https://doi.org/10.33472/AFJBS.6.2.2024.935-949

African Journal of Biological Sciences

Research Paper Open Access

An Overview about Mediastinal Bleeding After Cardiac Surgery

Ahmed Hassan Abdelsalam Abdallah [1], Mahmoud Ahmed M. Mahgoub [2], Alaa Ibrahim Abdelhafeez Boriek [2], Kareem Mohamed Medhat El-Fakharany [2]

1 Specialist of Cardiothoracic Surgery, Al-Ahrar Teaching Hospital

2 Cardiothoracic Surgery Department, Faculty of Medicine, Zagazig University

*Corresponding author: Ahmed Hassan Abdelsalam Abdallah

Email: Hsnahmd86@gmail.com

Article History

Volume 6, Issue 2, April 2024

Received:19 April 2024

Accepted: 31 May 2024

Published: 31 May 2024

doi: 10.33472/AFJBS.6.2.2024.935-949

Abstract: Background: Bleeding after cardiac surgery is a well-known serious complication. Cardiac surgical patients are particularly susceptible to postoperative mediastinal bleeding. Postoperative bleeding gradually tapers over the course of several hours in the majority of patients, but about 1–3% of patients will require re-exploration in the operating room for persistent mediastinal bleeding. Prompt and aggressive treatment upon arrival in the ICU may frequently arrest "medical bleeding," but evidence of persistent or increasing amounts of bleeding should prompt early exploration. Re-exploration for bleeding is associated with prolonged hospital stay and increased complications e.g. sternal wound infection (SWI), renal impairment, and postoperative arrhythmias. Every effort should be exerted to avoid postoperative bleeding and to manage it properly if happens. Variability of perioperative blood loss and rate of re-exploration among centers and surgeons were reported Morbidity and mortality after cardiac surgery can be caused by excessive bleeding which is common and preventable cause.

Keywords: *Bleeding, cardiac surgery*

Introduction

Bleeding after cardiac surgery is a well-known serious complication. Cardiac surgical patients are particularly susceptible to postoperative mediastinal bleeding. Postoperative bleeding gradually tapers over the course of several hours in the majority of patients, but about 1–3% of patients will require re-exploration in the operating room for persistent mediastinal bleeding. Prompt and aggressive treatment upon arrival in the ICU may frequently arrest "medical bleeding," but evidence of persistent or increasing amounts of bleeding should prompt early exploration [1].

Excessive postoperative bleeding needs to be treated in a timely fashion, using allogeneic blood transfusion, pharmacological hemostatic agents, or thoracic re-exploration if indicated. Any of these interventions performed to mitigate the harms of bleeding is associated with a worse clinical outcome, even increasing postoperative thrombotic complications[2].

It would be ideal for the cause of perioperative coagulopathy to be diagnosed quickly and the most appropriate intervention chosen to fix the problem. However, coagulopathy after cardiac surgery commonly is multifactorial, and the etiology of bleeding is often difficult to determine. If diagnosed quickly, surgical bleeding is a correctable cause of postoperative bleeding [3].

In this issue of the Journal of Cardiothoracic and Vascular Anesthesia, Biancari et al. performed a meta-analysis of 18 studies that included more than 50,000 patients, focusing on the sources of bleeding in cardiac surgical patients. Surprisingly, they reported that a surgical source of bleeding was found in roughly two-thirds of patients due to bleeding or pericardial tamponade. Furthermore, in-hospital and 30-day mortalities in re-explored patients with a coagulopathic bleeding were worse than in those patients in whom a surgical bleeding source was found [4].

Re-exploration for bleeding is associated with prolonged hospital stay and increased complications e.g. sternal wound infection (SWI), renal impairment, and postoperative arrhythmias. Every effort should be exerted to avoid postoperative bleeding and to manage it properly if happens. Variability of perioperative blood loss and rate of re-exploration among centers and surgeons were reported Morbidity and mortality after cardiac surgery can be caused by excessive bleeding which is common and preventable cause[5].

The main causes of excess bleeding after cardiac operation using cardiopulmonary bypass (CBP) is categorized to surgical or medical reasons. Understanding the main risk factors associated with bleeding could help reduce the incidence of this complication[6].

CPB causes qualitative and quantitative platelet dysfunction. The concentration of pro-coagulants decreases due to haemodilution. Inflammatory, coagulation, complement and fibrinolytic pathways are activated. Thromboelastography can help in knowing the cause of bleeding diathesis. Bleeding is greater with prolonged bypass time, redo-surgery and preoperative use of anticoagulants[7].

Studies have shown decreased blood loss and transfusion requirement in cardiac surgery patients with prophylactic anti-fibrinolytics. Effective fibrinolysis inhibition requires a loading dose of 10 mg/kg for tranexamic acid (TA) followed by 1 mg/kg/h or 50 mg/kg of epsilon-aminocaproic acid followed by infusion of 25 mg/kg/h. High doses of TA may increase the risk of seizures (~5%–7%)[8].

Post-operative transfusion increases mortality after the administration of 4-6 red blood cell packets (Hazard Ratio (HR) 2.01, 95% CI 1.06-3.80) and after the administration of more than 7 red blood cell packets (HR 5.22, 95% CI 2.78-9.79). The incidence of bleeding more than usual is reported to range from 3.6% in coronary bypass to 52.9% in more complex surgeries and is a predictor of adverse events[9].

