The Year in Coagulation: Selected Highlights from 2020

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This is the second annual review in the Journal of Cardiothoracic and Vascular Anesthesia to cover highlights in coagulation for cardiac surgery. The goal of this article is to provide readers with a focused summary from the literature of the prior year’s most important coagulation topics. In 2020, this included a discussion covering allogeneic transfusion, antiplatelet and anticoagulant therapy, factor concentrates, coagulation testing, mechanical circulatory support, and the effects of coronavirus disease 2019.

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THE AIM of this article is to provide a focused review of the literature on the most relevant topics in coagulation as they apply to cardiothoracic anesthesiology and surgery. The authors thank the Journal leadership for the opportunity to continue this series of annual highlights in coagulation.1 In this second annual review, highlights from 2020 included the effect of allogeneic blood transfusion on patient outcomes; updates on the management of antiplatelet and anticoagulant therapy; the expanding use of factor concentrates; the continued role for viscoelastic testing (VET), bleeding and thrombosis in mechanical circulatory support; and the effects of coronavirus disease 2019 (COVID-19).

Effect of Blood Transfusions on Clinical Outcomes

There are several indications for the transfusion of blood products in cardiac surgery, including but not limited to volume resuscitation as a result of blood loss and for the management of coagulopathy. The benefits and risks of allogeneic blood component therapy have been extensively investigated over the years, with greater emphasis currently being placed on the associated risks. Even though the argument for the use of red blood cell (RBC) transfusion can be made in hemodynamically unstable patients, actively bleeding patients, or symptomatic patients, the majority of transfusions do not occur in these settings. Rather, they often are given to patients whose condition is stable and often given “prophylactically.”2 With
the risks of transfusion, such as hemolytic transfusion reactions, acute lung injury, and circulatory overload, it is not surprising that methods to limit unnecessary transfusion continue to be explored. Multiple studies have compared the use of liberal versus restrictive transfusion strategies, with a greater focus on the effect of transfusion on clinical outcomes. This focus on patient outcomes again was observed in 2020, with several analyses not only looking at RBC transfusion, but also the effect of plasma and platelet transfusion in the cardiac surgery population. This becomes a critical topic given the role of these blood component therapies in coagulation management.

The negative effect of exposure to allogeneic RBC transfusion during cardiac surgery has been well-described. The incremental risk of adverse outcomes with each RBC unit includes a greater risk of mortality. The effect that fresh frozen plasma (FFP) and platelet transfusion may have on clinical outcomes has been investigated previously, but their direct role on outcomes often was confounded by cotransfusion of RBCs. During 2020, cardiac anesthesiologists gained a better understanding of the outcomes associated with FFP or platelet transfusion. In a large retrospective review (n = 8,238 patients) at two cardiac surgery centers, mortality was observed in 1.3% of patients. Transfusion of any blood component therapy (RBC, FFP, and/or platelets) was associated with a higher rate of mortality (2.0% v 0.18%; p < 0.01). Using propensity score-matched pairs, the authors further analyzed the risks when looking individually at each of the three blood component therapies. Again, they reported an increased risk of mortality with each transfused unit of RBCs (odds ratio [OR] 1.18, 95% confidence interval [CI] 1.14-1.22), FFP (OR 1.24, 95% CI 1.18-1.30), or platelets (OR 1.12, 95% CI 1.07-1.18). The same investigation also found an independent association between the transfusion of RBCs, FFP, or platelets (>2 U) and postoperative infection after cardiac surgery. Interestingly, a smaller analysis of 197 patients from a single-center study also looked at the relationship between blood transfusion in cardiac surgery and postoperative infection. Infection included pneumonia, sepsis, colitis, mediastinitis, deep surgical site infection, myocarditis, pericarditis, and endocarditis. The results demonstrated no difference in rates of infection (p = 0.902) for those who did and did not receive blood transfusions, which included RBCs, FFP, and/or platelets. The authors suggested that transfusion should not be withheld based on a concern for infection. Although the authors acknowledged the small sample size of their study, a major concern with their analysis was the high rate of transfusion in general (93.4% of patients transfused), which made for a small number of control patients (no transfusion).

A retrospective study on the association of blood product transfusion and postoperative acute kidney injury (AKI) also was conducted in 2020. Again, RBC transfusion as a risk factor for AKI after cardiac surgery has been more widely accepted, but the association between FFP and platelets remains less clear. In an analysis of 1,960 patients undergoing cardiac surgery with cardiopulmonary bypass (CPB), transfusion data were collected intraoperatively and until the first postoperative day. With an AKI incidence of 27.7%, the authors found that transfusion of RBCs, FFP, and platelets all were independently associated with Kidney Disease: Improving Global Outcomes stages 2 and 3. However, when adjusting for AKI risk factors and the use of complementary products (confounding effect), only RBC administration was associated with the development of AKI.

To further investigate the effect of intraoperative plasma transfusion on outcomes in cardiac surgery, a single-center, retrospective study examined the influence of plasma volume on postoperative parameters such as need for additional transfusion, redo surgery for bleeding, and intensive care unit (ICU) and hospital lengths of stay. In the 1,794 patients included, an international normalized ratio (INR) was measured before plasma transfusion and was required to be > 1.1 to be included in the analysis. The results suggested that intraoperative plasma dose (per unit) was associated with multiple negative outcomes. For each additional unit of plasma, there was an association with an increased odds of RBC transfusion in the first 24 hours after surgery (OR 1.12, 95% CI 1.04-1.20) and a decrease in hospital-free days (p = 0.04). In addition, higher pre-transfusion INR values were associated with an increased OR for RBC transfusion and redo surgery and with fewer ICU- and hospital-free days. For a given plasma volume, patients in whom a greater correction in the pre-INR-to-post-INR value was achieved were noted to have more favorable outcomes. Interestingly, changes in pre-transfusion and post-transfusion R-times, as measured by thromboelastography (TEG) (Haemonetics, Boston, MA), were not significantly associated with these outcomes. The authors concluded that higher plasma transfusion volumes can lead to worse clinical outcomes in this patient population, but additional studies are needed to determine optimal transfusion volumes.

