

Blood Management Issues: Getting Clots Together When You Want Them

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Abstract: Coagulation is a complex process that allows whole blood to form clots at tissue and vessel sites where damage has occurred. Activation of the hemostasis system causes platelets and fibrin-containing clot to stop the bleeding. Perfusionists must find ways to preserve the coagulation system if we are to avoid bleeding in the cardiopulmonary bypass patient. It is still unclear what techniques are best to continue maintaining hemostasis and avoiding transfusion in patients requiring cardiopulmonary bypass (CPB). There are numerous factors that come into play with the use of CPB including deactivating the coagulation system with anticoagulants, hemodilution of the circulating blood volume,

inflammatory response, and a possible pro-coagulant response from protamine with heparin reversal once the surgical procedure has been completed and CPB terminated. All these factors make achieving hemostasis post CPB extremely difficult. This review attempts to assess what is currently being discussed in the literature, which may improve hemostasis with cardiopulmonary bypass. There is still no one technique that will improve hemostasis post CPB. Perhaps the answer may lie in a combination of reported techniques that may in some way lead to the preserving of coagulation factors during CPB. **Keywords:** cardiopulmonary bypass, coagulation, hemostasis. *JECT. 2011;43:P52–P57*

Coagulation is a complex process that results in blood forming clots at tissue and vessel sites where damage has occurred, thereby stopping bleeding. Cardiac surgery extensively alters the normal coagulation process both intentionally and unintentionally. More often than not, cardiac surgery uses cardiopulmonary bypass (CPB) for intervention and surgical correction. Before initiating cardiopulmonary bypass the coagulation system is deactivated with anticoagulants, such as heparin, to prevent blood clotting from CPB associated surface activation and tissue damage. Once the surgical procedure has been completed the coagulation system must be reactivated so that normal hemostasis may proceed to stop surgical bleeding at the site of the assaulted tissues. Furthermore, confounders such as hemodilution, platelet consumption, CPB-induced inflammation, and a potential procoagulant response associated with heparin reversal may make clotting less likely to occur.

To promote post cardiac surgery clotting—clotting when you want it—a multi-disciplinary approach is required.

This includes optimizing the patient's hematological profile before CPB, minimizing the deleterious effects of CPB on the blood by circuitry selection and anticoagulation strategy, and promoting post CPB clotting by reducing the dilution and consumption of red blood cells, platelets, and plasma proteins. It is also important to quickly identify why clotting is not occurring and correct any deficiencies in the coagulation system.

Point-of-Care Testing—Real Time Monitoring

The monitoring of the coagulation system assists with blood clot formation after cardiac surgery by allowing for early and pre-emptive intervention during the operative procedure whereby appropriate steps can be taken to maintain the coagulation system's integrity. Although the hematology laboratory plays a vital role in the preoperative prediction of bleeding problems, once the patient enters the operating room its role begins to diminish due to the response time of results. The time from collecting an intraoperative blood sample and sending it to the laboratory for analyses and posting a result can be up to an hour. Meanwhile, the continuous changes in the patient's fluid and hematological status reduce the relevancy of the test results.

There are a number of point-of-care (POC) coagulation analyzers that measure a variety of coagulation parameters

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such as the Ichors Platelet works device, (Helena Laboratories, Beaumont, TX) (1,2) or the thromboelastograph (TEG® Haemoscope Corp, Niles, IL). Enriquez and Shore-Lesserson (2) concluded in their review of POC coagulation testing and transfusion algorithms that the benefits of POC testing in the surgical patient include rapid turn-around times and specific measurements of hemostasis defects that can direct therapy.

Before the commencement of CPB using POC analyzers, thromboelastograph and Ichors Platelet works, patients are baseline with further tests repeated during the rewarming phase of CPB to help identify potential problems. While the patient is fully heparinized on CPB, measurement of clot integrity is undertaken with the use of heparinase cups in the TEG; platelet counts and function are analyzed with the Ichor. Fibrinogen levels can also be determined while heparinized using the hematology laboratory. These tests help us to understand what is happening with the patient's coagulation system and—in conjunction with transfusion algorithms—predict whether blood products or factor supplements would be required following the patient's disconnection from CPB and reversal of the heparin induced coagulopathy.

