting cascade and platelet function preservation. However the heparin monitoring machines require training, and their use is cumbersome compared to the more straightforward direct monitoring of the ACT.

Consequently the 2011 update to the STS / SCA Blood Conservation Clinical Practice Guidelines recommended that: “Use either protamine titration or empiric low dose regimens (e.g. 50% of total heparin dose) to lower the total protamine dose and lower the protamine / heparin ratio at the end of CPB may be considered to reduce bleeding and blood transfusion requirements (class IIb, level of evidence B)”

2. The assistant surgeon suggests you to administer DDAVP? What do you think of this? What are the considerations for using DDAVP in these circumstances?

Desmopressin acetate (1-deamino-8-d-arginine vasopressin) or DDAVP is a peptide analogue of the antidiuretic hormone (ADH) or arginine vasopressin (AVP) that is approved for use in hormone replacement therapy for patients with decreased pituitary function. It offers the great advantage that when compared to vasopressin it has little effect on blood pressure, uterus, or vasoconstriction. DDAVP acts as an analog at the V2 receptor releasing endogenous factor VIII precursors, t-PA, and von Willebrand factor multimers stored in the Weibel Palade bodies of the vascular endothelium. Desmopressin has been shown to improve platelet function and shorten the bleeding time of patients with mild forms of hemophilia A or von Willebrand’s disease. In this setting, DDAVP used for reversal of such hemostatic abnormalities before surgery is associated with significant decreases in bleeding and blood transfusions. DDAVP is also used frequently in bleeding hemodialysis patients.

DDAVP has been used with variable success in cardiac surgery patients with intractable bleeding, with only minor effect when given indiscriminately for minor bleeding after
It has been suggested that because critically ill patients are often receiving vasopressin, there is little benefit to adding DDAVP in such circumstances.\textsuperscript{87}

The variable results of studies addressing the efficacy of DDAVP in limiting bleeding during cardiac surgery prompted the 2011\textsuperscript{27} Update to The STS/SCA Blood Conservation Clinical Practice Guidelines to maintain the recommendations from the 2007 document as follows:\textsuperscript{25} (1) “Use of 1-deamino-8-D-arginine vasopressin (DDAVP) may be reasonable to attenuate excessive bleeding and transfusion in certain patients with demonstrable and specific platelet dysfunction known to respond to this agent (e.g., uremic or CPB-induced platelet dysfunction, type I von Willebrand’s disease). Class IIb, level of evidence B. (2) “Routine prophylactic use of DDAVP is not recommended to reduce bleeding or blood transfusion after cardiac operations using CPB (class III, level of evidence A)\textsuperscript{27}.

3. At this point, you realize that the patient’s core temperature is 34.5°C. The room air temperature and the forced air warming system temperatures are optimized at your request. What are the implications of hypothermia for hemostasis? What are the pathophysiologic changes induced by hypothermia in the coagulation system?

The effects of hypothermia on the hemostatic system were already summarized at the beginning of the discussion. In conclusion, the various degrees of hypothermia have an influence on both cellular and plasmatic components of coagulation. Hypothermia also has synergistic effects on thrombin generation and fibrinolysis, with deleterious clinical consequences. Of particular importance, the reversible platelet dysfunction associated with CPB is progressively worse when the patient has been hypothermic for prolonged periods of time.\textsuperscript{1,86} Interestingly, there is evidence suggesting that the phenomenon of hypothermia-induced platelet aggregation, which occurs during CPB at temperatures between 15 to 32.8°C, is a significant source of emboli and is associated with an increase in postoperative cognitive dysfunction / decline.\textsuperscript{88}

4. The surgical team continues to correct possible causes of surgical bleeding, but there is persistent clinical evidence of coagulopathy despite appropriate continued blood products transfusion? The surgeon requests administration of activated recombinant Factor VII. What are the considerations for its use and the associated risks of this medication?