The association of platelet transfusion on outcomes after cardiac surgery also remains unclear. As previously mentioned, there is a recent concern for mortality and postoperative infection. To examine the effect of platelet transfusion in a large-scale fashion, Yanagawa et al. performed a systematic review and meta-analysis that included nine observational studies and more than 100,000 patients. When comparing patients who received platelet transfusions with those who did not, those who received platelets were older and had more comorbidities. They also were more likely to have more complex and nonelective surgery and were more likely to be on preoperative clopidogrel. When comparing the two groups without adjusting for these differences in baseline characteristics, the authors reported that perioperative morbidity was greater in the group that received platelet transfusions. However, when analyzing only matched/adjusted data, there were no significant differences between those who did and did not receive platelets. There was no increased risk in mortality (risk ratio [RR] 1.26, 95% CI 0.69-2.32), stroke (RR 0.94, 95% CI 0.62-1.45), myocardial infarction (RR 1.29, 95% CI 0.95-1.77), redo surgery for bleeding (RR 1.20, 95% CI 0.46-3.18), infection (RR 1.02, 95% CI 0.86-1.20), and dialysis (RR 0.91, 95% CI 0.63-1.32). Although the authors concluded that administering platelets in cardiac surgery may not be unreasonable for patients with thrombocytopenia or presumed...
platelet dysfunction, they acknowledged that their findings should be hypothesis-generating and should be confirmed with ongoing investigation. Future studies should aim to include the number of platelet units being given to determine whether there is a dose-dependent association with outcomes, and an examination of the indications for platelet transfusion.

Although results vary regarding the effect of allogeneic blood transfusion on outcomes after cardiac surgery, it is well-accepted that transfusion does carry some inherent risks. Regardless of the association with mortality, AKI, infection, or redo surgery, efforts to reduce unnecessary blood product use continue. The emphasis on the use of transfusion algorithms and point-of-care testing to help guide treatment continued during 2020. Similarly, prediction models to identify algorithms and point-of-care testing to help guide treatment continue. The emphasis on the use of transfusion algorithms and point-of-care testing to help guide treatment continued during 2020. Similarly, prediction models to identify

In another recent randomized controlled trial (RCT) including more than 11,000 patients with acute non-cardioembolic ischemic stroke, the combined therapy of ticagrelor and aspirin was advantageous in respect to recurrent stroke within 30 days compared with therapy with aspirin alone. However, bleeding events were significantly more frequent in the group with ticagrelor and aspirin. Again, this study might question the net clinical benefit of intensified antiplatelet therapy.

Interestingly, a recent case series published in the Journal of Cardiothoracic and Vascular Anesthesia suggested the use of bridging therapy with cangrelor as an alternative to longer-acting systemic antithrombotic therapy in patients who undergo endovascular aortic repair with lumbar drain placement. Despite no bleeding or neurologic complications reported, the supposed procedure certainly needs further evaluation regarding efficacy and safety of bridging therapy shortly after endovascular procedures with lumbar drain placement. Bleeding events might be rare but catastrophic.

In summary, more potent platelet inhibitors regularly reduce the risk of ischemic thromboembolic adverse events, but they commonly are associated with increased bleeding risk. Although it might be questionable to combine safety and efficacy endpoints in antithrombotic trials because of the previously described challenges in definition and variable severity of events, the net clinical effects are important for the patient, and physicians should include the patient-specific thrombotic and bleeding risk in decision-making.

Antiplatelet and Anticoagulant Therapy

Antiplatelet Therapy in Cerebrovascular and Coronary Disease

Dual-antiplatelet therapy (DAPT), including aspirin and P2Y12 receptor inhibitors, can reduce the risk of platelet-mediated thrombosis in not only coronary but also cerebral and peripheral vascular diseases. However, DAPT with potent P2Y12 receptor inhibitors, such as prasugrel and ticagrelor, also might be associated with increased risk of major and even fatal bleeding. The balance between ischemic benefit and bleeding risk remains a clinical challenge. Conclusive evidence is limited because of various definitions of ischemic benefit and relevant bleeding events. Potentially, individual endpoint definitions might specifically change the interpretation of the findings and hamper the comparison among different studies. Accordingly, the use of DAPT, including aspirin and ticagrelor, was associated with a mortality benefit in the large Platelet Inhibition and Patient Outcomes (PLATO) trial, but follow-up studies could not prove such a mortality benefit. In contrast, a recent large, retrospective analysis, including more than 62,500 propensity-matched patients with acute coronary syndrome who underwent percutaneous coronary intervention (PCI), compared the use of ticagrelor with clopidogrel. In that analysis, net clinical adverse events, defined as recurrent myocardial infarction, revascularization, ischemic stroke, hemorrhagic stroke, and gastrointestinal bleeding at 12 months in patients treated with ticagrelor, was questioned. Importantly, the endpoints in the study by You et al. were not totally comparable with those of the PLATO study, with the prior resulting in variable benefits with intensified antiplatelet therapy including ticagrelor.

Concurrent indications for multiple antithrombotic therapies are a common clinical scenario. It is estimated that atrial fibrillation (AF) occurs in about one-fourth of all individuals during their lifespan. Because of multiple shared risk factors, one-fourth-to-one-third of these patients also have coronary artery disease. Oral anticoagulation is advantageous in situations of low shear stress conditions for clot formation, such as in the left atrial appendage during AF, and antiplatelet therapy is mandatory for prevention of thrombotic complications after PCI. Each drug helps to reduce thrombotic complications in the specific setting, but their combined use might be indicated in certain situations, as previously described. However, combined anticoagulant and antiplatelet therapy significantly increases the risk of major bleeding events, which can be life- or organ-threatening. The recent American College of Cardiology (ACC) “Expert Consensus Decision Pathway” tried to provide “actionable knowledge” regarding clinical decision-making and treatment plans in patients with an indication for both anticoagulation and antiplatelet therapy, rather than a single correct answer for all patients and each situation. In order to choose the ideal antithrombotic drug in the optimal dosage or a combined therapy, the individual patient’s thrombotic and bleeding risk must be evaluated using established scores including CHA2DS2-VASc or HAS-BLED. Recent evidence suggests that direct oral anticoagulant (DOAC) therapy might...
be preferred over vitamin K antagonists (VKA) when a combined therapy with antiplatelet drugs is required. Furthermore, clopidogrel might be the preferred $P2Y_{12}$ inhibitor after PCI when combined anticoagulant and antiplatelet therapy is required. In addition, the overall duration of combined therapy should be kept as short as possible, and additional measures, such as the use of proton pump inhibitors or non-pharmacologic alternatives, such as closure devices, for the left atrial appendage must be evaluated.\(^{25-28}\)