Heparin and Protamine—The Right Balance

Since the beginning of CPB in the 1950s, there have been many changes in the CPB system including the oxygenator and circuit and surface coatings, yet little has changed in what is considered a safe level of heparin. Bull et al. (3) in 1975 first described the use of an “activated clotting time” (ACT) with what was considered an adequate level of heparinization for CPB. Bull's ACT of more than 480 seconds still remains unchallenged as an indicator of adequate heparinization required to undertake CPB.

Studies looking at customizing the dose of heparin using heparin dose response curves as determined by the “Hepcon HMS Plus” (Medtronic, Minneapolis, MN) include Garvin and colleagues (4) and Slight et al. (5). Garvin et al. examined heparin doses in 3880 cardiac surgery patients. The Hepcon HMS was used to individually identify the heparin dose for a target ACT. However, as there was a wide variation in the post heparin ACT, they concluded that this system poorly estimates heparin requirements in the pre-CPB period. In a randomized controlled trial by Slight et al., one group of patients received individualized heparin doses as indicated by the Hepcon HMS. A second group of patients received a standard weight-based heparin bolus with further doses as dictated by the ACT (Max-ACT, Helena Labs, Sunderland, UK). They concluded that the study showed no significant difference in efficacy between the weight-based heparin ACT and the Hepcon HMS heparinization strategies. Although the Hepcon system group received significantly greater amounts of heparin, this did not reduce postoperative blood loss or transfusion

requirements — ACT-based heparinization was found to be as efficacious as the Hepcon HMS.

What constitutes an adequate heparin dose for CPB and is there any advantage to be gained by reducing heparin levels? Several small studies have shown reduced postoperative bleeding in patients where low systemic dose heparin and heparin coated circuits were used (6–8). The perfusion community still awaits a large randomized trial to prove the benefits of this technique.

Heparin rebound—defined as the reappearance of anticoagulant activity after adequate neutralization with protamine—may also contribute to excessive postoperative bleeding after cardiac surgery. This phenomenon has been discussed since first reported by Kolff et al. (9) who described heparin rebound in 1956 as “a treacherous hemorrhagic phenomena.” Teoh and colleagues (10) suggested that heparin anticoagulant activity persists for up to 6 hours after surgery despite apparent protamine neutralization. Their observation suggests that after its administration, a large proportion of the heparin binds to plasma proteins and is incompletely removed by protamine. After protamine is cleared, the protein-bound heparin dissociates slowly and binds to anti-thrombin III to produce an anticoagulant effect. The authors concluded that postoperative protamine infusion was able to almost totally abolish heparin rebound. In the context of this study, protamine infusion resulted in reduced postoperative bleeding but the magnitude was insufficient to alter transfusion requirements. Martin et al. (11) suggest that significant postoperative bleeding following cardiac surgery is often ascribed to “heparin rebound phenomenon” and as such is often treated with additional empiric doses of protamine sulphate. However, inappropriate protamine administration has been reported to be associated with acute pulmonary hypertension. The significance of heparin rebound following cardiac surgery remains to be elucidated, and until such time a conservative administration of protamine in response to “rebound” is recommended (11).

In our experience, the TEG (using a heparinase cup) while heparinized and on CPB can appear normal; yet post protamine, the TEG appears coagulopathic. Thus it appears that the appropriate protamine dosage is still unclear. Further aspects about issues with protamine were investigated by Shore-Lesserson, Reich, and DePerio (12) and Griffin et al. (13). Shore-Lesserson et al. reported that weight-based heparin and protamine dosing strategies for CPB do not take into account patient variability in drug sensitivity and therefore may result in excessive bleeding. In their study, the incidence of incomplete heparin neutralization and heparin rebound were not different between the two groups of heparin and protamine titration system and standard weight based management with regard to heparin dose and that postoperative bleeding and transfusion requirements also did not differ. However, they concluded

