PERIOPERATIVE COAGULATION MANAGEMENT DURING CARDIAC SURGERY

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Purpose of review
Cardiac surgery patients commonly present bleeding complications that negatively influence patient’s clinical outcome. Therefore, fast and detailed diagnoses as well as early and specific therapy of perioperative coagulopathy are of high clinical relevance. The so-called point-of-care (POC) methods for coagulation analyses are increasingly used in perioperative care. It is the purpose of this review to present modern aspects of coagulation management, discuss the effect of the implementation of POC methods in perioperative care, and present substantial components of hemotherapy algorithms to manage coagulopathy in cardiac surgery patients.

Recent findings
Recent studies suggest that implementation of point-of-care testing in hemotherapy algorithms which inclose stepwise therapeutic escalation may reduce perioperative blood loss and the transfusion rate of allogenic blood products. This should improve patient’s clinical outcome and reduce costs.

Summary
Prospective randomized multicenter studies are needed to confirm the hypothesis that algorithm-based specific hemotherapy in conjunction with POC testing minimizes patient’s exposure to blood products and improves clinical outcome.

Keywords
cardiac surgery, coagulation management, coagulopathy, hemostasis, point-of-care coagulation testing

INTRODUCTION
Patients undergoing cardiovascular surgery are at particular risk for the development of perioperative coagulopathy. In addition to coagulopathy, other independent risk factors that have an impact on postoperative morbidity and mortality include excessive blood loss, the use of allogenic blood products, and reoperation for bleeding [1,2]. Algorithm-based hemostatic therapy has been shown to be superior to empiric hemostatic therapy that is based on clinical judgment [3]. Thus, there is a clear need to improve algorithms of hemotherapy in the setting of cardiovascular surgery.

Efficient hemotherapy should treat the coagulopathy, prevent thromboembolic events, and reduce blood loss, thereby reducing transfusion requirements and risk of transfusion-related adverse events and save costs. These challenges highlight the need for an effective hemotherapy that necessitates both a specific hemotherapy algorithm, and the availability of point-of-care (POC) diagnostics to enable a fast and comprehensive diagnosis of the multifactorial causes of perioperative hemorrhage.

DIAGNOSIS OF COAGULOPATHY
Fast and comprehensive diagnoses of the underlying causes of perioperative coagulopathy are of elementary clinical relevance and represent a clinical challenge because particularly in cardiac surgery patients, the causes of coagulopathy are of multifactorial origin.

Multifactorial cause of coagulopathy
There are several surgery-related factors during cardiac surgery procedures that increase the risk of coagulopathy. These include the use of heparin to

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shortfalls of conventional coagulation testing. After a median turnaround time of 23 min (interquartile range 21–24 min), test results are available earlier as compared with conventional laboratory analyses [7]. None of the currently available methods of POC coagulation testing can alone provide an adequate picture of the entire coagulation spectrum; thus, only various methods in conjunction may serve as a comprehensive diagnostic system. A combination of aggregometric and viscoelastic methods yields a marked broader diagnostic spectrum than the conventional laboratory testing of blood clotting. Aggregometric measures are used to screen for disorders of primary hemostasis, such as (acquired) platelet dysfunctions and allow the quantification of the effect of antiplatelet medications. Viscoelastic POC techniques are based on thromboelastography, which was described decades ago by Hartert [8]. They are used to measure the time until clot formation begins, the dynamics of clot formation, and the solidity and stability of clots over time. They enable parallel measurements to be performed on a single blood sample after clotting has been activated using a variety of agonists. A special advantage of viscoelastic techniques is that they can directly detect hyperfibrinolysis.

**Implementation of point-of-care testing in perioperative care**

Up to now, seven prospective randomized trials studied the effect of perioperative POC coagulation testing during cardiac surgery [3,9–13,14]. All studies focused on potential differences in the transfusion requirements; four of them also analyzed perioperative blood loss as primary study endpoints [3,11–13]. In five studies, solely viscoelastic tests were used, and in two studies [3,14], viscoelastic and aggregometric tests were combined. In two studies patients also in the control group received hemotherapy according to a therapy algorithm [3,14], and in two studies, the authors exclusively focused on coagulopathic patients [11,14]. All authors with the exception of Westbrook et al. [13] reported a POC-associated decrease in transfusion requirements. Reduced postoperative blood loss was observed in those two studies that only included coagulopathic patients [11,14]. Improved clinical outcome (expressed as fewer rethoracotomies [11] or postoperative mechanical ventilation time, composite adverse events and shorter 6-month mortality [14]) was also observed only in those two studies which included exclusively coagulopathic patients. A retrospective study including 3865 cardiac surgery patients who...
received conventional or POC-guided hemotherapy found comparable results [15*].