The risk of re-exploration for bleeding has been associated with various patient-related and intraoperative factors, such as advanced age, small body surface area, renal insufficiency, type and extent of procedure, greater number of distal anastomoses, emergency status and preoperative exposure to platelet inhibitors [10].

Excessive bleeding and re-exploration have been linked to a substantially increased incidence of postoperative complications including myocardial infarction (MI), acute kidney injury (AKI), stroke, infections (including deep sternal wound infection), transfusion-related events and increased length of hospital stay and hospital costs. Correspondingly, numerous studies have shown a strong association between re-exploration for bleeding and early mortality, with a reported two- to six-fold increased risk of death in the early (within 30 days) postoperative period [11].

In addition, re-exploration after cardiac surgery increases the risk of mediastinitis, which has an adverse impact on outcome, hospital stay and costs. For these reasons, re-exploration is considered an important outcome parameter for all projects aiming at quality improvement in cardiac surgery. 'Meetbaar Beter' (English: Measurably Better) is a Dutch foundation, initiated to facilitate quality improvement by publishing patient-relevant outcome measures of heart centres in the Netherlands[12].

Implementing the principles of the value-based health care (VBHC) theory of Porter, 'Meetbaar Beter' promotes transparent reporting of results of care and sharing the processes leading to these results. Patient-relevant outcome measures are selected for different medical conditions, including coronary artery disease. The outcome measure hierarchy is used as a framework for the selection of a range of both short- and long-term outcome measures that are relevant to patients. The sets of outcome measures are aligned with the indicator sets of the International Consortium for Health Outcomes Measurement [13].

Re-exploration after Cardiac surgery is selected by 'Meetbaar Beter' as one of the most relevant outcome measures for patients undergoing Cardiac surgery. Earlier data of 'Meetbaar Beter', published in 2014, showed a relatively high incidence of re-exploration in the Catharina Hospital (9% for all cardiac procedures) [14].

Internal analyses did not lead to relevant hypothesis in order to improve the results, as there were no obvious patterns found in the data. As shown in earlier studies, postoperative bleeding was the most common cause of re-exploration. In 2013, Loor et al. described a policy to minimize the technical causes for re-exploration for bleeding. This was achieved through the implementation of a checklist. This 'Cleveland Clinic reoperation for bleeding checklist' was also presented at the 'Meetbaar Beter' symposium in 2014 [15].

Subsequently, Elassal et al reported that low rate of re-exploration for bleeding can be achieved by strict preoperative preparation, intraoperative checklist for hemostasis implemented by senior surgeons and adopting an algorithm for management [1].

Although there are many strategies employed with the aim of reducing postoperative bleeding after cardiac surgery, such as intraoperative haemostasis checklists and point of care monitoring of coagulation status, bleeding remains an important complication. Significant postoperative bleeding is associated with re-exploration and blood transfusion, both associated with inferior outcomes [16].

A recent review concluded that patients who bleed significantly and undergo re-exploration have increased mortality and experience greater morbidity. Similarly, studies have demonstrated an association between blood transfusion and increases in short- and long-term mortality, with a correlation between the amount of blood transfused and morbidity[17].

These studies have driven a shift from more liberal use of blood products to a more restrictive and goal-directed approach. There is also evidence that bleeding itself is harmful, independently of re-exploration and significant blood transfusion, with studies demonstrating association with increased postoperative mortality risk [18].

Bleeding and Surgical Re-exploration

Cardiac surgery is a generic term for various types of major surgery performed on the heart and great vessels, usually performed on cardiopulmonary bypass with full systemic anticoagulation. CPB has detrimental effects on hemostasis, resulting in dilution and consumption of clotting factors, platelets activation and hyperfibrinolysis that persist after reversal of the heparin effect by protamine [6].

The risk of significant blood loss and subsequent allogenic transfusion is therefore higher than for other types of surgery. Expected and unexpected bleeding occur frequently in patients undergoing cardiac surgery; cardiac surgery patients use 10% to 25% of the blood products transfused annually in the United States[19].

Although unexpected bleeding after this surgery is common, reducing this bleeding is a desirable clinical goal, because such bleeding is associated with adverse outcomes. Unlike other settings, however, overly aggressive treatment of bleeding is also likely to be associated with adverse outcomes, because induction of a hypercoagulable state might be associated with early graft failure [20].

Bleeding and surgical re-exploration are both independent predictors of an adverse outcome. Bleeding after cardiac surgery can be broadly divided into two groups: surgical (unrecognized bleeding vessel, anastomosis, or other suture line) or nonsurgical bleeding (caused by coagulopathy). Factors influencing both surgical and nonsurgical bleeding can be further broken down into those occurring preoperatively and those that occur intraoperatively and postoperatively [21].

Bleeding definitions

A variety of definitions of excessive bleeding in the postoperative cardiac surgery patient have been proposed (Table 1). Using these definitions, excessive bleeding occurs in about 5% of cases. Patients with significant bleeding often require reoperation; rates of reoperation for bleeding vary between 3% and 14%; a surgically correctable source of bleeding is found in 50% to 67% of patients [22].

According to the severity of bleeding, the universal definition of perioperative bleeding in adult cardiac surgery was proposed [23].