that in cardiac surgical patients, heparin and protamine titration does predict a lower protamine dose but this did not result in an improvement in postoperative hemostasis. Griffin et al. examined the antiplatelet effects of heparin, protamine, and varying heparin/protamine ratios in an *in vitro* physiological model. They also further elucidated the mechanism of the antiplatelet and anticoagulant effects of protamine. Their study suggested that the protamine reversal of heparin's antiplatelet effect occurs within a narrow window because protamine also has a direct antiplatelet effect. The issue of protamine reversal was addressed in an editorial by Levy and Tanaka (14): "is too much of a good thing [protamine] bad?" They concluded: ". . . Yes. That we administer far too much protamine to treat bleeding in patients who don't need it".

Cardiopulmonary Bypass—Closed versus Open

The extracorporeal circuit, its foreign surfaces, the blood to air interface, and variations in temperature may all activate the haemostatic system. Koster, Bottcher, and colleagues (15) investigated attenuating this activation by comparing three different perfusion regimens for coronary artery bypass grafting in 30 patients (10 in each group). The first group used a closed CPB system with cardiomy suction line and active venting of the heart; group two used a closed CPB system and avoided cardiomy suction but included active venting of the heart; while the third group used a closed system with avoidance of cardiomy suction and with passive venting of the heart into the collapsible venous reservoir. The results showed that minimizing the blood/air interface significantly reduced hemostatic activation.

Further studies supporting the hematological benefits of using closed CPB systems were found by Casalino et al. (16), Hussaini et al. (17), and Lindholm and colleagues (18). Casalino et al. compared the transfusion rates in 60 patients undergoing cardiopulmonary bypass randomly assigned to two different circuits: an open circuit and a closed circuit. The number of packed red cells transfused was significantly higher in the open system group compared to the closed system group. They concluded that with preoperative conditions predictive for the need of transfusions, the use of a closed CPB circuit could diminish the amount of transfused blood products. Hussaini et al., using 20 randomized pigs, evaluated the efficacy of low-dose heparin in conjunction with thrombotic-resistant surfaces, closed perfusion systems (heparin bonded circuit [HBC] group) versus the conventional strategy of non-thrombotic-resistant open circuits with high-dose heparin (non heparin bonded circuit [nhb] group), during three hours of CPB. Pigs in the HBC group showed over a third reduction in post-CPB blood loss in comparison with the NHB group. Their study concluded that using low-dose heparin and closed thrombotic-resistant circuits reduces adverse hematological and pro-inflammatory responses induced

by CPB. Lindholm et al. (18), in a prospective, randomized study, investigated the inflammatory response, coagulation, and fibrinolytic activation differences between a closed-circuit (complete heparin coating and a centrifugal pump) and a conventional system (uncoated circuit, roller pump, and a hard-shell venous reservoir) in 41 elderly patients undergoing coronary artery bypass grafting or aortic valve replacement. Their conclusion was that the closed perfusion system improves cardiopulmonary bypass by reducing inflammatory and hemostatic activation.

HEMODILUTION—NOT JUST ANEMIA

Hemodilution is an unavoidable consequence of CPB. Hemodilution is usually considered in terms of reducing hemoglobin and hence oxygen carrying capacity of the blood. However, as hemodilution affects the entire coagulation system, platelet count, fibrinogen level, and other coagulation factors also need to be considered. A number of techniques have been developed to assist in reducing the hemodilution associated with the priming volume of CPB circuits.

Acute normovolaemic hemodilution (ANH)—a technique to preserve autologous platelets and improve coagulation post CPB—entails the removal and collection of some of the patient's whole blood while replacing the lost blood volume with a sanguinous fluid. Joviæ et al. (19) performed ANH in 226 patients having an Hct greater than 36% in a prospective trial of 310 consecutive patients after open heart procedures. During their hospital stay, 142 patients did not get homologous blood and all were in the ANH group. However, these benefits of ANH were not seen by Zisman et al. (20) when evaluating the influence of ANH and subsequent autologous blood transfusion on post CPB coagulation disturbances as evaluated by TEG. They randomized 62 patients undergoing elective cardiac surgery requiring CPB into either an ANH group or a control group requiring homologous blood if required. Although an autologous blood transfusion did not affect post CPB coagulopathy, neither did it decrease blood loss or homologous blood products transfusion in the early postoperative period.

