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Special Article

Coagulation and Transfusion Updates From 2021

Michael Fabbro II, DO*[,1], Prakash A. Patel, MD[†], Reney A. Henderson Jr, MD[‡], Daniel Bolliger, MD[§], Kenichi A. Tanaka, MD, MSc[‖], Michael A. Mazzeffi, MD[¶]

*University of Miami School of Medicine, Miami, FL
†Yale School of Medicine, New Haven, CT
‡University of Maryland School of Medicine, Baltimore, MD
§University Hospital Basel, Basel, Switzerland
‖College of Medicine, University of Oklahoma, Oklahoma City, OK
¶George Washington School of Medicine, Ross Hall, NW, Washington, DC

2021 and the COVID 19 pandemic have brought unprecedented blood shortages worldwide. These deficits have propelled national efforts to reduce blood usage, including limiting elective services and accelerating Patient Blood Management (PBM) initiatives. A host of research dedicated to blood usage and management within cardiac surgery has continued to emerge. The intent of this review is to highlight this past year's research pertaining to PBM and COVID-19–related coagulation changes.

2021 AND THE COVID-19 pandemic have brought unprecedented blood shortages worldwide. [1] These deficits have propelled national efforts to reduce blood usage, including limiting elective services and accelerating Patient Blood Management (PBM) initiatives. National PBM initiatives have been in place for years through the Society for the Advancement of Patient Blood Management and the American Society of Anesthesiologists and their respective guidelines.[2,3] In 2021, a strong endorsement statement for following PBM guidelines was put forth by the American Society of Anesthesiologists PBM Committee in light of pandemic-driven blood deficits.[4] A recent survey published by the Society of Cardiovascular Anesthesiologists members in *Anesthesia and Analgesia* highlighted new widespread implementation of these recommendations.[5] As high utilizers of blood products, cardiac anesthesiologists are at the forefront of blood conservation measures. There are many components to PBM, and updates on important topics within PBM are highlighted in this review. COVID-19–related updates also are highlighted.

Updates in Viscoelastic Coagulation Testing

At the present time, point-of-care testing for coagulation is highly recommended in all PBM guidelines. Multiple viscoelastic coagulation test (VCT) devices are on the market, and different platforms and reagents are available to suit clinical needs. Although it is nice for practitioners to have options, standardization and comparisons across the different test platforms have become complex. De Anda et al recently reported their observational data comparing thromboelastography (TEG) (TEG 5000, Haemonetics, Braintree, MA) and a newer cartridge-based Quantra QPlus System (HemoSonics, Charlottesville, VA) in 28 patients undergoing cardiac surgery. Both test formats use kaolin (contact activator) for clotting time calculation, and the clot strength can be calculated (hecto Pascal [hPa] for Quantra, and dynes/cm^2 converted to hPa for TEG 5000).[6] Notably, only a single-channel kaolin test was used on TEG, and no other tests, such as functional fibrinogen and rapidTEG, were included. Despite these limitations, their study provided clinically pertinent information in terms of data

[1]*Address correspondence to* Michael Fabbro II DO, Associate Professor of Anesthesiology, University of Miami Miller School of Medicine, 1400 NW 12th Ave. Ste #3075 Miami, Fl 33136

E-mail addresses: mxf790@miami.edu (M. Fabbro), Prakash.patel@yale.edu (P.A. Patel).

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exchangeability and application. First, clotting time values were recorded within 5 minutes on Quantra, 12 minutes earlier than the kaolin TEG reaction time. Whole blood clot strengths between the 2 devices overall correlated well (r = 0.84), but TEG clot strength (in hPa) was numerically lower than that of Quantra. The authors also compared TEG clot strength with platelet-specific and fibrin-specific clot strengths of Quantra, but these comparisons should have been done using TEG functional fibrinogen. The newer version of TEG6s (Haemonetics) is a cartridge-based system, and the following 4 separate tests are performed simultaneously: kaolin, kaolin plus heparinase, rapidTEG, and functional fibrinogen. At present, rapidTEG does not report reaction time. The reference range of functional fibrinogen differs from Quantra or fibrin-based thromboelastometry (FIBTEM) on rotational thromboelastometry (ROTEM) (Instrumentation Laboratory, Bedford, MA).[7,8] Taken together, De Anda et al's data demonstrated that test turnaround time and cut-off values could vary significantly among the devices. Additionally, different tests report different sets of values, further emphasizing the need for localized reference values and algorithms.

VCT-Guided Prothrombin Complex Concentrate Administration

In a pilot, prospective randomized trial, Karkouti et al compared 4-factor prothrombin complex concentrate (PCC) (Octaplex; Octapharma AG, Lachen, Switzerland) and fresh frozen plasma (FFP) transfusions in patients at 2 Canadian teaching hospitals who underwent postcardiopulmonary bypass (CPB) with serious bleeding.[9] EXTEM (extrinsically activated) clotting time >90 seconds or the international normalized ratio (INR) >1.5 was used as an indication for an investigational medical product (IMP: PCC or FFP). IMP was dosed at 25 international units per kg for PCC and 12.5 mL/kg for FFP. The primary endpoints were the need for any additional hemostatic therapies, cumulative numbers of allogeneic blood component units after the use of IMP, and avoidance of red blood cell (RBC) transfusion. One hundred thirty-one patients were randomized, and, in the final analysis, 101 subjects were included in the analysis (n = 54 in PCC and n = 47 in the FFP group). The demographic data showed that their patients were at a median age of 66-to-67, and the majority were White (56.4%) and Asian (21.7%) patients, with a mean body mass index of 23-to-24 kg/m^2. CPB time was long (mean, 166-172 minutes), and nonelective surgical cases were included (20.4% in PCC *v* 31.9% in the FFP group). EXTEM data were not reported from the trial, but the transfusion algorithm was similar to the one used in the previous study on hemostasis testing after CPB.[10]