It included five classes [23]:

1. Class 0, insignificant (<600 mL);

2. Class 1, mild (601–800 mL);
3. Class 2, moderate (801–1000 mL);
4. Class 3, severe (1001–2000 mL); and
5. Class 4, massive (>2000 mL) within the first 12 h.

Common definitions of excessive and critical bleeding post–cardiac surgery are represented in Table 1.

Table (1): Common definitions of excessive and critical bleeding post–cardiac surgery [24].

Excessive bleeding	• Greater than 1L per procedure • At least 5 units of red blood cells within 24 h • Greater than 10 units of red blood cells per procedure • Greater than 100 mL of sanguineous drainage per hour
Critical bleeding—re-exploration	• 500 mL of sanguineous drainage in first hour • 400 mL per hour for 2 h • 300 mL per hour for 3 h • 200 mL per hour for 6 h

Mechanisms of bleeding

- **Preoperative risk factors**
  - **Pharmacologic agents**

Emergency cardiac surgery after thrombolysis or percutaneous coronary interventions requires surgery in patients who have received one or more of a variety of antithrombotic or thrombolytic agents. Perhaps the most common drug used in patients likely to come to cardiac surgery is acetylsalicylic acid. Despite its clear antiplatelet activity, the impact of acetylsalicylic acid on bleeding in cardiac surgery is unclear; for example, although it has been demonstrated that the bleeding time is increased in patients not having stopped acetylsalicylic acid within 7 days of surgery, two papers suggest that this infrequently translates into increased blood loss [25].

Preoperative acetylsalicylic acid predicted increased postoperative bleeding. In the absence of clear guidance, most centers discontinue acetylsalicylic acid 5 to 7 days before surgery. An increased number of patients come to cardiac surgery on a combination of antiplatelet drugs. The addition of clopidogrel to acetylsalicylic acid increases postoperative hemorrhage. Also, Acetylsalicylic acid and clopidogrel increased postoperative bleeding sevenfold. These observations suggest that discontinuing all antiplatelet therapy 1 week before surgery may be prudent. Although many patients take warfarin, guidance about optimal preoperative warfarin dosing is sparse[26].

A preoperative international normalized ratio (INR) of greater than 1.7 was reported as a risk factor for bleeding. Most clinicians withhold warfarin for about 5 days before surgery, and an INR of 1.5 or less is widely espoused as a safe threshold for surgery. Further discussion on preoperative anticoagulants and antithrombotics and their reversal appears later[27].

- **Inherited disorders of coagulation**

Patients with inherited disorders of coagulation (eg, von Willebrand's disease and hemophilia) have an enhanced risk for bleeding[28].

- **Acquired coagulopathies**

A variety of acquired coagulopathies may afflict patients undergoing cardiac surgery. Table 2 summarizes medical conditions of particular relevance. One particular type of acquired bleeding disorder relevant to patients with cardiac disease is an acquired deficiency of the high-molecular-weight multimers of von Willebrand's factor. This deficiency seems to develop in patients with congenital heart defects or aortic stenosis

and is associated with increased risk of gastrointestinal bleeding. Patients with this disorder are effectively treated with surgical correction of their cardiac disease [29].

Table (2): Medical conditions contributing to postoperative hemorrhage[24].

Medical condition	Pathophysiology
End-stage renal disease and uremia	Platelet dysfunction
Hepatic disease	Coagulation factor deficiency or failure to clear profibrinolytic factors
Malabsorption	Vitamin K deficiency with consequent coagulation factor deficiency
Systemic lupus erythematosum	• Thrombocytopenia • Medication-induced platelet dysfunction secondary to lupus antibodies • Prothrombin deficiency secondary to lupus-type inhibitor
Amyloidosis	• Capillary fragility secondary to amyloid infiltration • Factor X deficiency secondary to absorption by amyloid
Malignancy	• Platelet deficiency secondary to chemotherapy or bone marrow infiltration. • disseminated intravascular coagulation

- **Intraoperative and postoperative factors**

Mediastinal bleeding is somewhat arbitrarily categorized as surgical or medical in nature. Significant bleeding after uneventful surgery is usually surgical in nature, especially when initial coagulation studies are fairly normal. However, persistent bleeding depletes coagulation factors and platelets causing a coagulopathy that is self-perpetuating[4].

In contrast, bleeding that is noted after complex operations with long durations of CPB is frequently associated with abnormal coagulation studies and is considered medical in nature. However, even after correction of coagulation abnormalities, discrete bleeding sites may be present that will not stop without re-exploration. Thus, the initial approach to bleeding is to try to ascertain any contributing factors that can account for the degree of bleeding and then take the appropriate steps to correct them[6].

1. **Surgical bleeding is usually related to:** [30]
   - Anastomotic sites (suture lines)
   - Side branches of arterial or venous conduits
   - Substernal soft tissues, sternal suture sites, bone marrow, periosteum
   - Raw surfaces caused by previous surgery, pericarditis, or radiation therapy
2. **Anticoagulant effect related to heparin**

Residual heparin

Residual heparin effect may result from inadequate neutralization with protamine. Administering fully heparinized "pump" blood as the protamine infusion is being completed may reintroduce unneutralized heparin into the blood. Similarly, residual heparin in cell saver blood given after protamine administration may reintroduce unreversed heparin[31].