Retrograde autologous priming (RAP) of the CPB circuit at the initiation of bypass replaces the priming solution with the patient's own blood. One hundred and four patients were entered into a prospective, randomized, controlled study by Balachandran et al. (21). They were able to remove a mean volume of approximately 800 mL of prime from the CPB circuit. This resulted in a higher hematocrit on admission to the intensive care unit and at discharge from hospital. Further evidence purporting to the benefits of RAP were provided by Saczkowski and colleagues (22). In their meta-analysis they identified six randomized trials comparing RAP to a prospective control group. The combined patient population studied in the six trials was

mainly primary isolated coronary artery bypass surgery. The pooled data suggested that RAP significantly reduced intraoperative and postoperative packed red cell transfusions. However, once homologous red blood cells were required intraoperatively, RAP did not provide any clinical benefit in reducing the number of homologous units further transfused.

The use of a hemofilter during CPB for ultrafiltration of plasma water to concentrate the cellular and protein components of blood was investigated by Raman and colleagues (23). They compared two groups of patients undergoing high-risk cardiac surgery with or without hemofiltration. This included 118 patients who underwent complex cardiac surgical procedures during 12 months. Age, procedure times, and mortality rates were similar in both groups. Postoperative serum hemoglobin, hematocrit, platelet, and albumin levels were all significantly higher in the hemofiltration group. They concluded that hemofiltration during CPB attenuates postoperative anemia, thrombocytopenia, and hypoalbuminemia, and may reduce post-operative bleeding.

Modified ultrafiltration (MUF)—a technique to concentrate the blood by ultrafiltration of plasma water at the termination of CPB (via an in situ arterial line) — is commonly performed in pediatrics. Boodhwani et al. (24) randomized adults (under 65 kg) undergoing CPB to MUF (29 patients) or a sham (circulation without ultrafilter, 36 patients), both for 15 minutes at termination of CPB. The MUF procedure removed on average 1000 mL with a subsequent increase in hemoglobin immediately after intervention. The authors concluded that MUF was effective for hemoconcentration after CPB in patients of low body weight, but it is associated with an increased need for vasopressor support. However, the red cell transfusion rate was not significantly different between the groups.

Following termination of bypass, the CPB circuit itself contains a significant volume direct transfusion, or processing of this blood via a blood cell processor to retain washed red blood cells for retransfusion. These techniques produce a reinfusion product that is either dilute whole blood or a concentration of red cells free of plasma proteins and platelets. An alternative technique is the use of a Hemobag (Global Blood Resources, Hartford, CT) to concentrate the pump blood by ultrafiltration. Roeder et al. (25) assessed the Hemobag ultrafiltration system following CPB in a porcine model; the circuit contents were transferred into a Hemobag and processed. There were significant elevations in pre-Hemobag versus post-Hemobag hematocrit, total protein, and fibrinogen. They concluded that the Hemobag effectively concentrates post-bypass circuit volume providing a product that is high in red blood cells and plasma proteins and may provide an alternative to current techniques for circuit volume salvage. Beckmann and colleagues (26) compared salvaging residual circuit blood by either Hemobag or by cell processor after CPB.

Use of the Hemobag technique for salvaging blood was associated with significant increases in the patient's blood plasma protein and cellular components as compared with cell processor.

Although many investigators have investigated what constitutes an optimal hematocrit, fewer studies have explored the issue of CPB hemodilution of coagulation factors and fibrinogen (27–31). If a patient requires red cells on pump, should perfusionists consider also transfusing plasma units rather than using crystalloid or colloid replacement for volume loss? Is it prudent in the hemodiluted patient to give further fluid to dilute the coagulation system and wait for the patient to be weaned from bypass before plasma (or even platelets) is given?