The initial intervention occurred at 1.0-to-1.2 hours from the end of CPB, and the second IMP was utilized in 9.3% in the PCC group and 19.1% in the FFP group (p = 0.25). The use of VCT-guided PCC administration resulted in numerically lower allogeneic blood component usage, including FFP units and 24-hour chest tube drainage, compared to the FFP group. In addition, re-exploration for bleeding and recombinant factor VIIa usage trended lower in the PCC group. This study did not suggest increased adverse event rates from PCC administration, and the median days of hospitalization were reduced in the PCC group (9.3 *v* 12.3 days in the FFP group). Taken together, Karkouti et al's data supported the role of VCT in the selection of post-CPB hemostatic intervention. Notably, EXTEM utilizes tissue factor (TF) as an activator, but other automated devices, such as TEG6s and Quantra, currently do not offer TF-based clotting time measurements. Further clinical validation studies are required to determine if kaolin-activated clotting time (ACT) can be used effectively to titrate PCC.

Controversies in the Diagnosis of COVID-19–Related "Fibrinolysis Shutdown" on VCT

The pandemic has drawn major attention to thromboinflammation because both arterial and venous thromboses have been reported in the presence of elevated cytokines in patients with severe COVID-19.[11] Plasma fibrinogen and D-dimer are tested frequently in these patients, and an increased D-dimer level has been considered a prognostic marker of disease progression and mortality.[12] There has been increasing interest in testing for impaired fibrinolysis in critically ill patients using VCT devices, given their ability to track clot growth and clot dissolution over time. VCT has been used to diagnose accelerated fibrinolysis, using lysis index or maximum lysis (ML), in liver transplantation and severe trauma. Several investigators observed impaired fibrinolysis on TEG or ROTEM in severe COVID-19 associated with thrombotic events, and proposed to use VCT to diagnose delayed fibrinolysis coined, "fibrinolysis shutdown."

It is important to recognize that a small fibrinolysis-like pattern on TEG and ROTEM can be platelet-mediated clot retraction; therefore, if fibrinolysis is occurring in a whole blood sample, lysis patterns should be observed in both native and platelet-inhibited channels (eg, EXTEM and FIBTEM). Indeed, FIBTEM is more sensitive to fibrinolysis induced by tissue plasminogen activator (tPA).[13] A small case series by Creel-Bulos et al reported "fibrinolysis shutdown" in 25 patients with COVID-19.[14] An EXTEM-ML below 3.5% was used as a cutoff for the shutdown, and 11 of 25 (44%) patients met this criterion, with a median ML of 1.0%. These patients frequently had venous thromboembolism (8 of 11), and their D-dimers trended higher than those in nonshutdown patients (median of 5,215 *v* 1,431 ng/mL; p = 0.11). Platelet counts and fibrinogen levels were similar between the shutdown and nonshutdown patients. As previously pointed out by Dr. Ton Lisman, "fibrinolysis shutdown" based on a single TEG and ROTEM trace is likely a misnomer, and elevated D-dimers suggest that fibrinolysis is occurring in vivo.[15] The half-life of tPA is 5-to-10 minutes, and localized fibrinolysis cannot be reflected in a systemic blood sample on TEG and ROTEM.[16] Creel-Bulos et al did not report FIBTEM-ML (%) in their series, which would have been a better test given its higher sensitivity to tPA.[13] Emphasizing this point, an observational series of hospitalized patients with COVID-19 (n = 543) and

those without (n = 288), by Thangaraju et al, simultaneously assessed thrombin generation triggered by TF and plasmin generation triggered by exogenous tPA. The investigators found that both the rate and peak thrombin generation were significantly elevated in plasma from patients with COVID-19 older than 65 years compared to non-COVID samples.[17] Conversely, the plasmin generation rate and peak level were significantly decreased in plasma from older patients with COVID-19. Reduced plasmin generation also was found in plasma from COVID patients whose age was <65 years. Overall plasmin generation peak and rate were decreased by 9% and 18%, respectively, between COVID and non-COVID plasma samples ($p < 0.0001$). In contrast to standard TEG and ROTEM tests that only account for circulating tPA, plasmin generation utilizes exogenously added tPA (0.7 μg/mL). To address this gap in existing VCT devices, a new VCT system, ClotPro (enicor GmnH, Munich, Germany) introduced a tPA test utilizing exogenous tPA (0.65 μg/mL). Bachler et al recently reported a case series of 20 critically ill patients with COVID-19 compared to 60 healthy volunteers.[18] Lysis time (LT) was used as a main endpoint of the tPA test and was defined as a duration to achieve a 50% reduction in maximum clot firmness. A prolonged LT more than 393 seconds was considered impaired fibrinolysis based on their local reference range. The median LT (25%-75% range) was increased by more than 2-fold in patients with COVID-19 compared to healthy subjects—508 (365-827) versus 210 (186-261) seconds ($p < 0.01$). D-dimer levels trended lower in patients with prolonged LT, but statistical significance was not reached. The study was not designed to assess any associations between impaired fibrinolysis and clinical outcomes, including thromboembolism and mortality. However, a tPA challenge test can be applied to other VCT platforms,[19] and it may better delineate impaired fibrinolysis that underlies thromboinflammation. Further studies are warranted to assess the clinical utility of a tPA challenge test in guiding the use of fibrinolysis modulators in critical illness.

Updates on Factor Concentrates in Cardiac Surgery

The use of factor concentrates in cardiac surgery remains an important area of investigation for managing certain preoperative anticoagulants, as well as treating postbypass coagulopathy. The advantages of these potent agents are well-established in terms of targeted factor replacement without the volume overload. Not surprisingly, recommendations for the use of factor concentrates for both drug-induced and non−drug-induced bleeding increasingly are present in PBM guidelines.[2] Numerous ongoing investigations continue to determine efficacy and safety profiles. In the past year, several studies have contributed a great deal of information to the current knowledge of concentrates, such as PCC and fibrinogen concentrates.