Heparin rebound

Large heparin doses are administered before and during CPB. To prevent thrombosis of the extracorporeal circuit sufficient heparin is given to maintain an activated clotting time (ACT) greater than 250 seconds. After completion of CPB and on achieving surgical hemostasis, protamine sulfate is usually administered to neutralize remaining heparin. Protamine doses are not standardized. The effective half-life of protamine is less than that of heparin when given in doses appropriate for CPB; rebound heparin activity (manifest by reappearance of a prolonged ACT sometime after protamine administration) is commonly observed and has been shown to be a cause of postoperative bleeding [32].

Re-emergence of heparin effect requires additional doses of protamine if the anticoagulant effect is believed to be clinically significant; care should be exercised in administering protamine because large doses have been associated with an anticoagulant effect, although the clinical significance of this observation has been questioned. Additional doses are generally safe given the first administration was uneventful. Potential side effects of protamine include hypotension, anaphylactoid reactions, and pulmonary vasoconstriction[33].

3. Platelets

CPB decreases both the number and function of platelets. The average decline in the platelet count during CPB is about 50%. Additionally, within minutes of the initiation of CPB the bleeding time increases independent of platelet number [34].

Quantitative platelet defects [35].

- Preoperative thrombocytopenia may result from use of heparin, in which case testing for heparin antibodies is essential to rule out heparin-induced thrombocytopenia. Drug reactions (especially to antibiotics) and hypersplenism in patients with liver disease may be causative. Occasionally, mild thrombocytopenia is present for no identifiable reason.
- Hemodilution on CPB and consumption in the extracorporeal circuit reduce the platelet count by about 30–50%; thrombocytopenia will be progressive as the duration of CPB lengthens.
- Protamine administration transiently reduces the platelet count by about 30%.

Qualitative platelet defects [36].

Qualitative platelet defects are a major concern with the liberal use of antiplatelet agents in patients with acute coronary syndromes.

- Preoperative platelet dysfunction may result from antiplatelet medications (aspirin, clopidogrel), glycoprotein IIb/IIIa inhibitors (abciximab, tirofiban, eptifibatide), herbal medications and vitamins (fish oils, ginkgo products, vitamin E), or uremia.
- Exposure of platelets to the CPB circuit with α-granule release and alteration of platelet membrane receptors impairs platelet function. The degree of platelet dysfunction correlates with the duration of CPB and the degree of hypothermia after bypass.

4. Coagulation Factors

With initiation of CPB a predictable fall in the levels of coagulation factors II, V, VII, IX, X, XIII is observed, likely as a result of unavoidable hemodilution. Von Willebrand's factor levels also fall on CPB; however, this process is unrelated to hemodilution [37].

The impact of these falls in the levels of coagulation factor is unknown. It is currently held that the levels remain within those generally believed to be adequate for hemostasis. Vetri et al. (2020) reported that Factor V Deficiency was associated with Bleeding and can be a significant cause for Bleeding after Cardiac Surgery [38].

5. Thrombin and fibrinolysis

Patients undergoing CPB have evidence of enhanced fibrinolysis. Enhanced fibrinolysis is likely caused by release of tissue plasminogen activator as a result of endothelial activation. The coupling of enhanced fibrinolysis with diffuse activation of coagulation leads to the generation of high levels of markers of fibrinolytic activity (eg, D-dimer). The high levels of products of fibrinolysis derived from both endovascular and extravascular sources may compromise hemostasis, a process that is worsened by longer duration of CPB [39].

Predictor models of bleeding

Excessive bleeding is associated with adverse outcomes. Predicting which patients have an increased bleeding tendency allows for implementation of additional measures. Risk factors for postoperative hemorrhage have been explored by several groups. Factors that have demonstrated consistency within these studies are as follows: [24]

- Increased age
- Nonelective surgery
- Low body surface area
- Prolonged CPB time (> 150 minutes)
- Combined intracardiac and bypass surgery
- Number of bypass grafts (≥ 5)
- Reoperative surgery
- Preoperative antiplatelet agents.

Prevention of Perioperative Bleeding

A. Preoperative assessment of the patient's coagulation system

Preoperative assessment of the patient's coagulation system should entail measurement of a prothrombin time (PT), partial thromboplastin time (PTT), and platelet count. Any abnormality should be investigated and corrected, if possible, prior to surgery [40].

B. Heparin-induced thrombocytopenia (HIT)

Heparin-induced thrombocytopenia (HIT) may develop in patients receiving intravenous heparin for several days before surgery. Thus, it is very important to recheck the platelet count on a daily basis in these patients. If the patient develops thrombocytopenia and has confirmation of heparin antibodies by serologic testing or a serotonin release assay, an alternative means of anticoagulation will be necessary [41].

C. Medications with antiplatelet or anticoagulant effects

Cessation of medications with antiplatelet or anticoagulant effects is essential to allow their effects to dissipate in order to minimize blood loss. Specific recommendations are as follows: [42]

1. Warfarin

Warfarin should be stopped 4 days before surgery to allow for resynthesis of vitamin K–dependent clotting factors and normalization of the international normalized ratio (INR).26 If interim anticoagulation is required, heparin is substituted. If the patient requires urgent surgery, vitamin K should be given (two doses of 5 mg IV should suffice) to normalize the INR. If emergency surgery is indicated, fresh frozen plasma (FFP) may be necessary[43].