Shaz et al. (32) investigated the relationship of the ratio between plasma, platelets, and cryoprecipitate to red cells with its effect on mortality in massively transfused patients. They showed, using data from military and civilian centers, that mortality is decreased in massively transfused patients by increasing the transfusion ratio of plasma, platelets, and fibrinogen to red blood cell products during resuscitation and surgery. A total of 214 patients received massive transfusion secondary to traumatic injury. High versus low transfusion ratios were associated with improved 30-day survival in trauma patients. However, further clinical trials are required to determine the optimal transfusion ratios.

Plasma transfusions are often performed without clear consensus on indications. Murad and colleagues (33) reviewed the literature to summarize the evidence regarding the benefits and harms of plasma transfusion in common clinical settings. They identified 37 studies that enrolled adult patients that were transfused with plasma and compared to a control group. In patients undergoing massive transfusion, plasma infusion at high plasma, red blood cell ratios were associated with a significant reduction in the risk of death. However, in patients undergoing surgery without massive transfusion, plasma infusions were associated with a trend toward increased mortality. Plasma transfusions were also associated with increased risk of developing acute lung injury. Therefore there was low-quality evidence suggesting that a plasma infusion in the setting of massive transfusion for trauma patients may be associated with a reduction in the risk of death and multiorgan failure. However, a survival benefit was not seen in most other transfusion populations.

It has been suggested that preoperative plasma fibrinogen concentration is independently associated with postoperative blood loss after cardiac surgery. Karlsson et al. (34) hypothesized that a prophylactic infusion of fibrinogen concentrate may reduce postoperative bleeding. Twenty elective coronary artery bypass graft patients were randomized to receive an infusion of 2 g fibrinogen concentrate or no infusion before surgery (control group). There were no clinically detectable adverse events of fibrinogen

infusion except for one subclinical vein graft occlusion. Fibrinogen concentrate infusion reduced postoperative blood loss by 32%. Hemoglobin concentration was also significantly higher 24 hours after surgery in the fibrinogen group. Interestingly, prophylactic fibrinogen concentrate infusion did not influence global postoperative hemostasis as assessed by TEG. The authors concluded that preoperative fibrinogen concentrate infusion reduced bleeding after coronary artery bypass grafts without evidence of postoperative hypercoagulability. However, larger studies are necessary to ensure safety and confirm efficacy of prophylactic fibrinogen treatment in cardiac surgery.

Further evidence for the role of fibrinogen in managing dilutional coagulopathy was provided by Bolliger and colleagues (35). They performed an in-vitro study hypothesizing that there is a minimal fibrinogen concentration in diluted whole blood above which the rate of clot formation approaches normal. The target plasma concentration for fibrinogen replacement was predicted by these in-vitro results to be greater than 200 mg per dL, as only these concentrations optimized the rate of clot formation. The study suggested that the fibrinogen concentration needs to be twice the level suggested by the current transfusion guidelines. However, although improved, clots were prone to fibrinolysis indicating that the efficacy of fibrinogen therapy may be influenced by any co-existing fibrinolytic tendency occurring during dilutional coagulopathy.

Summary

It is a team approach to “getting clots together” by all specialties who must be diligent in their tasks at all stages of the cardiac surgical patient’s care and recognize that hemodilution not only affects hemoglobin but also the factors, fibrinogen, and platelets of the coagulation system. In patients where excessive hemodilution has occurred and the transfusion of homologous red cells are required to maintain the hemoglobin, should consideration be given to the effects the dilution has also had on the coagulation system? Further studies, such as the work by Karlsson et al. (34), are required to assess the benefits of early intervention with coagulation products and transfusion protocols for massive hemodilution as suggested by Murad and colleagues (33) that may have some benefit for a selective group CPB of patients.

There is no magic recipe to stop a patient bleeding post CBP; it is simply a matter of attentiveness and willingness to spend time to take all possible avenues by all specialties to reduce blood loss.

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