Prothrombin Complex Concentrates

Despite the growing off-label uses of PCC, the United States Food and Drug Administration-approved indication for warfarin reversal remains the only indication for 4-factor PCC administration.[20] Given that warfarin reversal with PCC, rather than FFP, has been the preferred approach for several years, more recent investigations have instead focused on dosing strategies for reversal. Current recommendations use a variable dose based on the patient's INR, and range from 25-to-50 U/kg.[21] Advocates for fixeddosing of 4-factor PCC argue that a fixed dose allows for a faster preparation time, lower dosing, and fewer adverse events. A recent meta-analysis of 10 studies that included 988 patients compared the 2 approaches for warfarin reversal.[21] The results found that the time required for goal INR (mean 191 *v* 206 minutes, $p = 0.509$) and the rate of thromboembolic events were similar between the 2 groups, with the fixed-dose 4-factor PCC group having a lower cumulative dose (mean 1360.4 *v* 2028.9 units, $p < 0.001$) and faster time to administration (68 *v* 87.75 minutes, $p < 0.001$).[21]

Asides from warfarin reversal, the off-label use of PCCs in cardiac surgery for the management of direct oral anticoagulants remains an option when specific reversal agents (idarucizumab or andexanet alfa) are not available.[2,22,23] Although PCC is recommended as an alternative in this situation, it should be acknowledged that an effective response may be variable.[2] Use in managing bleeding due to oral factor Xa inhibitors (eg, rivaroxaban or apixaban) often gets more attention over dabigatran-related bleeding. Although this primarily is due to the cost of andexanet alfa, it is also a preferred option in certain cardiac surgical patients because of concern for heparin resistance caused by early andexanet alfa administration.[24] This recently was demonstrated in an ablation case in which the patient was given andexanet alfa due to apixaban-related bleeding. Unfortunately, emergent cardiac surgery was needed to address the cardiac injury, and the patient was unable to achieve an adequate ACT, which led to visible thrombi in the operating field and in the bypass circuit.[25] An additional concern with andexanet alfa in the cardiac surgery population, even when the drug is given after bypass, is the potential need to return to bypass, which would again lead to a similar heparin-resistant state. Therefore, the use of high-dose 4-factor PCCs (as high as 50 U/kg) has been proposed as a reasonable option for factor Xa inhibitor reversal. However, a recent investigation looking at lower-dose PCC (25 U/kg) found a similar hemostatic effectiveness rate when compared to high-dose PCC (50 U/kg).[26] Unfortunately, there are limited data that directly compare PCC to andexanet alfa in the cardiac surgery population, but outcomes of direct comparisons in noncardiac settings likely can be extrapolated to cardiac patients. A retrospective comparison of andexanet alfa and 4-factor PCC for bleeding due to factor Xa inhibitors demonstrated similar outcomes in terms of effective hemostasis ($p = 0.7$) without differences in thromboembolic events ($p = 0.99$) and mortality ($p = 0.39$).[27] Another recent comparison in intracranial hemorrhage patients also found no difference between the 2 options in terms of imaging stability, functional outcome, or thromboembolic events.[28] Finally, a larger meta-analysis (andexanet alfa: 438 patients; PCC: 1,278 patients) also revealed similar effectiveness for treating factor

Xa inhibitor-associated bleeding, while also demonstrating a trend toward greater thromboembolic events in the andexanet alfa group.[29] Given these findings and the implications on potential cost savings, randomized controlled trials comparing andexanet alfa and 4-factor PCC are warranted to determine the optimal choice for factor Xa inhibitors in cardiac surgery.

The value of PCC administration for non–drug-induced bleeding, such as coagulopathy after cardiopulmonary bypass, increasingly is becoming recognized. PBM guidelines in cardiac surgery from 2021 now state that PCC is a reasonable option over FFP as first-line therapy for refractory coagulopathy in select situations (Class IIA recommendation; level of evidence B).[2] A small randomized trial comparing PCC and FFP for bleeding within 24 hours of cardiac surgery found that a PCC dose of 1,000-to-1,500 units was as effective as 4-to 5-units of FFP in terms of correcting coagulation abnormalities.[30] These findings were especially meaningful given the differences in the total volume being administered. The previously mentioned trial comparing VCT-guided PCC administration versus FFP administration also favored PCC use, with 24-hour cumulative allogeneic transfusion being lower in the PCC group and differences in RBC transfusion being statistically significant (1.5 *v* 4.0 units, p = 0.05).[9] An additional observational investigation in postcardiac surgery bleeding compared 415 patients who received either PCC only (n = 72) or FFP only (n = 343).[31] The primary outcome assessment included RBC and platelet transfusion needs in the first 24 hours after bypass. The analysis demonstrated that each unit of FFP was associated with an increase in odds of RBC and platelet transfusion; whereas every 500 units of PCC were associated with a decrease in the odds of RBC and platelet transfusion. As with other studies, adverse events were again similar between the 2 groups. Continued research with larger randomized studies, although challenging, still is needed in this patient population to further determine efficacy and safety.[32]

Despite the above data suggesting no significant thrombotic complications with PCC, there remains hesitancy in utilizing PCC for coagulopathy during use of mechanical circulatory support. This past year has provided some additional insight into the use of PCC for left ventricular assist device (LVAD) implantation or exchange. A retrospective analysis of 160 LVAD patients found that PCC use decreased the need for intraoperative transfusion when compared to no PCC; however, this difference did not reach statistical significance. Similarly, there was a nonsignificant trend toward higher LVAD pump thrombosis with PCC (2.6% *v* 0.8%, p = 0.98).[33] In another retrospective investigation of activated PCC (factor VIII inhibitor bypassing activity [FEIBA]) for post-LVAD coagulopathy, FEIBA use was associated with no increase in 14-day thrombotic outcomes (11.0% *v* 7.6%, p = 0.343) or mortality rate (3.7% *v* 1.3%, p = 0.179).[34] Although the authors suggested a favorable risk-benefit profile for FEIBA use in LVAD surgery, they acknowledged that future studies still are required to fully assess the safety profile.