2. Unfractionated heparin

Unfractionated heparin is reversible with protamine and is commonly used for acute coronary syndromes. It can be continued up to the time of surgery without any increased morbidity during line placement[44].

3. Low-molecular-weight heparin

Low-molecular-weight heparin, generally given in a dose of 1 mg/kg SC q12h for acute coronary syndromes, should be stopped at least 12 hours prior to surgery, since it is only 80% reversible with protamine. Studies have shown increased bleeding when it is administered within 12 hours of surgery[45].

4. Aspirin

Aspirin should be stopped at least 3 days prior to surgery to ensure adequate restoration of platelet function and reduce transfusion requirements. Preoperative cessation of aspirin has become controversial because

several studies have demonstrated reduced rates of infarction and mortality when aspirin is continued up to the time of surgery. Aprotinin and tranexamic acid are useful in reducing bleeding associated with preoperative use of aspirin[46].

Willemsen et al. (2021) reported that aspirin sensitivity was associated with 12-hour blood loss after cardiac surgery, suggesting that preoperative aspirin testing could identify patients undergoing cardiac surgery at high risk for perioperative bleeding[47].

5. Clopidogrel

Clopidogrel has antiplatelet effects that last for the life span of the platelet, and it should therefore be stopped 5–7 days prior to elective surgery. However, it is commonly used in acute coronary syndromes and in anticipation of a stenting procedure. Although inhibition of platelet activity occurs about 2 hours after the drug is administered, achievement of a steady state with 50% inhibition of platelet aggregation occurs about 6 hours after a loading dose of 300 mg or after about 4–5 doses of 75 mg[48].

If surgery is then required on an urgent basis, significant bleeding may be encountered. Aprotinin may be successful in reducing bleeding in patients receiving this medication (although this has not been studied), but platelets are often required. If the active metabolite of clopidogrel is still present in the bloodstream, exogenously administered platelets may be ineffective[49].

6. Ticlopidine

Ticlopidine has been replaced by clopidogrel in patients undergoing stenting, although some patients still receive it for the management of cerebrovascular disease. Since its activity also lasts the life span of the platelet, it should be stopped at least 7 days prior to surgery. If bleeding is encountered, platelets may be needed. An abnormal bleeding time caused by ticlopidine can be normalized within 2 hours by methylprednisolone 20 mg IV[42].

7. Tirofiban and eptifibatide

Tirofiban (Aggrastat) and eptifibatide (Integrilin) are short-acting IIb/IIIa inhibitors that allow for recovery of 80% of platelet function within 4–6 hours of being discontinued. They should be stopped about 4 hours prior to surgery. Some studies have shown that continuing these medications up to the time of surgery may preserve platelet function on pump, leading to increased platelet number and function after bypass with no adverse effects on bleeding [50]

8. Abciximab (Reopro)

Abciximab (Reopro) is a long-acting IIb/IIIa inhibitor used for high-risk percutaneous coronary intervention that has a half-life of 12 hours. If surgery must be performed on an emergency basis, platelets are effective in producing hemostasis since there is very little circulating unbound drug. Ideally, surgery should be delayed for at least 12 hours and preferably for 24 hours since recovery of platelet function takes up to 48 hours. Although abnormal bleeding times and platelet aggregation tests are still abnormal in up to 25% of patients at this time, there is little hemostatic compromise at receptor blockade levels less than 50%[51].

9. Thrombolytic therapy

Thrombolytic therapy is an alternative to primary angioplasty in patients presenting with ST-segment elevation myocardial infarctions. Although currently used agents have short half-lives measured in minutes, the systemic hemostatic defects persist much longer. These effects include depletion of fibrinogen, reduction in factor II, V, and VIII levels, impairment of platelet aggregation, and the appearance of fibrin split products. If surgery is required for persistent ischemia after failed thrombolytic therapy, it should be delayed by at least 12–24 hours. If it is required emergently, plasma and cryoprecipitate will probably be necessary to correct the anticipated coagulopathy[51].

D. Anti-fibrinolytic therapy

Antifibrinolytic therapy should be used to reduce intraoperative blood loss.

1. Aprotinin

Aprotinin is a serine protease inhibitor that is extremely effective in reducing blood loss and transfusion requirements. It preserves adhesive platelet receptors during the early period of CPB, exhibits antifibrinolytic

properties by inhibiting plasmin, and also inhibits kallikrein, blocking the contact phase of coagulation and inhibiting the intrinsic coagulation cascade. Although it has been recommended for primary coronary bypass operations, it is very expensive and is usually reserved for complex operations and reoperations[52].

2. ε-aminocaproic acid (Amicar)

ε-aminocaproic acid (Amicar) is an antifibrinolytic agent that may preserve platelet function by inhibiting the conversion of plasminogen to plasmin. It is effective in reducing blood loss and, because of its low cost, is usually the drug of choice for all first-time operations and anticipated uncomplicated reoperations. Most studies suggest it is not as effective as aprotinin [53].

3. Tranexamic acid

Tranexamic acid (Cyclokapron) has similar properties to ε-aminocaproic acid. It has also been shown to reduce perioperative blood loss. It is more expensive than ε-aminocaproic acid but much less expensive than aprotinin. Some studies have shown its efficacy to be equivalent to that of ε-aminocaproic acid; others have shown it to be as effective as aprotinin [54].