**Anticoagulant and Antiplatelet Therapy After Transcatheter Aortic Valve Replacement**

Patients undergoing transcatheter aortic valve replacement (TAVR) are another group with potential for combined antithrombotic therapy (either as a combination of oral anticoagulants and $P2Y_{12}$ receptor antagonists or as DAPT). Two recent European randomized multicenter studies investigated the role of anticoagulation and antiplatelet therapy in patients undergoing TAVR. Nijenhuis et al. randomly assigned 313 patients undergoing TAVR, who were receiving long-term oral anticoagulation for an appropriate indication, to receive either clopidogrel or not receive the drug for three months after valve implantation.\(^{30}\) Bleeding events, most of them within the first month after intervention, were more common in the group that received oral anticoagulants plus clopidogrel than in patients on oral anticoagulants alone (34.6% vs 21.7%; $p = 0.01$). In contrast, thromboembolic events, including stroke and myocardial infarction, were similar in both groups. The group with oral anticoagulation alone therefore showed a net clinical benefit compared with the combined therapy including clopidogrel.\(^{30}\) Of note, that study also included patients receiving either VKA (73% of patients) or a DOAC (23%). The use of a DOAC rather than VKA might be associated with fewer bleeding events;\(^{27}\) however, that trial was not powered to assess differences between patients on VKA or DOAC.

The same group of investigators also studied patients without an indication for long-term oral anticoagulation. In 665 patients undergoing TAVR, the authors compared the clinical benefit of combining aspirin with clopidogrel for three months after TAVR compared with aspirin alone.\(^{31}\) Again, bleeding events occurred more commonly in patients with aspirin plus clopidogrel than in patients with aspirin alone (26.6% vs 15.1%; $p = 0.001$). However, there was no difference between the groups in respect to thromboembolic events at one year. Therefore, the therapy with aspirin alone resulted in a net clinical benefit compared with patients on DAPT with aspirin and clopidogrel.

In summary, these two RCTs suggested that antithrombotic therapy after TAVR can be reduced safely to aspirin or oral anticoagulants alone, compared with a combined antithrombotic therapy, to minimize the bleeding risk without increasing the ischemic or thromboembolic risk.

**Management of Bleeding Patients on DOAC Therapy**

With a continuously aging population, the number of patients with indications for anticoagulation is increasing. Among these indications, AF is the most common indication. Recent surveys show a steadily increasing use of DOACs in patients with AF or venous thromboembolism.\(^{32}\) In parallel with the increased use of oral anticoagulants, including use beyond established and approved indications,\(^{33}\) acute bleeding complications might occur. Whereas it commonly is recommended to use prothrombin complex concentrates (PCCs) to treat bleeding patients on a VKA,\(^{32}\) optimal therapeutic options in bleeding patients treated with DOACs are less evident.\(^{34}\) Recently, the ACC updated its “Expert Consensus Decision Pathway” regarding therapeutic approaches in bleeding patients on oral anticoagulants. The use of specific reversal agents was proposed as first-line therapy for life-threatening bleeding in patients on DOACs.\(^{35}\) Whereas the use of idarucizumab for urgent/emergency before procedural reversal of dabigatran has been studied and is rather well-established and supported by the 2020 ACC “Expert Consensus Decision Pathway,” the use of andexanet alfa for oral factor Xa inhibitors is less clear for several reasons.\(^{35}\) First, it is not ubiquitously available. Second, andexanet alfa is not selectively specific for Xa antagonists and can interact with several endogenous substances. Recently, heparin resistance has been suspected with the administration of andexanet alfa in patients undergoing emergency cardiovascular surgeries requiring higher doses of heparin.\(^{36-38}\) Finally, andexanet alfa is very expensive.\(^{39}\) In emergency cardiovascular procedures with planned heparinization, the administration of andexanet alfa potentially should be considered only after protamine administration. Instead, PCC at a dose of about 2,000 U might be considered. The latter is also the second-choice treatment in bleeding patients on factor Xa inhibitors when no specific reversal is available.\(^{32,34,35}\)

**Antiplatelet and Anticoagulant Therapy in COVID-19**

Severe acute respiratory syndrome coronavirus-2, the virus that causes COVID-19, frequently is associated with hypercoagulopathy. COVID-19 coagulopathy has some common features with disseminated intravascular coagulation (DIC) or pre-DIC secondary to an increased inflammatory state. In contrast to bacterial infection–induced DIC, COVID-19 coagulopathy commonly is associated with relatively minimal changes in thrombocyte count, antithrombin levels, or laboratory coagulation tests such as prothrombin time or activated partial thromboplastin time (aPTT). Even though COVID-19 coagulopathy could involve microangiopathy, local thrombus formation, large- vessel thrombosis, or pulmonary embolism, the common lack of thrombocytopenia indicates that it is a prothrombotic but not consumptive coagulopathy typical for DIC.\(^{39,40}\) Often, these patients are treated with heparin agents. However, the use of antiplatelet therapy also might be beneficial. Although no clinical trials have shown protective or therapeutic effects of antiplatelet therapy in COVID-19 until now, some studies have suggested improved patient outcomes with aspirin.\(^{31,42}\) Despite the advantages of safety and low costs of aspirin, randomized trials are necessary before the use of aspirin in COVID-19 patients can be generally recommended. In
the meantime, it seems advisable that hospitalized patients with COVID-19 who are taking anticoagulant or antiplatelet therapy should continue their treatment unless significant bleeding develops or other contraindications interfere with their administration.

**Factor Concentrates in Cardiac Surgery**

Modern hemostatic therapy in cardiac surgery optimally is guided by point-of-care VET. When implemented in an institutional transfusion algorithm, VET allows for the identification of the cause of coagulopathic bleeding and helps to guide targeted treatment with factor concentrates. Unlike transfusion of allogeneic blood products, the administration of recombinant or purified factor concentrates has clear advantages, among them immediate availability, low administration volume, and high degree of viral safety. During 2020, a number of new articles addressed the topic of factor concentrates and their use in cardiac surgery.