Fibrinogen Concentrates

The impact of cardiopulmonary bypass on dilution, consumption, and loss of coagulation factors, including fibrinogen, is well-known.[35] Fibrinogen levels may decrease by as much as 50%, and concentrations below 200 mg/dL may be associated with impaired hemostasis.[35,36] The restoration of adequate fibrinogen levels with fibrinogen concentrates in this situation remains off-label in the United States. Although rare in cardiac surgery, an on-label indication was reported recently in a young woman with congenital afibrinogenemia undergoing pulmonary thromboendarterectomy with deep hypothermic circulatory arrest.[37] Given the higher use acquired for (rather than congenital) hypofibrinogenemia, ongoing investigation over the past year on the efficacy and safety of fibrinogen concentrates in cardiac surgery continues.

Since the results of a 2019 randomized trial comparing fibrinogen concentrates to cryoprecipitate demonstrated noninferiority for fibrinogen replacement after cardiac surgery, the arguments for fibrinogen concentrates over cryoprecipitate have strengthened.[36,38] These arguments are further supported by the fact that fibrinogen concentrate use did not result in a significantly higher rate of thromboembolic events.[38] Advantages of fibrinogen concentrates include greater dose predictability given the known fibrinogen content, lower risk of viral transmission, and rapid reconstitution. Concerns with fibrinogen concentrates, aside from higher costs, include lower efficacy in more complex cardiac patients in whom fibrinogen supplementation alone may not be sufficient to restore hemostasis.[36] Despite this concern, recent clinical practice guidelines in critically ill patients have recommended the empirical use of fibrinogen concentrates in cardiac surgery patients with nonmassive bleeding.[39] Either a fixed dose of 2-to-4 grams or dose titration based on rotational thromboelastometry (FIBTEM) is suggested.

Although fibrinogen supplementation may be required for acquired hypofibrinogenemia, simultaneous replacement of other factors after certain cardiac cases also may be needed, as mentioned above. A recent single-center investigation, combining fibrinogen concentrates and PCC, was performed in patients undergoing surgery for congenital heart disease.[40] This combination was well-tolerated and allowed for adequate hemostasis when compared to standard treatment with FFP alone. Another study examined the value of adding factor XIII concentrates to fibrinogen concentrates in treating coagulopathy.[41] There is a low level of evidence to support the use of factor XIII concentrates alone, but perhaps there would be a benefit with a combined approach for improved clot formation and stability. Unfortunately, this in vitro analysis demonstrated no value of a combined approach, as determined by thromboelastometry parameters.[41]

Another area of interest over the past year has included the assessment of different fibrinogen concentrate formulations. Although fibrinogen is the primary clotting factor, currently available products differ based on the manufacturing process and content.[42] An in vitro study recently compared 3 commercially available fibrinogen concentrates by supplementing

2.5 g of fibrinogen per 70 kg of body weight to postoperative blood collected from 23 cardiac surgery patients. Clot strength was improved in all 3 formulations, as assessed by viscoelastic testing; however, there were notable differences among the concentrates when looking at changes in clot formation time and maximum clot firmness ($p < 0.001$).[42] As fibrinogen concentrate use continues to rise in cardiac surgery, these findings may impact the product of choice, as well as dosing.

Updates on Transfusion Studies in Cardiac Surgery

Anemia in patients on CPB continues to be an important topic for investigators in cardiac surgery.[2,43,44] The risks of intraoperative RBC transfusion and increased postoperative morbidity and mortality persist in anemic cardiac surgery patients.[43-45] Recent evidence, however, has shown that hemoglobin thresholds for increased risk may vary between men and women and between younger and older patients.[45-49] Combined with evidence suggesting RBC transfusion may not eliminate the risk of organ dysfunction and is associated with impaired outcomes, transfusion best practices remain elusive.[2,43,50,51] Contributing to uncertainty, 2 large randomized controlled trials in cardiac surgery did not show an impaired outcome with a more liberal transfusion strategy compared to a restrictive regimen.[47,48] Adding even more confounders, a recent large retrospective analysis in healthcare data from >700,000 patients showed that non-White ethnicity was associated with increased rates of blood transfusion.[52] The authors suggested potential bias related to physicians and providers may account for these differences.[52] Considerable debate around transfusion practices persists.

This debate was highlighted in a recently published survey among United States cardiac anesthesiologists, which demonstrated that around 30% accepted a hemoglobin value <7.0 g/dL as an RBC transfusion trigger.[5] This transfusion trigger is distinctly lower than the thresholds investigated in 2 key transfusion trials, TRICS-III and TITRe-2.[47,48] It also is below the threshold of 7.0-to-8.0 g/dL used in most studies for the restrictive transfusion groups.[53] It is also in spite of some of the suggested benefits of a more liberal transfusion strategy.[47,48] Recent survey data suggest an increased adoption of low transfusion triggers in cardiac surgery-based controversial evidence.