E. Autologous blood withdrawal

Autologous blood withdrawal before instituting bypass protects platelets from the damaging effects of CPB. It has been demonstrated to preserve red cell mass and reduce transfusion requirements. However, its efficacy in reducing perioperative bleeding is controversial. It can be considered when the calculated on-pump hematocrit after withdrawal remains satisfactory (greater than 20–22%).This can be calculated using the following equation: amount that can be withdrawn = EBV – [0.22 (EBV + PV + CV)]/HCT, where EBV is the estimated blood volume (70 × kg), PV is the priming volume, CV is the estimated cardioplegia volume, and HCT is the prewithdrawal hematocrit [55].

F. Platelet-rich plasmapheresis

Platelet-rich plasmapheresis entails the withdrawal of platelet-rich plasma using a plasma separator at the beginning of the operation with its readministration after protamine infusion. This improves hemostasis and reduces blood loss. Although it might be beneficial in reoperations, it is expensive, time-consuming, and probably of little benefit when prophylactic antifibrinolytic medications are used [56].

G. Meticulous surgical technique

Meticulous surgical technique is the mainstay of hemostasis. Warming the patient to normothermia before terminating bypass improves the function of the coagulation system [4].

H. CPB considerations: [57]

- The use of heparin-coated circuits during bypass allows for a reduction in heparin dosing and has been associated with reduced perioperative blood loss.
- Retrograde autologous priming of the extracorporeal circuit entails withdrawal of crystalloid prime to minimize hemodilution, thus maintaining a higher hematocrit and colloid oncotic pressure on pump. In some studies, this has been shown to reduce the rate of transfusion.
- Avoidance of cardiotomy suction may reduce perioperative bleeding. Blood aspirated from the pericardial space has been in contact with tissue factor and contains high levels of factor VIIa, procoagulant particles, and activated complement proteins, and exhibits fibrinolytic activity.

Assessment of Bleeding in the ICU

A. The appropriate assessment of bleeding in the ICU requires the following steps: [58]

1) Frequent documentation of the amount of blood draining into the collection system and attention to tube patency

2) Determination of the color (arterial or venous) and pattern of drainage (sudden dump when turned or continuous drainage)

3) Monitoring of hemodynamic parameters with ongoing awareness of the possibility of cardiac tamponade

4) Identification of potential causative factors by review of coagulation studies

5) Suspicion of undrained blood in the mediastinum or pleural spaces by review of a chest x-ray, auscultating decreased breath sounds on examination, or noting elevation of peak inspiratory pressures on the ventilator.

B. Quantitate the amount of chest tube drainage.

Make sure that the chest tubes are patent because the extent of ongoing hemorrhage may be masked when the tubes have clotted or blood has drained into an open pleural space. When patients are turned or moved, they occasionally drain a significant volume of blood that has been accumulating in the chest for several hours. This may suggest the acute onset of bleeding and the need for surgical exploration. The presence of dark blood and minimal additional drainage are clues that this does not represent active bleeding. Serial chest x-rays may be helpful in identifying residual blood [59].

C. Swan-Ganz catheter: [60]

Assess hemodynamics with the Swan-Ganz catheter. Maintenance of adequate filling pressures and cardiac output is essential and is generally accomplished using crystalloid or colloid solutions. However, in the bleeding patient, these will produce hemodilution and progressive anemia[61].

1) If filling pressures are decreasing and nonheme fluid is administered, one needs to anticipate a decrease in the hematocrit from hemodilution, but more so with ongoing bleeding. The administration of volume in the form of clotting factors and platelets to promote hemostasis must be accompanied by red cell transfusions to maintain a safe hematocrit. It should be reiterated that unstable hemodynamics are frequently seen in the bleeding patient even if filling pressures are maintained.

2) Evidence of rising filling pressures and decreasing cardiac outputs may suggest the development of cardiac tamponade. Equilibration of intracardiac pressures may be noted with postoperative tamponade, but, more commonly, accumulation of clot adjacent to the right or left atrium will produce variable elevation in intracardiac pressures that are also consistent with right or left ventricular failure, respectively.

3) If hemodynamic measurements suggest borderline cardiac function and tamponade cannot be ruled out, transesophageal echocardiography (TEE) is invaluable in making the correct diagnosis. Tamponade should be suspected when hemodynamic compromise is associated with excessive bleeding, bleeding that has abruptly stopped, or even minimal chest tube drainage caused by clotted tubes or spillage into the pleural space. TEE is often more accurate than a transthoracic study in detecting clot around the heart because the latter may be compromised by inability to obtain acoustic windows necessary to adequately identify an effusion[62].

D. Coagulation Studies

Obtain coagulation studies upon arrival in the ICU and serial hematocrits if the patient is bleeding. Coagulation studies need not be ordered if the patient has minimal mediastinal bleeding. However, if hemostasis was difficult to achieve in the operating room or hemorrhage persists (generally greater than 100 mL/h), lab tests may be helpful in assessing whether a coagulopathy is contributing to mediastinal bleeding. Tests for some of the more common nonsurgical causes of bleeding (residual heparin effect, thrombocytopenia, and clotting factor deficiency) are readily available, but documentation of platelet dysfunction requires additional technology [63].