**Diagnosis of Hypofibrinogenemia With VET**

In a diagnostic test accuracy study with systematic literature review, nine journal articles met the eligibility criteria of reporting sensitivity and specificity of a point-of-care VET device for the detection of hypofibrinogenemia in patients undergoing cardiac surgery. Overall, the results indicated that identification of hypofibrinogenemia with VET was associated with a high false positive rate (30%-58%) and a low false negative rate (2%-26%) for detecting FIBTEM A10 < 7.5-to-8 mm compared with the gold standard of laboratory fibrinogen measurement. The authors of the diagnostic test accuracy study supported the use of VET and acknowledged its important role as a point-of-care test for hypofibrinogenemia in cardiac surgery. The fast turn-around time and associated rapid availability of results in the bleeding patient are reasons for preferring the assay over standard laboratory fibrinogen testing, which is associated with processing times of up to 45 minutes. Moreover, the low false negative rate and the high negative predictive value (96%-98%) for FIBTEM > 8 mm support withholding the administration of fibrinogen concentrates when the FIBTEM amplitude is not decreased. In this case, other causes of bleeding should be evaluated.

**Prophylactic and Preoperative Administration of Fibrinogen Concentrate**

A normal plasma fibrinogen level (200-450 mg/dL) is a prerequisite for adequate perioperative hemostasis. Under severe bleeding conditions, fibrinogen levels decrease rapidly, and fibrinogen reaches, as the first coagulation factor, a critically low plasma level. According to European guidelines, plasma fibrinogen levels in a bleeding patient should be kept > 150-to-200 mg/dL, corresponding with a FIBTEM A10 of > 8-to-10 mm.

The prophylactic administration of fibrinogen concentrate appears to be an interesting option in this context. Following up on related publications in previous years, a 2020 study, with a prospective, randomized, and double-blinded design, investigated prophylactic fibrinogen administration in 58 patients undergoing elective high-risk cardiac surgery. Patients were given either fibrinogen concentrate or placebo after weaning off CPB and protamine administration. The study medication was administered independent of the clinical assessment of bleeding and solely based on VET results. These were obtained toward the end of CPB, and they were used to calculate the dose of fibrinogen concentrate for a target FIBTEM maximum clot firmness (MCF) of > 15 mm. The primary outcome was the cumulative number of any blood products given within the first 24 hours. Although VET parameters were improved in the treatment group, the authors could not demonstrate a significant difference in the primary and secondary outcomes. Because of limitations in the study design and statistical analysis, it is advisable to interpret the results with caution.

More information on the preoperative plasma fibrinogen level and its association with bleeding and transfusion rate was provided by two recent single-center, retrospective studies in elective cardiac surgery patients. Both studies concluded that high preoperative plasma fibrinogen levels represent a risk factor for severe perioperative bleeding and increased transfusion requirements. The correlation in this respect is U-shaped, indicating that both a low level and a very high level (> 580 mg/dL) of plasma fibrinogen promote bleeding. The latter cannot yet be fully explained, but presumably is associated with systemic inflammation, hyperfibrinolysis, and dysfibrinogenemia, with the appearance of alternate fibrinogen forms having antithrombotic activity.

**Effect of Cell Salvage on Postoperative Plasma Fibrinogen Levels**

Intraoperative cell salvage, when used as a PBM strategy, is ubiquitous in cardiac surgery. In this respect, any measure to avoid exposure to allogeneic red blood cells clearly is recommended and contributes to improved patient outcomes. A recent ex vivo study investigated the effect of different amounts of salvaged blood on postoperative coagulation, specifically on FIBTEM values in cardiac surgery. The authors concluded that retransfusion of a high amount of salvaged blood (corresponding to > 18.5% of a patient’s blood volume) may impair fibrinogen contribution to the clot, especially in individuals with a low preoperative fibrinogen level. This also may decrease FIBTEM MCF < 8 mm and trigger administration of fibrinogen concentrate. A related editorial put the study findings into perspective and pointed out limitations that had not been discussed by the authors. In conclusion, intraoperative cell salvage should not be abandoned because of the changes in the coagulation profile that are taken for granted after processing the patient’s blood. Rather, a better understanding of coagulation processes and close monitoring of coagulation are necessary, especially in complex surgeries with a high amount of volume turnover through the cell saver.
Risk of Thromboembolic Events With Fibrinogen Concentrate

In a retrospective, single-center cohort study of more than 5,000 patients undergoing elective cardiac surgery, the incidence of a composite endpoint of thromboembolic events and death within one year after surgery was investigated. The authors demonstrated that administration of fibrinogen did not increase the incidence of the composite endpoint at 30 days (occurrence 3.5%) or at one year (10.5%) after surgery. Consistent with previous studies, this large-scale study contributed knowledge of the safety of fibrinogen concentrate. In this regard, however, the following two points must be considered: (1) adjusting statistical analyses for perioperative variables, such as transfusion rate, is important because the authors were able to identify excessive bleeding as a factor promoting thromboembolic complications and (2) monitoring of thromboembolic events should be continued in the late postoperative phase and afterwards. Thus, attention should be paid not only to evident thromboembolic complications, such as venous thromboembolism and ischemic stroke, but also to other possibly associated clinical (e.g., myocardial infarction) and subclinical events.