Alternatively, the use of physiologic triggers of adequate tissue oxygenation potentially could address some of these controversies.[43,54] In a recent randomized controlled trial, patients with postoperative hemoglobin <9.0 g/dL admitted to cardiac care units after cardiac surgery were randomized to receive either a transfusion with 1 RBC unit (control group) or a transfusion only if the central venous oxygen saturation was <70% (study group).[55] The study group received fewer RBC transfusions without increasing in-hospital morbidity or mortality.[55] This study did show that RBC transfusion triggers using physiologic parameters, in combination with hemoglobin values, reduced overall transfusions. One key limitation of this study, however, was that the transfusion trigger of 9.0 g/dL was higher than the recommended thresholds in the recent clinical guidelines.[2]

Institutional and national PBM programs continue to work to address these variations in transfusion practices. At the foundation of these efforts is conserving the patient's own blood reserves in the perioperative period. The PBM definition recently has been updated, now focusing on a patient-centered, systematic, and evidence-based approach to improving patient outcomes by using the different PBM tools as a bundle.[56] In addition, the clinical practice guidelines on PBM have been updated in the last year.[2] These consensus recommendations were supported recently by a retrospective propensity score-matching analysis, including nearly 8,000 patients undergoing cardiac surgery at a large Chinese center. This study showed that a comprehensive blood conservation program during adult on-pump cardiac surgery was effective in reducing the transfusion of RBC without adversely affecting outcomes.[49]

An additional key component of PBM is optimizing the patient's own blood reserves before surgery. This approach was assessed in a retrospective Canadian cohort study, including 532 patients referred to an outpatient blood conservation clinic before cardiac surgery.[57] The authors found that the preoperative treatment with iron and erythropoietin significantly increased hemoglobin values. Based on their analyses, intravenous iron at a dose of at least 600 mg, and erythropoietin alfa at doses of at least 80,000 units, were necessary to increase hemoglobin values.[57] This study highlighted 2 major problems in current preoperative PBM programs: First, the number of eligible patients was limited, given that roughly 530 included patients were recruited over a time period of about 10 years. Second, the high doses of iron and erythropoiesis-stimulating agents required for hemoglobin optimization might question the cost-effectiveness. Therefore, PBM practices should be introduced after critical and potentially individual assessment.[58] In agreement, a recently published large network meta-analysis, including 393 randomized trials with nearly 55,000 enrolled patients, found a reduction in exposure to RBC by about 40% by multiple PBM means, but no statistically significant treatment effect in respect to mortality and major morbidity.[59] However, this meta-analysis was criticized by many experts, given conflicting evidence demonstrating PBM programs reduce RBC transfusion and improve the quality of care in patients undergoing cardiac surgery.[53,56]

Updates on Anticoagulation for Cardiopulmonary Bypass

Imperative to ongoing PBM measures is the appropriate management of anticoagulation during CPB. A timely review in 2021 in the *Journal for Cardiothoracic and Vascular Anesthesia* by Hessel et al detailed the most important points related to anticoagulation management in cardiac surgery from the European Association of Cardiothoracic Anesthesiology guidelines on CPB.[60,61] The key recommendation related to CPB and anticoagulation management encouraged individualized heparin and protamine doses. This guidance was supported by level II evidence; however, a paucity of information was included regarding "individualized" doses. Heparin

concentration monitoring is potentially one way to individualize doses, but previous consensus statements published by the Society of Cardiovascular Anesthesiologists pointed out that support for these monitors is lacking.[62] In consideration of this, ACT remains the gold standard for monitoring anticoagulation goals. With a plethora of point-of-care ACT monitors on the market, authors in 2021 compared 4 of the commonly used devices for accuracy. The Hemochron Elite (Werfen) demonstrated the least reproducibility and most variation; whereas the Medtronic HMS Plus (Medtronic) and Abbott i-STAT systems (Abbott Laboratories) showed strong correlation and better reproducibility.[63] These are considerations for centers implementing or revising current PBM standards, especially within cardiac surgery and when budget constraints are prominent.

Comparison of anticoagulation monitoring devices is not the only important investigation on coagulation management from 2021. Miles et al attempted to determine the most optimal protamine dosing strategy in their publication appearing in *Perfusion*.[64] Current guidelines recognize the controversy among various reversal strategies and provide little guidance beyond limiting protamine doses to <2.6 mg protamine per 100 units of heparin.[62] These ratio strategies remain commonplace but notoriously have significant variation. Protamine-to-initial heparin dose can be used, and protamine-to-total heparin dose also has been described. Additionally, weight-based heparin dosing itself varies among centers. To continue investigating the issue, Miles et al compared fixed-ratio dosing to modeling-based dosing.[64] Models were derived from compartmental models in consideration of protamine pharmacology. Previous investigations into complex dosing calculations have had mixed results and lacked any formal support.[62] The authors did, however, find that the compartmental modeling group received statistically less protamine. Investigations supporting ratios below 1:1 also have been published in the past.[64] More studies still are needed to elucidate optimal protamine dosing strategies to limit both under- and over-dosing. In consideration of the work of Miles et al. and other studies, it seems likely lower ratios of protamine-to-heparin are more important than dose calculation methods.

Other important work on anticoagulation management in 2021 focused on patients with heparin-induced thrombocytopenia (HIT) undergoing cardiac surgery. Several guideline statements provided direction for managing this patient group, and a complete review can be found in the *Journal of Cardiothoracic and Vascular Anesthesia*.[65] In summary, the consensus was to wait until HIT is resolved and move forward using heparin. In those urgent/emergent situations, alternative anticoagulants are supported, and, if possible, plasmapheresis may be considered. Authors from Duke presented safety data in 2021 for intraoperative therapeutic plasma exchange in 24 patients with HIT.[66] Preoperative antibody titers only were available in about half of these patients, and postoperative titers were demonstrably lower. Some patients did have postoperative thrombotic events; however, many were high-risk advanced heart failure patients. Concerns around this technique may be warranted when considering data presented by Brown et al, that showed mortality after cardiac surgery was significantly higher in patients who developed HIT.[67] Interestingly, mortality was not different among those patients with HIT with thrombotic events and those without.

In summary, anticoagulation management advances in 2021 focused on important areas that still trouble cardiac anesthesiologists today, including "individualized" heparin and protamine dosing and HIT management within cardiac surgery. In the face of extreme national blood shortages, these efforts and all PBM-related activities never have been more important.