Up to now, only one monocenter study had a prospective randomized and controlled study design, which enrolled only coagulopathic patients and used hemotherapy algorithms for both, the POC and the conventional group [14**]. A multicenter study with a larger study population is needed to analyze whether the results of this study (hemostatic therapy based on POC testing reduced patient exposure to allogenic blood products and provided significant benefits with respect to clinical outcomes) can be reproduced in other facilities.

HEMOTHERAPY ALGORITHM

Avidan et al. [3] showed that algorithm-based hemotherapy was superior to hemotherapy based on clinical judgment. Thus, perioperative coagulation management should be based on a hemotherapy algorithm that is implemented in institutional standard care. Each therapy should involve a preoperative assessment of the patient’s individual bleeding risk, in particular considering preoperatively performed antiplatelet therapy. Intraoperative and postoperative coagulation management consists of frequent evaluation and correction of basic physiological conditions required for hemostasis and effective antagonism of heparin. When indicated, replacement of deficient coagulation factors and improving the hemostatic potential of the primary hemostasis are consecutive steps in therapy escalation. Ultima ratio options are off-label use of factor XIII and recombinant factor VIIa.

Evaluate patient’s bleeding risk

The first step of any effective therapy algorithms should evaluate the patient’s individual bleeding risk. This should be done by conducting a preoperative standardized questionnaire, which highlights any unusual bleeding in the patient’s history, any hereditary coagulopathy, for example, von Willebrand disease and any anticoagulatory medication the patient is taking. There are almost no costs associated with such questionnaires and they can be effective in discovering preoperative factors that may contribute to coagulopathy.

Maintain optimal physiological conditions for hemostasis

During the perioperative period, anesthesiologists should frequently evaluate and if necessary correct basic physiologic conditions for hemostasis. The patient’s physiological pH and core temperature should be maintained at more than 7.3 or 36°C, respectively. Calcium is an elementary cofactor in several enzymatic processes during coagulation [16]. It is important to maintain a plasma-ionized calcium concentration of more than 1 mmol/l. With respect to the rheological properties of red blood cells and the provision of thromboxane A2 and ADP for platelet aggregation, we suggest that the hematocrit should be maintained at a concentration of more than 25% following extracorporeal circulation in coagulopathic patients.

Antagonize heparin

After cardiopulmonary bypass, protamine is used routinely to antagonize 100% of the initial heparin dose. However, in cases of ongoing bleeding, it is necessary to exclude any persistent heparin effects. If the activated clotting time remains more than 130s, or viscoelastic measures indicate persistent heparin effects, it may be necessary to administer additional protamine (30 IU/kg) and to re-evaluate its therapeutic effect.

Maintain adequate levels of coagulation factors

If coagulopathy persists following reversal of the anticoagulant effects of heparin, it should be ensured that adequate levels of coagulation factors are maintained. Fibrinogen is the first coagulation factor to fall below lower reference values during bleeding [17]. As the precursor to fibrin, and as a ligand for platelet aggregation, fibrinogen plays a key role in clot formation [18]. Thus, if plasma levels of fibrinogen drop below 150–200 mg/dl, or if viscoelastic tests indicate a deficiency, it is necessary to administer a fibrinogen substitute. In the past, fresh frozen plasma (FFP; 15–30 ml/kg) has been used as a source of replacement fibrinogen. However, the transfusion of FFP is associated under certain conditions with volume overload, sepsis, multiple organ failures, and increased perioperative mortality [19,20]. An alternative source of fibrinogen is fibrinogen concentrate, which should be used at a concentration of 25–50 mg/kg. A recent review of trials in which fibrinogen concentrate was used in perioperative settings or in cases of massive hemorrhage suggests that this form of substitution is both effective and well tolerated [21].

If coagulopathy persists following supplementation of fibrinogen, the next stage of the therapy algorithm should be to analyze and – if necessary – correct a potential deficiency of prothrombin
complex coagulation factors II, VII, IX, and X. Substitution of factors II, VII, IX, and X should be considered if the INR is more than 1.4, or if viscoelastic measures reveal a deficiency. A dosage of 15–30 ml/kg FFP is necessary to increase the concentration of these factors. However, the use of a prothrombin complex concentrate, which depending on the product contains factors II, VII, IX, and X, proteins C and S, heparin, and antithrombin, represents an attractive alternative due to the much smaller volumes required to supplement the deficiency (recommended dose 20–301U/kg) [22].

Platelets

After the substitution of coagulation factors, the therapy algorithm should lead to a consideration of both platelet count and function. Importantly, temperature has a strong impact on platelet function [23]. In addition to temperature, the use of extracorporeal circulation negatively impacts on primary hemostasis [24]. Extracorporeal circulation causes irreversible platelet damage mainly due to mechanical defragmentation and reduction of platelet surface glycoproteins (GPIb and GPIIb/IIIa), which are important for platelet adhesion and aggregation. Extent surface contact during extracorporeal circulation causes significant platelet dysfunctions [25].