Effectiveness of PCC

To investigate the effectiveness of PCC in the treatment of bleeding, a case series involving nine patients and a systematic review with meta-analysis of 17 observational studies were published in 2020. In the case series, a fixed dose of up to 2,000 U (median 14 U/kg) of a four-factor PCC was used to treat bleeding in complex cardiac surgery patients who refused allogeneic blood transfusion. Acceptable hemostasis could be achieved in the majority of patients receiving PCC. However, other concentrates (factor VIIa, fibrinogen concentrate, antifibrinolytics) and blood conservation measures (intraoperative cell salvage, retrograde autologous circuit priming) also were used in the PCC group according to PBM recommendations. Interestingly, three of nine patients developed thrombotic complications (ischemic stroke or deep venous thrombosis) and were investigated further with regard to risk factors. Unfortunately, because of the small sample size, the combination of PCC with other prothrombotic agents, the lack of a control group, and the lack of a predefined transfusion protocol, the validity of the results remains limited. In contrast, the aforementioned systematic review could not demonstrate an increase in thromboembolic events ($p=0.38$, $I^2=0\%$) with PCC usage, either in the overall population or in a subgroup of cardiac surgery patients. Moreover, the authors demonstrated a reduction in blood loss ($p=0.02$, $I^2=86\%$), and especially in cardiac surgery, a decreased need for red blood cell transfusion by 2 U with PCC usage ($p=0.003$, $I^2=81\%$). A weakness of that study was the inclusion of only observational studies with considerable heterogeneity in the study population.

Another RCT compared the effectiveness and safety of PCC (intervention arm, 15 U/kg) versus FFP (standard arm, 15 mL/kg) in 50 adults who experienced bleeding within 24 hours after cardiac surgery. Although the study was a pilot trial aiming to determine the recruitment rate for an upcoming larger trial, the results are valid and can be interpreted independently because of the clear and comprehensible methodology and study design. Similar to prior studies, the study did not indicate an increase in thromboembolic complications with PCC, and there were no differences in all-cause mortality or stroke between the PCC and FFP groups. Likewise, transfusion requirements were similar for the intervention and the standard arms. At one hour, levels of fibrinogen; factors V, VII, and XIII; alpha2-antiplasmin; and antithrombin significantly were increased in the FFP group compared with baseline but not in the PCC group. In contrast, the PCC group demonstrated significant increases in factors II and X at the same timepoint. At 24 hours, no differences in the clotting factors were detectable between the two groups.

The First European Consensus on PCC

Because of the large variability in dosing strategies and associated lack of evidence, a systematic literature review was needed to reach agreement among experts with regard to dosing, efficacy, safety, and monitoring of PCC. The Writing Committee agreed on an initial PCC bolus of 25 IU/kg for massively bleeding cardiac or non-cardiac patients whose coagulation is affected by the preoperative intake of VKA therapy. In individuals at risk for thromboembolic events, especially those undergoing cardiac surgery without prior VKA therapy, an initial half-dose bolus with 12.5 IU/kg was recommended to treat severe bleeding. It further was agreed that 25 IU/kg PCC is suitable to reverse the effect of DOACs when no other antidotes are available. Despite consensus on additional areas (e.g., monitoring of PCC effect and therapy guided by tissue-factor-activated, factor VII-dependent, and heparin insensitive assays), the experts emphasized the urgent need for large international registries to improve current knowledge of PCC.

Coagulation Testing in Cardiac Surgery

Clinical Effect of VET (Transfusion Algorithms)

The COVID-19 pandemic has had a major effect on healthcare systems around the world, causing more emphasis on techniques to address shortages within the supply chain. Global quarantines and closure of many blood donation centers, which typically support 80% of the national blood supply, have forced hospitals to adapt to more stringent blood administration guidelines and splitting of platelet units into two doses. Approximately 40%-to-50% of cardiac surgical patients will require a blood transfusion during their index hospitalization, enhancing the spread of PBM efforts. VET has become a mainstay in many institutional transfusion algorithms for cardiac surgery, but there has been a paucity of evidence of improved morbidity, mortality, and outcomes. The meta-analysis by Serraino et al. on the routine use of VET (rotational thromboelastometry [ROTEM; Instrumentation Laboratory, Bedford, MA] and TEG) in cardiac surgery,
showed no reductions in mortality (RR 0.55, 95% CI 0.28-1.10), major bleeding, ventilation time, or hospital length of stay. There were a reduced frequencies of RBC transfusion (RR 0.88, 95% CI 0.79-0.97) and platelet transfusion (RR 0.78, 95% CI 0.66-0.93). These authors concluded that VET is not useful in reducing mortality in cardiac surgery and that no additional controlled trial should be performed. Recently, Santost et al. reevaluated the results of this meta-analysis with their own systematic review and found significant reductions in the risk of death (7.3% vs 12.1%, RR 0.64, 95% CI 0.43-0.96; p = 0.03) and risk of acute renal failure (10.5% vs 17.6%, RR 0.53, 95% CI 0.34-0.83; p = 0.005) with the use of VET. There was a greater reduction in the risk of death in patients who were coagulopathic or massively bleeding (14.8% vs 26.8%, RR 0.58, 95% CI 0.32-1.07; p = 0.08). This finding was non-significant, most likely secondary to its small sample size. In similar opposition, a meta-analysis by Meco et al. of VTE use compared seven studies encompassing 1,035 patients, in which a transfusion algorithm with ROTEM or TEG was used in 522 patients. Not only were there reductions in RBC (OR 0.61, 95% CI 0.37-0.99; p = 0.04) and FFP (risk difference 0.22, 95% CI 0.37-0.99; p < 0.0001) transfusions, but also a reduction in 12- and 24-hour chest tube drainage (mean difference [MD] 178.7, 95% CI −308.9 to −48.4; p = 0.007 and MD −175.4, 95% CI −305.78 to −40.9; p = 0.01), respectively. Reductions also were seen with redo surgery for bleeding (OR 0.51, 95% CI 0.28-0.94; p = 0.03) and ICU length of stay (OR −4.03, 95% CI −6.28 to −1.78; p = 0.005). Similar to the meta-analysis by Serraino et al, a significant difference in mortality was not found, nor was a reduction in platelet transfusion. One main cause in variability in outcome measures could be secondary to the lack of standardized transfusion algorithms across institutions. Therefore, randomized studies are warranted to further clarify the true value of VET.