Updates in Coagulation Changes and Management for Mechanical Support Devices

Extracorporeal Membrane Oxygenation

In 2021, several mechanistic studies shed light on the pathophysiology of coagulopathy that occurs during extracorporeal membrane oxygenation (ECMO). In a study that included 20 patients on venoarterial (VA) ECMO and 10 on venovenous (VV) ECMO, the authors obtained blood samples from all patients on ECMO on days 1 and 3 and after ECMO decannulation. They also obtained samples from 10 healthy volunteers and 15 patients with coronary artery disease. The authors analyzed the density of multiple platelet surface receptors at baseline and in response to different agonists. The main study findings were that patients on ECMO had reduced activation of glycoprotein (GP) IIb-IIIa in response to agonists, including adenosine diphosphate (ADP) and thrombin receptor agonist protein and lower surface GPVI and GP1bα density, when compared to controls. These defects in adhesion and aggregation receptors may contribute to the severe bleeding that occurs in many ECMO patients.[68]

Another study of 39 patients on ECMO (17 VA ECMO and 22 VV ECMO) highlighted important differences in the coagulation profiles of patients on either VA ECMO or VV ECMO. In this study, patients had blood samples obtained every 48 hours during the first week on ECMO and every week after until the time of decannulation. Patients on VA ECMO had lower platelet counts, lower fibrinogen, lower antithrombin III activity, and comparable acquired von Willebrand syndrome (VWS) when compared to patients on VV ECMO.[69] The heparin dose required to obtain a target activated partial thromboplastin time was approximately one-third in patients on VA ECMO when compared to VV ECMO, perhaps because of lower procoagulant factor activity.[69]

Tissue factor pathway inhibitor (TFPI) is an endogenous anticoagulant that inhibits factor Xa and factor VIIa. Systemic heparinization is known to increase TFPI levels, as heparin displaces TFPI from endothelial cell surfaces and increases TFPI release from endothelial cells.[70] In a study of 20 patients on VA ECMO, the authors found that TFPI levels were increased approximately 2-fold compared to control plasma.[71] Increased TFPI levels correlated with increased TF-triggered lag time on a calibrated automated thrombin generation assay.[71] These findings suggested that patients on ECMO who

receive systemic heparinization may have slowed TF-triggered thrombin generation; in part, because of elevated TFPI levels.

There are continued efforts to develop new anticoagulants for patients on ECMO. In an animal model, a group from Duke University tested a ribonucleic acid-based aptamer to factor IXa (DTRI-178). The authors compared anticoagulation adequacy and surgical bleeding in pigs treated with DTRI-178 against pigs treated with intravenous heparin. After running the ECMO circuits for 12 hours, the authors examined oxygenators under microscopy and found minimal clot burden in both groups (<2% of oxygenator surface).[72] Further, the authors found that there was less surgical bleeding (at cannulation sites) in the group of pigs treated with DTRI-178.[72] In a second animal study that used rabbits, an ECMO circuit that was impregnated with poly-carboxybetaine was combined with a factor XIIa inhibitor (FXII900), and the outcomes were compared against systemic heparin.[73] Pharmacologic shutdown of factor XIIa, in combination with a poly-carboxybetaine circuit, led to minimal macroscopic clot formation at 60 minutes and low fibrinopeptide A levels, suggesting minimal fibrin formation.[73] The importance of factor XII in the pathophysiology of thrombosis during ECMO was further highlighted in an observational study, which showed that increased factor XII activity was associated with thrombosis during ECMO (odds ratio [OR] = 3.0 for every tertile increase in factor XII activity).[74]

Anticoagulation with heparin versus direct thrombin inhibitors remains a controversial topic in adult patients receiving ECMO therapy. In 2021, there were several studies comparing direct thrombin inhibitors versus heparin. In a propensity-matched cohort study from a major European ECMO center, the authors found that bleeding rates were similar between patients anticoagulated with heparin and argatroban; however, argatroban was more expensive.[75] Interestingly, patients who received argatroban had higher platelet counts at the time of ECMO decannulation (141 v 107 $\times$ 10^9/L), but the clinical significance was not clear.[75] In a systematic review that included more than 300 patients from 13 studies, the authors similarly found that patients anticoagulated with argatroban had comparable bleeding and thrombosis rates when compared to patients who were treated with heparin.[76] In a large single-center observational study (N = 422), the authors compared patients who were anticoagulated with heparin versus those anticoagulated with bivalirudin.[77] They found lower mortality in patients who received bivalirudin (OR = 0.39), and also a lower transfusion rate during the first 24 hours in pediatric ECMO patients treated with bivalirudin (OR = 0.28).[77] Patients who received heparin had a 12% incidence of HIT, which was higher than in prior studies.[77] Although intriguing, this study had multiple limitations, including a lack of adjustment for confounding by the year of treatment.[78] In the early study period, heparin was used preferentially, and there was a shift to bivalirudin over time. It is likely that ECMO practices and PBM improved in the authors' center over time, and this coincided with the change from heparin to bivalirudin.[78]

Another noteworthy study related to anticoagulation during ECMO was a systematic review from Willems et al in which anti-Xa monitoring was compared with ACT and activated partial thromboplastin time monitoring in more than 2,000 patients who received heparin anticoagulation. In this study, patients who had anti-Xa monitoring had a 51% lower odds of having a bleeding complication during ECMO (OR = 0.49), and also significantly lower mortality (OR = 0.61).[79] There was no significant difference in thrombosis between the 2 groups.[79]

Ventricular Assist Devices

Several interesting studies were published in 2021 describing coagulation changes in patients with ventricular assist devices (VADs). In a study of 39 patients with left ventricular assist devices (LVADs), the authors compared platelet surface-receptor expression in patients with and without coagulopathic bleeding (N = 19 and N = 20, respectively). In the study, the authors found that patients with coagulopathic bleeding had an approximately 25% lower expression of surface GP1bα, lower levels of ADP-stimulated P selectin and platelet endothelial cell adhesion molecule-1, and greater markers of oxidative stress.[80] They concluded that these platelet abnormalities might contribute to coagulopathic bleeding in patientsr receiving an LVAD.[80]

In a second study, the authors explored the potential impact of circulating platelet-derived microparticles (PMPs) on thrombotic risk in 43 patients receiving an LVAD. In this study, there were 8 patients who developed a thrombotic complication, and they had higher levels of PMPs and thrombin generation.[81] Mean PMP levels more than doubled after LVAD implantation compared to baseline.[81] In patients with thrombotic complications, PMPs were approximately 2-fold higher, and this correlated with higher thrombin generation.[81] The authors concluded that PMP measurement might allow for improved risk stratification in patients receiving an LVAD.[81] Of note, PMPs rose relatively quickly after LVAD implantation and remained relatively stable over the first year.