Activated recombinant factor VII (rFVIIa) is approved for replacement therapy in congenital factor VII deficiency or for treatment of bleeding in hemophilic patients with inhibitors.\textsuperscript{87} It is recognized that a significant element of postoperative hemostasis is the generation of thrombin and fibrin by the extrinsic pathway via factor VII/tissue factor complex.\textsuperscript{89,90} Importantly, only roughly 1% of circulating factor VII is activated, and it has no effect until bound with tissue factor. The hemostatic effects of rFVIIa are produced in part by forming a complex with tissue factor (which also activates factor X) expressed at the vascular injury site to locally produce thrombin, amplifying the coagulation process.\textsuperscript{86,87} When given in supraphysiological pharmacological doses (90 μg/kg), it is able to activate factor X by a second mechanism,
presumably via adsorption to activated platelet surfaces. Obviously, successful clot formation remains dependent on the presence of fibrinogen, factor X, and cofactors.86

Although the therapeutic rFVIIa dose in patients without hemophilia has not been established, it is increasingly used off-label for life-threatening hemorrhage. There are many citations reporting off-label rFVIIa use after cardiac surgery.91 Those publications show an excess of thrombotic complications with rVIIa in cardiac surgical patients when compared with the incidence reported in the studies for use in intracranial hemorrhage.92 There is also a higher incidence of arterial thrombotic events than venous, also with higher incidence in the elderly.86 However, the drug is typically administered as rescue therapy to patients who have already received multiple transfusions, have impaired coagulation, and are at high risk for adverse events.

In a recent prospective randomized controlled trial in cardiac surgical patients with severe bleeding 93, more adverse events occurred in the rFVIIa groups (including an excess of deaths in the rFVIIa group), but none of the outcomes reached statistical significance. However, after randomization, significantly fewer patients in the rFVIIa groups underwent reoperation because of bleeding, or required allogeneic transfusions.86,87 As a consequence, some centers only give access to this agent after discussion with a hematologist, and when acidosis, hypofibrinogenemia, thrombocytopenia, and other evident causes of coagulopathy have all been corrected.86

The 2011 Update to the STS / SCA Blood Conservation Clinical Practice Guidelines recommended 27: “Use of recombinant factor VIIa concentrate may be considered for the management of intractable nonsurgical bleeding that is unresponsive to routine hemostatic therapy after cardiac procedures using CPB (class IIb, level of evidence B)”27

5. Even though the bleeding improves with the administration of factor VII activated, the decision is to perform a temporary soft tissue but not sternal closure. The plan is correcting the coagulopathy in the ICU and to attempt sternal closure after the clinical bleeding has improved. The patient requires transfusion of multiple blood products in the CTICU but demonstrates progressive improvement. There is no need for additional surgical intervention in order to correct the bleeding. After complete resolution of the coagulopathy, the patient returns to the operating room for mediastinal exploration / washout and chest closure. What are the long-term implications of massive transfusion for patient outcome?

The adverse outcomes attributable to the consequences of massive transfusion are recognized in the literature. An observational study in cardiac surgery patients with CPB found massive transfusion to be independently associated with mortality with an eight-fold increase in the odds of death.94 Alternatively, another study concluded that cardiac surgical patients who required re-sternotomy for massive bleeding had longer ICU stay, use of intra-aortic ballon counterpulsation, and increased mortality.95 More importantly, in the majority of patients, a hemostatic defect was detected, and a surgical cause of bleeding was identified in only about half of the patients. Those findings emphasize the significance of coagulopathy and massive bleeding in this population.
In this context, a possible cause for adverse outcomes is the deleterious effects of blood product transfusion such as immunomodulation or the reduced end-organ oxygen delivery. Another possible explanation for the increased mortality associated with massive transfusion and blood loss is that the process of large-volume resuscitation is inherently harmful and independent of the effects of transfusion. In this regard, large-volume resuscitation is known to lead to marked physiologic perturbations, including acid-base and electrolyte abnormalities, tissue edema, hemostasis impairment, immune and inflammatory system modulation, and their consequent end-organ ischemia and multi-organ system dysfunction.

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