**VET (Blood Conservation)**

Additional components of PBM include blood conservation techniques such as cell salvaging, acute normovolemic hemodilution (ANH), and factor concentrate administration. Recently VET has been used to improve guidance on implementation and clarification of mechanistic advantages of these techniques. Since 1996, it had been believed that large amounts of cell saver transfusion could cause increased bleeding and blood transfusion. Cell salvaging also has been shown to reduce the risk of allogeneic blood transfusion by 33% in cardiac surgery. How much cell salvaging is too much to require supplementation of non-RBC transfusions? Adam et al. performed a prospective, observational study on the effect of intraoperative cell salvaging in cardiac surgical patients. Pre-processed (reservoir blood) and post-processed (cell saver bag) autologous blood samples were gathered, and coagulation factor levels were tested. All coagulation factor levels were found to be reduced when comparing pre-processed versus post-processed autologous blood. Specifically fibrinogen; antithrombin; von Willebrand factor (vWF); and factors II, VII, X, and XII were measured. A greater than 50% reduction was found in each factor, with the greatest reduction of 93% in vWF activity. Autologous blood from cell saver has been found to be devoid of a meaningful level of coagulation factors, risking hemodilution with increased volume transfused. The recent study by Son et al. was summarized earlier in this review to demonstrate the effect of cell salvage on fibrinogen levels. Along with a reduction in the FIBTEM MCF with a high volume of cell salvage, the authors also noted an increase in the INTEM clotting time (CT)/HEPTEM CT ratio from 1.07 (1.03-1.12) to 1.16 (1.11-1.20) (p ≤ 0.001) with 18.5% of salvaged blood added to postoperative samples. This indicates the effect of residual heparin, similar to findings in other studies regarding cell salvaged blood. Clinicians should understand that although the effect of cell salvaged blood may reduce transfusions, the greater volume used increases the risk of heparin rebound and dilutional coagulopathy. Additional prospective studies are needed to add clinical correlation to the replacement of 18.5% of blood volume with cell salvaged blood and when factor replacement should be considered. ANH is another blood conservation technique in which the clinical effect and volume needed for optimal effects are unclear. A meta-analysis by Barile et al. showed a reduction of 12% in overall allogeneic transfusions in patients undergoing cardiac surgery with a minimal volume of 650 mL of ANH. Other studies have suggested that a greater volume of ANH results in increased reduction of RBC transfusion and non-RBC transfusion. Recently Smith et al. performed a prospective study to assess changes in coagulation after reinfusion of ANH versus control patients. Eighty patients undergoing cardiac surgery requiring CPB (40 ANH and 40 control) were enrolled. A median of 890 mL (794-909 mL) of autologous blood was removed from the ANH group and 0 mL from the control group. Blood samples were drawn at the following 2 timepoints: (1) 5 minutes before protamine and (2) 30 minutes after the first blood draw. Blood samples were analyzed for fibrinogen, aPTT, hemoglobin, platelet count, and TEG (R-time, maximum amplitude (MA), α-angle, and LY-30/60). A statistical significance was found at timepoint 2 with increased hemoglobin (11.3 [9.8-12.8] vs 11.5 [10.5-12.5], 95% CI 0.1-0.8; p = 0.024) and fibrinogen levels (236 mg/dL [199-283] vs 221 mg/dL [167-275], 95% CI 1-26; p = 0.04) in the ANH group after inverse probability treatment weighting and controlling for the value of timepoint 1. The aPTT level (29.7 [24.8-34.6] vs 27.7 [24.2-31.2], 95% CI −2.7 to 0; p = 0.044) also was reduced in the ANH group at timepoint 2 when controlling for timepoint 1. No significant difference was found with evaluation of TEG measurements. Markers of hemostasis were improved in the ANH group compared with the control group, although not apparent on TEG. This could have been secondary to short bypass times, unknown patient selection process, and a low overall transfusion rate of approximately 8%. Henderson et al. recently performed a prospective, observational study using ROTEM to assess the ANH effect on coagulation in cardiac surgical patients. Fifty patients were enrolled (25 ANH and 25 control) with a median of 1,200 mL (1,116-1,280) autologous blood removed from the ANH group...
and a median of 0 mL (0-328) from the control group. Blood samples were drawn at the following 3 timepoints: T1, baseline; T2, on CPB after aortic cross-clamp removal; and T3, 30 to 60 minutes after protamine administration. ROTEM parameters showed a significant shortening at T3 in EXTEM CT (MD = −11.4 s [−21.4 to −1.4]; p = 0.3) and a significant percentage increase in EXTEM A10 (MD 7.8% [95% CI 1.1\%-14.5%]; p = 0.02) from T2 to T3 in the ANH group compared with the control group.\(^{80}\) Other coagulation proteins were tested without any significant variance. Clinically, there was a decrease in the overall transfusion during the index hospitalization by 44\% in the ANH group. Only 9 U of allogenetic products were used in the ANH group versus 50 U in the control group. In addition, increased hematocrit levels in the ANH group at 24 hours and discharge were similar to those in other studies.\(^{78,81}\) When calculating the amount of coagulation factors in the autologous blood bags, Henderson et al. found 2.5 g (2.0-2.9) of fibrinogen and 2.6 (2.1-2.9) × 10\(^{11}\) of platelets. With 2.5 g of fibrinogen reinfused, the authors expected a change in FIBTEM A\(_{10}\) parameters, which was not found to be significant. This study concluded that ANH may improve hemostasis, although the mechanism should be investigated further.