Gastrointestinal bleeding historically has been a major problem for continuous-axial flow patients receiving an LVAD. In a case series of 8 patients with a Heartware HVAD (Medtronic), the authors reported on the use of tamoxifen to reduce major gastrointestinal bleeding.[82] Tamoxifen has been used to treat hereditary telangiectasia and is thought to modulate (upregulate) transforming growth factor-beta signaling, which reduces abnormal angiogenesis and potentially augments vascular repair. Tamoxifen also may reduce vascular endothelial growth factor release from platelets.

Acquired VWS is a well-described complication in patients with durable LVADs; however, there are relatively few studies in patients with percutaneous catheter-mounted axial-flow VADs (ie, Impellas [Abiomed]). In a study of 60 patients with catheter-mounted VADs (20 right ventricular [RV] and 40 LV), the authors found that acquired VWS occurred in 88% of patients with LV support, whereas only 58% of patients with RV support developed acquired VWS.[83] They hypothesized that lower pressures and lower shear stress with a right ventricular assist device (RVAD) might explain these findings.[83] In

the study, more than 50% of patients had major bleeding with a median of 3 days of support.[83]

Selective serotonin reuptake inhibitors (SSRIs) are used commonly to treat major depression and anxiety. SSRIs also have mild antiplatelet effects and increase bleeding risk in patients with cardiovascular disease who are taking antiplatelet drugs.[84] In a study of 100 patients with a durable VAD (mostly Heartmate 3 [Abbott]), the authors had an overall 36% hospital readmission rate for major bleeding.[85] After stratifying by SSRI use, the authors found that patients who were taking SSRIs were more commonly readmitted for major bleeding (46% *v* 15%, hazard ratio [HR] = 2.3, p = 0.004).[85] The authors concluded that SSRI use in patients with a VAD may be associated with significant bleeding risk and should be evaluated further in prospective randomized studies. Also, patients who take SSRIs may need to have their anticoagulation regiment altered to reduce bleeding risk.

Aspirin is the most commonly used antiplatelet drug in patients with a durable VAD. In a small cohort study of 28 patients with a VAD, aspirin's antiplatelet effects were assessed over time using aggregometry (Aspirin VerifyNow Platelet Reactivity). In this study, the authors found that only 7% of patients were aspirin-resistant in the immediate perioperative period; however, approximately one-third of patients were aspirin-resistant at 3 and 6 months.[86] They concluded that a tailored approach to antiplatelet therapy may be needed, rather than a "one-size-fits-all" approach. Most patients who received an increase in their aspirin dose achieved an adequate response, suggesting that tailored monitoring and therapy has the potential to reduce complications.

Updates on Antiplatelet Agents in Cardiac Surgery and COVID-19

Antiplatelet drugs, as either single-antiplatelet therapy or combined with aspirin (ASA) as dual- antiplatelet therapy (DAPT), remain commonplace for antithrombotic prevention in cardiac patients. Efforts investigating best practices regarding the perioperative continuation of therapy continued in 2021. Current guidelines and evidence supported the continuation of ASA perioperatively to reduce early postoperative thrombotic events and mortality after coronary artery bypass grafting (CABG) surgery.[2,87] A recent propensity-matched retrospective study by Hassan et al further supported this practice by demonstrating reductions in 30-day mortality and major cardiac events with ASA administration $\leq$24 hours before CABG surgery.[88]

Concerns with perioperative ASA use have focused on the variable response to ASA detailed in prior research.[89] A recent prospective pilot study by Chatterton et al highlighted this issue as it relates to ASA hyper-responders. The authors in this study tested preoperative platelet function in patients on aspirin scheduled for CABG surgery, using the point-of-care VerifyNow aspirin assay (Werfen). Aspirin reaction unit values in the lower 50th percentile were used as a cutoff to determine hyper-responders. Hyper-responders were found to have an increased incidence of transfusion compared to nonresponders (70% *v* 38.7%, p = 0.014). In a multivariate analysis, hyper-responders also were found to be an independent predictor for transfusion (OR = 3.7; 95% CI: 1.3-10.7, p = 0.016).[90] With variation in patient response to ASA, the benefit of continuation of therapy prior to cardiac surgery may be patient-specific.

Adding to the debate, a recent study of 18,000 patients undergoing CABG surgery compared patients on DAPT with ASA and clopidogrel to ASA alone. The DAPT group had a lower risk of all-cause death (HR = 0.61; 95% CI: 0.41-0.90; p $<$ 0.001), myocardial infarction (HR = 0.55; 95% CI: 0.40-0.74; p $<$ 0.001), and cerebrovascular accident (HR = 0.5 8; 95% CI: 0.46-0.74; p $<$ 0.001) 6 months postoperatively without increasing incidence of major bleeding.[91] These findings were in spite of current recommendations to discontinue $P2Y_{12}$ receptor inhibitors ticagrelor, clopidogrel, and prasugrel at 3 days, 5 days, and 7 days, respectively, prior to surgery.[2,92] One key application of these findings is in patients with recent intracardiac stents, in whom interruption of therapy may be harmful. Alternatively, bridging with intravenous antiplatelet agents has been proposed but lacks evidence at this time. Lastly, new antiplatelet drugs currently are being developed to decrease bleeding risk while maintaining antithrombotic benefits. Selatogrel is a novel $P2Y_{12}$ receptor inhibitor that can be subcutaneously administered. When used in patients with acute myocardial infarction, Selatogrel averaged a platelet-reacting unit with VerifyNow of 9 and 51 in 15 minutes without bleeding complications, showing promise for earlier intervention for acute coronary syndrome.[93] Additional novel antiplatelet drugs are directed at different platelet receptors to limit platelet inhibition, such as protease-activated receptors 1 and 4, GPVI ligand, and protein disulfide isomerase. One such GPVI ligand is revacept, which competitively binds to GPVI expressed by exposed collagen, preventing collagen-induced platelet activation.[94] With the continued development of novel antiplatelet drugs, clinicians will be presented with new challenges to assess platelet function to determine associated bleeding risks.