Conventional laboratory analyses are of limited informative value as they only provide a quantitative measure of platelet numbers without providing any information regarding platelet functionality. In contrast, aggregometric measures allow the assessment of platelet function by measuring the amount of platelet aggregation induced in the presence of common platelet agonists such as thrombin, arachidonic acid, ADP, epinephrine, or collagen. Results of aggregometric measures allow monitoring of the effects of preoperatively performed antiplatelet therapy as well as analyzing the extent of intraoperative acquired platelet dysfunctions [26].

If platelet function has been proven to be deficient, the administration of desamino-D-arginine vasopressin (DDAVP) represents a therapy option. DDAVP (0.3 μg/kg) has been shown to induce a three-fold increase in von Willebrand factor and factor VIII [27]. These factors promote an increase in platelet–endothelial cell adhesion via the GPIb receptor and platelet–platelet aggregation via the GPIIb/IIIa receptor. A further option to increase the hemostatic potential of the primary hemostasis is to transfuse platelet concentrates. In general, transfusion of one unit of platelet concentrate will increase the platelet count by approximately 30 000 per μl. However, there are inherent risks associated with the transfusion of platelet concentrates, in particular, the risk of transmission of bacterial and/or viral infections. Additionally, the number and functionality of platelets in platelet concentrates decreases in dependency of storage time [28–30].

Ultima ratio

If coagulopathy persists and surgical causes for bleeding have been ruled out, off-label usage of two additional coagulation factor concentrates, factor XIII and activated factor VII, represents an ‘ultima ratio’ therapy approach. Factor XIII enhances blood clot stability by cross-linking fibrin monomers and integrating α2 antiplasmin into developing clots. There is no routinely available test parameter that may indicate a factor XIII deficiency. In addition, there are currently no standardized reference values. However, on the basis of the clinical experience, the authors recommend using 1250–2500 units of coagulation factor XIII as a single shot infusion.

Administration of recombinant factor VIIa (90 μg/kg) induces a so-called ‘thrombin burst’. As the final stage of the therapy algorithm, it may potentially reverse life-threatening coagulopathy. However, several preconditions such as plasma pH 7.2 or more, fibrinogen concentration more than 150 mg/dl, platelet count more than 50 000 per μl, hematocrit 25% or more, ionized calcium concentration more than 1 mmol/l, and body temperature more than 36°C should be met before factor VIIa is administered. However, as highlighted in a recent systematic review, the effectiveness of recombinant factor VIIa in reducing the transfusion rate of allogeneic blood products or the perioperative blood loss remains unproven [31].

CONCLUSION

Viscoelastic and aggregometric methods should be implemented in perioperative care. They provide a detailed analysis of perioperative hemorrhage and allow an early, goal-directed, and efficient hemotherapy. Implementation of POC methods in hemotherapy algorithms reduces the transfusion rate of allogeneic blood products and may beneficially influence patient’s clinical outcome.

Hemotherapy should be based on a hemotherapy algorithm consisting of consecutive steps of therapy escalation with special regard to preoperatively performed anticoagulatory therapy.
Cardiovascular anesthesia

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Conflicts of interest

C.F.W. has received speakers’ honoraria from CSL Behring, TEM international, Verum Diagnostica GmbH and Roche AG. K.Z. has received speakers’ honoraria and is currently receiving a study grant from CSL Behring. For M.K. none were declared.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
■ of special interest
■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 101–102).


8. The median turnaround time for conventional coagulation tests performed in the central laboratory of 53 min (interquartile range: 45–63 min) was studied to be longer than the median turnaround time for thromboelastometric results, which were available after 23 min (interquartile range: 21–24 min).


A retrospective study which included 3865 patients undergoing cardiovascular surgery at University Hospital Essen before and after implementation of coagulation management algorithms based on POC testing. The authors concluded that first-line administration of coagulation factor concentrates combined with POC testing was associated with decreased incidence of blood transfusion and thrombotic/thromboembolic events.


The authors performed a systematic review of studies that analyzed efficacy and safety of fibrinogen concentrate substitution and found that administration of fibrinogen concentrate was well tolerated and effective.

26. Dickenste G, Pragst I. Prothrombin complex concentrate vs fresh frozen plasma for reversal of dilutional coagulopathy in a porcine trauma model. A retrospective study which included 3865 patients undergoing cardiovascular surgery at University Hospital Essen before and after implementation of coagulation management algorithms based on POC testing. The authors concluded that first-line administration of coagulation factor concentrates combined with POC testing was associated with decreased incidence of blood transfusion and thrombotic/thromboembolic events.


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