Factor concentrate-guided therapy is an evolving field in cardiac anesthesia. VET has been studied as a guide to administer factor concentrate. Fibrinogen concentrate has been studied extensively recently on its effect on bleeding in cardiac surgery.\(^{82}\) Fibrinogen is an integral component of stable clot formation and is one of the first proteins lost in massive bleeding or hemodilution. Guidelines have been created to use ROTEM FIBTEM for fibrinogen administration because the prophylactic use of fibrinogen concentrate has not improved clinical outcomes.\(^{49,83}\) ROTEM FIBTEM MCF measurements can be affected by hematocrit levels, although the correlation is acceptable when compared with Clauss fibrinogen levels at a hematocrit <25\% (\(r = 0.88\)).\(^{84}\) The Quantra QPlus (Hemosonics, Charlottesville, VA) is a fully automated, cartridge-based VET that uses sonorheometry (acoustic deformation) to measure clot formation. Quantra QPlus, similar to ROTEM, is able to isolate fibrinogen clot formation to assist fibrinogen replacement algorithms. Recently, Naik et al. observed patients undergoing cardiac and orthopedic surgery comparing Quantra QPlus threshold values for fibrinogen contribution to clot stiffness (FCS) and platelet contribution to clot stiffness (PCS) to fibrinogen level and platelet count. FCS <1.9 correlated with a fibrinogen level of <200 mg/dL with a sensitivity of 87.9\% and negative predictive value of 95.2\%. PCS <14.1 correlated with a platelet count <100,000 with a sensitivity of 89.5\% and negative predictive value of 98.5\%.\(^{85}\) Using suggested threshold values for FCS and PCS, Quantra QPlus could be a reliable VET to guide fibrinogen and platelet replacement. The clinical correlation is inconclusive warranting further examination. Quantra QPlus also was affected by hematocrit; low levels generated higher stiffness. ROTEM-guided transfusion protocols in cardiac surgery have been shown to reduce patient cost by approximately $5,000.\(^{86}\) When compared with ROTEM measurements in cardiac and orthopedic surgery, Quantra QPlus had a correlation of \(r > 0.8\) for INTEM, HEP-TEM, EXTEM, and FIBTEM values.\(^{87}\) Zghaib et al. compared Quantra QPlus with TEG measurements and standard laboratory tests in cardiac surgical patients.\(^{83}\) Using different threshold values than those of Niak et al., Quantra QPlus had a very high negative predictive values for PCS <13.5 (97.4\%), FCS <2 (89.6\%), and CT >159 seconds (70.5\%) compared with PLT <100,000, MA <50 mm, and R-time >10 seconds, respectively.\(^{88}\) With poor positive predictive values, Quantra QPlus was not able to predict the need for blood transfusion.\(^{89}\) In order to conclude a benefit, additional studies are needed to apply threshold values to clinical treatment.

**New Tools in VET**

Limitations in the use of VET include the requirement of individually trained operators and the complexity of interpretation. This is a challenge for expanded implementation of VET. TEG and ROTEM are the most commonly used VET devices, and both have become automated, with models TEG 6s and ROTEM sigma using a ready-to-use cartridge. Quantra QPlus also uses an automated system and has a user-friendly, color-coded display to aid in interpretation. Rössler et al. developed Visual Clot as an alternative way to interpret ROTEM measurements by creating a real-time visual representation of ROTEM results. Sixty physicians were enrolled and randomly assigned into 12 Visual Clot or standard ROTEM scenarios. The Visual Clot had a median of 100\% (interquartile range 83-100) versus 44\% (interquartile range 25-50) (\(p < 0.001\)) in the ROTEM standard in correct therapeutic decision.\(^{90}\) A mixed regression model showed an OR of 22.1 (95\% CI 13.4-36.5; \(p < 0.001\)) for the correct decision with Visual Clot compared with standard ROTEM. Visual Clot may be able to improve interpretations of ROTEM, making it easy to use throughout the hospital and operating room. The application of Visual Clot was limited to artificially created ROTEMs versus real clinical situations; thus, additional clinical studies are needed for validation in improved decision-making.

**VET and COVID-19**

Because of the emergency nature of cardiac surgery, it is inevitable to encounter a patient with COVID-19. COVID-19 has been shown to cause abnormal coagulation profiles of elevated D-dimers, elevated fibrinogen levels, lower antithrombin levels, reduced thrombin time, and decreased fibrinolysis.\(^{91,92}\) Therefore, COVID-19 patients are hypercoagulable, which may lead to difficulty in treating coagulopathy during cardiac surgery. Currently there are no data regarding transfusion practices in COVID-19 patients, but the use of VET still is recommended.\(^{93}\) This recommendation may be warranted because Hranjec et al. used TEG with platelet mapping to guide anticoagulation management of COVID-19 patients. Treatment guided by TEG with platelet mapping resulted in an 82\% decrease in mortality (\(p = 0.0002\)). Non-algorithm-guided patients had an increased risk for ventilation (RR 10.9; \(p < 0.0001\)) and AKI (RR 2.3; \(p = 0.0017\)) and a 10.3-fold
increased mortality risk (p = 0.0001). The limitations of that study included its observational nature, non-randomized design, and unequally matched cohorts. Given these limitations, conclusions of beneficial effects were not verified, requiring a need for additional investigation.

Coagulation in Mechanical Circulatory Support and COVID-19 Considerations

Left Ventricular Assist Device – Related Bleeding, Thrombosis, and Anticoagulation

Bleeding complications, particularly gastrointestinal (GI) bleeding, continue to be a major morbidity in patients with continuous-flow left ventricular assist devices (LVADs). In a systematic review that included more than 1,000 LVAD patients with GI bleeding, the mortality rate was 21% at a mean follow-up of 14.6 months. Notably, the incidences of stroke and LVAD thrombosis were high in patients with GI bleeding, suggesting that when anticoagulation is held, there is an increased risk for thrombotic complications. Another study published in 2020 described the use of octreotide (30 mg every 28 days) in patients with recurrent GI bleeding, and found that it decreased the risk of recurrent GI bleeding, with 60% of patients having no recurrence.

LVAD thrombosis is less common with contemporary centrifugal-flow LVADs but still presents a difficult clinical challenge for some patients. In 2020, a study was published suggesting that treatment with tirofiban (0.1 μg/kg/min × 5 d) may be an effective medical therapy. In a cohort of 12 patients, the authors found a 75% efficacy. Of note, seven patients in that study also experienced bleeding complications. A second study described the use of alteplase (20 mg) in 28 patients with LVAD thrombosis (HeartWare HVAD [Medtronic, Dublin, Ireland] and HeartMate II [Abbott, Chicago, IL]), for which the efficacy rate was 61%. The rate of intracranial hemorrhage was 4.5% in that study.

Although DOACs are not approved by the US Food and Drug Administration for anticoagulation in patients with LVADs, there are increasing reports of their use. In 2020, a single-center cohort study was published describing seven patients with an LVAD who were anticoagulated with apixaban or rivaroxaban. Although the study was small, there were no apparent differences in complication rates compared with warfarin.