Platelet Function Monitor Updates

Platelet function testing (PFT) is used increasingly to reduce surgical waiting times and tailor antiplatelet therapy regimens. These tests also are being incorporated into transfusion algorithms. Light-transmission aggregometry is the gold standard for PFT, but, due to its lack of standardized values, prolonged processing, and need for a specialized technician, its clinical use is limited. Currently used PFTs are Platelet Function Analyzer 100 (Dade-Behring), Quantra, Multiplate (F. Hoffman-La Roche Ltd), VerifyNow, and TEG Platelet Mapping (Haemoscope Corporation). Widespread adoption of these devices has been limited by cost and conflicting evidence.

Of these devices, Quantra is the newest point-of-care coagulation analyzer. The automated cartridge tests whole blood clot function and can provide platelet-specific information represented by platelet contribution to clot stiffness. In a recent prospective cohort study in cardiac surgical patients, Quantra

was shown to have a correlation of (r = 0.71) to platelet count and (r = 0.67) to the more established PFT, Multiplate.[95] In light of this, the Quantra system may be a promising viscoelastic monitor to assess platelet count and platelet function.

TEG Platelet Mapping, which uses Activator F (reptilase and activated factor XIII) mixed with either ADP or arachidonic acid to initiate platelet activation and fibrinogen polymerization, has been of interest, but extensive processing has limited its application. The newer cartridge-based TEG6s has improved this limitation, and more research is needed on this newer platform.[96] A recent study in 10 healthy volunteers compared Multiplate, VerifyNow, and TEG6s while titrating ticagrelor to effective concentrations (EC) of 10%, 50%, and 90%. TEG6s was able to distinguish all drug zones (<EC10, EC10-50, EC50-90, >EC90), whereas VerifyNow and MEA only could distinguish 3 and 2 drug zones, respectively.[97]

Updates on Clinical Trials using Platelet Function Monitors

Emphasizing the potential impact of perioperative PFT, Nakashima et al performed a randomized noninferiority trial in patients undergoing CABG surgery on DAPT and surgical planning with either standard treatment (5-7 days waiting period) or using Multiplate ADP ≥46 units. After randomization, 95 patients were stratified into each study group, resulting in an 85-hour (50h *v* 135 hours; $p < 0.001$) reduction in waiting time from surgical indication to surgical approval to proceed, a 24-hour (112 *v* 136 hours; $p < 0.001$) reduction in surgical indication to the beginning of the procedure, and a 58-hour (297 hours [interquartile range 256-412] *v* 355 hours [interquartile range 307-447]; $p = 0.009$) reduction in total hospital stay in the interventional group compared with the control group.[98] Overall, this resulted in a 6.4% ($p = 0.014$) decrease in median hospital expenses in the interventional group without an increase in 24-hour chest tube drainage.

More evidence supporting PFT ability to stratify bleeding risk also emerged this past year. In a prospective trial of 416 patients undergoing elective isolated CABG surgery, Multiplate-ADP and Multiplate-AA were conducted preoperatively for each patient. Multiplate-ADP ≤50 units was found to be 82.4% sensitive and 40% specific for bleeding >1000 mL. Additionally, Multiplate-ADP ≤50 units correlated with statistically significant increases in total transfusion (20%), RBC (15%), platelets (35%), and cryoprecipitate (10%).[99] These findings were similar to the results of previous studies.[100] Larger metanalysis have been conflicting on the ability of PFT to reduce transfusion and predict bleeding.[101,102]

COVID-19 Impact on Platelet Function

Unlike other viruses, COVID-19 causes increases in platelet consumption and apoptosis mediated by immunoglobulin G antibodies via the Fcγ IIA receptor on the platelet surface.[103] To account for this, antiplatelet or anticoagulant therapy has been recommended for patients with COVID-19 to improve outcomes. In an analysis, approximately 8,000 patients with COVID-19 presenting for hospitalization were enrolled in a registry to observe the effects of antiplatelet therapy. During hospitalization, 9% of patients received antiplatelet medication. The antiplatelet group had lower mortality rates (relative ratio 0.79; 95% CI: [0.70-0.94]) compared to the no anticoagulant or antiplatelet group.[104] There may be some opportunity for investigating viscoelastic testing in this application.

Though most studies have shown the hypercoagulable effects of COVID-19, Chiariello et al looked at cardiac surgical patients who were positive for COVID-19 in relation to bleeding events. During a 1-year span, they encountered 23 patients who tested positive for COVID-19, of whom 1 experienced COVID-19 symptoms, and compared them to 46 corresponding control patients. The COVID-19 group showed increased incidences of bleeding complications (48% *v* 2% $p = 0.0001$), surgical re-exploration (35% *v* 2% $p = 0.0001$), and transfusions (74% *v* 30% $p = 0.0006$) compared to the control group.[105] These findings are a consideration as COVID-19–related surgical policies evolve.

Conclusion

In summary, 2021 brought many important updates regarding coagulation management, transfusion medicine, and point-of-care testing. Some of these updates focused on timely problems, including blood shortages and the COVID-19 pandemic. A number of clinical problems were highlighted that continue to require ongoing investigations for clarity. Future updates, hopefully, will address some of these questions.

Conflicts of Interest

None.

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