Although no individual test correlates that well with the amount of bleeding, together they can usually direct interventions in a somewhat scientific manner. No matter what the results of coagulation testing are, clinical judgment remains paramount in trying to ascertaining whether the bleeding is more likely to be of a surgical nature (which tends to persist) or due to a coagulopathy (which might improve) [64].

It include the following tests: [65]

1) ***Prothrombin time*** measured as the INR assesses the extrinsic coagulation cascade. The INR may be slightly prolonged after a standard pump run, but clotting factor levels exceeding 30% of normal should allow for satisfactory hemostasis. An abnormal INR can be corrected with FFP.

2) ***Partial thromboplastin time*** assesses the intrinsic coagulation cascade and can also detect residual or recurrent heparin effect ("heparin rebound"). As an isolated abnormality or with slight elevation of the INR, protamine is beneficial in correcting the PTT and controlling bleeding.
3) ***Platelet count***. Although CPB reduces the platelet count by about 30–50% and also produces platelet dysfunction, platelet function is usually adequate to produce hemostasis. Platelet transfusions may be justified in the bleeding patient for thrombocytopenia (generally < 100,000/μL) or for suspicion of platelet dysfunction (usually for patients on aspirin or clopidogrel) [34].
4) ***Platelet function*** can be assessed by a variety of available technologies, including those that measure platelet aggregometry and other sophisticated tests of clot formation and retraction.
5) ***Additional tests*** may be considered for severe bleeding if a coagulopathy is suspected. However, if normal coagulation studies are present before or after the standard corrective measures are taken, surgical re-exploration is generally indicated.

Additional tests includes:[65]

a. D-dimer and Fibrinogen levels

Assessment for fibrinolysis entails measurement of D-dimer and fibrinogen levels. Fibrinolysis is associated with an elevation in the PT and PTT, and decreased levels of factor I (fibrinogen < 150 mg/dL) and factor VIII. However, an elevated D-dimer alone is not uncommon and may also be noted if shed blood is autotransfused.64 Use of aprotinin may be considered if fibrinolysis is confirmed, even if one of the other antifibrinolytic medications had been used during surgery, although it may contribute to a prothrombotic state [53].

b. Thromboelastography

Thromboelastography (**Figure 2**) gives a qualitative measurement of clot strength. It is used to evaluate the interaction of platelets with the coagulation cascade from the onset of clot formation through clot lysis. The thromboelastogram shows a distinct contour in patients with fibrinolysis [66]

c. Sonoclot Analysis

Sonoclot analysis (Figure 3) is another viscoelastic method for evaluating clot formation and retraction that allows for assessment of coagulation factors, fibrinogen, and platelet activity. The device measures the changing impedance to movement imposed by the developing clot on a small probe that vibrates at an ultrasonic frequency within a blood sample. Studies have suggested that both a thromboelastogram and a Sonoclot are more predictive of bleeding than routine coagulation studies. This modality has seen limited use but can direct appropriate therapy in patients with persistent bleeding [67].

d. Repeat a chest x-ray

A widened mediastinum may suggest undrained clotted blood accumulating within the pericardial cavity that could cause cardiac tamponade. Comparison with preoperative films can be misleading because of differences in technique, but any difference noted between the immediate postoperative supine film and a repeat film should be noted [68].

Also, Note the distance between the edge of the Swan-Ganz catheter in the right atrium or the location of the right atrial pacing wires (if placed on the right atrial free wall) and the edge of the mediastinal silhouette. If this distance widens, suspect clot accumulation adjacent to the right atrium. Moreover, Note any accumulation of blood within the pleural spaces that has not drained through the pleural chest tubes. This can be difficult to assess since fluid will layer out on a supine film, so a discrepancy in the haziness of the two pleural spaces should be sought[60].