Extracorporeal Membrane Oxygenation – Related Bleeding, Thrombosis, and Anticoagulation

Multiple prior studies have demonstrated an association among bleeding, RBC transfusion, and morbidity and mortality in adult patients undergoing extracorporeal membrane oxygenation (ECMO). In 2020, several studies confirmed that bleeding continues to be a major problem in adult ECMO patients and affects survival. In a single-center cohort study of 130 ECMO patients from Hong Kong, the authors reported a bleeding incidence of 42%, and patients with bleeding were slower to wean off ECMO. In a cohort study of 27 ECMO patients, for whom the incidence of bleeding was 59%, the INR was 90% sensitive and 72% specific for identifying patients who developed bleeding, whereas thromboelastometry parameters had lower sensitivity. In a cohort study of 243 ECMO patients in whom the incidence of major bleeding was 46%, the authors identified several risk factors for bleeding, including hypofibrinogenemia, hemoglobinemia, and low body mass index.

Over time there has been a trend toward using less anticoagulation during ECMO. In a systematic review that was published in 2020, the authors reported on 201 patients who were on ECMO for at least 24 hours without systemic anticoagulation. In that study, the pooled circuit thrombosis rate was 13.4%, and the pooled patient thrombosis rate was 9.5%. Interestingly, even with no systemic anticoagulation, 27.9% of patients had severe bleeding. Direct thrombin inhibitors have been used as an alternative to heparin in some ECMO centers. In 2020, one observational study that included 52 patients compared patients who were anticoagulated with bivalirudin with patients who were anticoagulated with intravenous unfractionated heparin. The authors found comparable rates of bleeding and thrombosis, but the study was underpowered to detect small differences in outcomes. An RCT of anti-thrombin supplementation in 48 venovenous (VV)-ECMO patients was published in 2020. In that study, patients were assigned randomly to receive antithrombin to maintain anti-thrombin activity between 80% and 120%, or placebo. The authors found no differences in bleeding or thrombosis between the two groups despite there being higher antithrombin activity in the treatment group. These findings suggested that routine antithrombin supplementation is probably of little value in VV-ECMO. In a systematic review and meta-analysis of studies that compared anti-Xa heparin monitoring with time-based strategies (aPTT, activated clotting time [ACT], VET), the authors concluded that the use of anti-Xa heparin monitoring was associated with less bleeding and no difference in thrombosis.

The mechanisms that contribute to ECMO-induced coagulopathy continue to be elucidated. Although in vitro studies have suggested that shear-induced blood trauma leads to platelet surface GP Ibα shedding and increased adherence of platelets to fibrinogen, a small cohort study that examined platelet surface receptor density in ten patients with cardio- genic shock on venoarterial (VA) ECMO showed reduced platelet surface activated GPIIb/IIIa levels during ECMO (suggesting impaired fibrinogen binding) and no difference in platelet surface GPIIb levels during and after ECMO.

Acquired von Willebrand syndrome is well-known to occur during ECMO, but there have been few studies of how to treat ECMO patients with acquired von Willebrand syndrome and bleeding. In 2020, one of the first reports of vWF concentrate treatment for acquired von Willebrand syndrome was published. In a small cohort of 17 adult ECMO patients treated with vWF concentrate, the authors demonstrated that treatment increased both vWF ristocetin cofactor activity and the ratio of vWF ristocetin cofactor activity-to
vWF antigen. In that study, there was one case of thrombosis that was deemed likely to be related to treatment, so prudence is important when using vWF concentrate.

**COVID-19 Considerations for ECMO**

The COVID-19 pandemic has led to an increased use of ECMO worldwide. As of January 5, 2021, there were almost 4,000 ECMO runs reported to the Extracorporeal Life Support Organization for COVID-19 patients, and survival to hospital discharge was 54%. COVID-19 is now well-described as a multisystem disease that is associated with elevated factor VIII activity; hyperfibrinogenemia; depleted endogenous anticoagulant levels (eg, antithrombin and protein C); and hypercoagulability in patients with severe disease. Several studies have demonstrated that COVID-19 infects endothelial cells causing endothelialitis. COVID-19 patients on ECMO require special consideration for anticoagulation because they are at increased risk for thrombosis compared with other ECMO patients. In a single-center cohort study of 12 COVID-19 patients who were treated with VV-ECMO, four patients developed thrombotic complications despite targeting an ACT of 150 to 220 seconds. Two patients died from thrombotic complications (one from pulmonary embolism and the other from oxygenator thrombosis). In a second single-center cohort study, seven of eight COVID-19 patients on VV-ECMO developed oxygenator thrombosis. Of note, in that study, a significant number of patients also experienced major bleeding including tracheal oonds. A retrospective cohort study that compared circuit shedding. The result is that when low-flow CPB. It seems likely that antithrombin replacement may be needed more frequently in COVID-19 patients undergoing cardiac surgery.

**COVID-19 Considerations for Cardiac Surgery**

There are few reports describing coagulation changes in COVID-19 patients undergoing cardiac surgery. One cohort study of 20 COVID-19 patients who underwent cardiac surgery did not report increased bleeding or thrombosis. Patients in the cohort had elevated fibrinogen concentrations (mean = 568 mg/dL) and low antithrombin activity (mean activity = 74%), suggesting that hypercoagulability was present. This may be of particular importance in patients undergoing coronary artery bypass grafting who could be at increased risk for graft thrombosis. One study of critically ill COVID-19 patients demonstrated that a very high percentage of patients (up to 80%) have heparin “resistance,” which is an important consideration when heparinizing patients for CPB. It seems likely that antithrombin replacement may be needed more frequently in COVID-19 patients undergoing cardiac surgery.

**Conclusions**

Coagulation and hemostasis add to the complexity of caring both intra- and postoperatively for the cardiac surgical patient. In 2020, new investigations continued to provide cardiothoracic anesthesiologists with insight into the management of antiplatelet and anticoagulant agents, including reversal options. Advances in blood management should limit unnecessary exposure to allogeneic blood therapy and its associated risks. The expanding use of factor concentrates may see a greater presence for managing post-CPB coagulopathy, which also can be guided with the use of point-of-care tests. The role of VET continues to grow in guiding existing blood conservation techniques. The balance between bleeding and thrombosis in patients with LVAD and ECMO continues to warrant further investigation. Finally, the effect of COVID-19 on all these coagulation aspects certainly will be revisited in the coming year.

**Conflicts of Interest**

None.

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