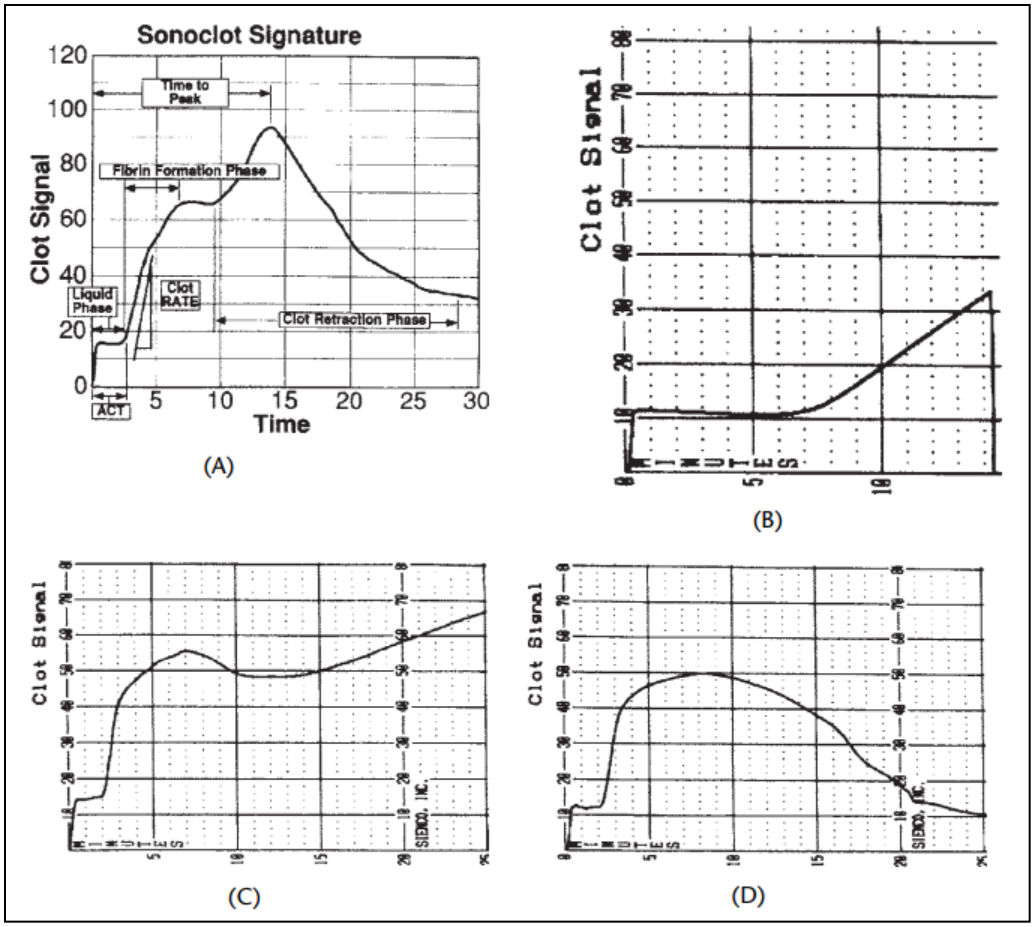

Fig. (3): Representative Sonoclot tracings. (A) The Sonoclot signature assesses the liquid phase of initial clot formation, the rate of fibrin and clot formation, further fibrinogenesis and platelet-fibrin interaction, a peak impedance after completion of fibrin formation, and a downward slope as platelets induce contraction of the completed clot. (B) Heparinization. (C) Poor platelet function (slow clot retraction). (D) Hyperfibrinolysis (no tightening associated with clot retraction) [68].

References:

1. [1] A. A. Elassal et al., "Re-exploration for bleeding after cardiac surgery: revaluation of urgency and factors promoting low rate," J. Cardiothorac. Surg., vol. 16, no. 1, pp. 1–11, Dec. 2021, doi: 10.1186/S13019-021-01545-4/TABLES/6.
[2] M. Ranucci, E. Baryshnikova, E. Ciotti, M. Ranucci, and S. Silvetti, "Hemodilution on Cardiopulmonary Bypass: Thromboelastography Patterns and Coagulation-Related Outcomes," J. Cardiothorac. Vasc. Anesth., vol. 31, no. 5, pp. 1588–1594, Oct. 2017, doi: 10.1053/J.JVCA.2017.04.014.
[3] A. K. Gupta, "Postoperative Complications Following Thoracic Surgery," Clin. Thorac. Anesth., pp. 315–333, 2020, doi: 10.1007/978-981-15-0746-5_24.
[4] F. Biancari et al., "Meta-analysis of the Sources of Bleeding after Adult Cardiac Surgery," J. Cardiothorac. Vasc. Anesth., vol. 32, no. 4, pp. 1618–1624, Aug. 2018, doi: 10.1053/J.JVCA.2017.12.024.
[5] N. Al-Attar et al., "Impact of bleeding complications on length of stay and critical care utilization in cardiac surgery patients in England," J. Cardiothorac. Surg., vol. 14, no. 1, pp. 1–10, Apr. 2019, doi: 10.1186/S13019-019-0881-3/FIGURES/3.
[6] K. Siemens, D. P. Sangaran, B. J. Hunt, I. A. Murdoch, and S. M. Tibby, "Strategies for Prevention and Management of Bleeding Following Pediatric Cardiac Surgery on Cardiopulmonary Bypass: A Scoping Review," Pediatr. Crit. Care Med., vol. 19, no. 1, pp. 40–47, Jan. 2018, doi: 10.1097/PCC.0000000000001387.

[7] E. Squiccimarro, F. Jiritano, G. F. Serraino, H. Ten Cate, D. Paparella, and R. Lorusso, "Quantitative and Qualitative Platelet Derangements in Cardiac Surgery and Extracorporeal Life Support," J. Clin. Med. 2021, Vol. 10, Page 615, vol. 10, no. 4, p. 615, Feb. 2021, doi: 10.3390/JCM10040615.

[8] C. Slattery, J. Kark, T. Wagner, and K. Verma, "The use of tranexamic acid to reduce surgical blood loss: A review basic science, subspecialty studies, and the evolution of use in spine deformity surgery," Clin. Spine Surg., pp. 46–50, 2019, doi: 10.1097/BSD.0000000000000808.

[9] B. L. Pearse et al., "Bleeding Management Practices of Australian Cardiac Surgeons, Anesthesiologists and Perfusionists: A Cross-Sectional National Survey Incorporating the Theoretical Domains Framework (TDF) and COM-B Model," J. Multidiscip. Healthc., vol. 13, p. 27, 2020, doi: 10.2147/JMDH.S232888.

[10] V. Fröjd and A. Jeppsson, "Re-exploration for Bleeding and Its Association With Mortality After Cardiac Surgery," Ann. Thorac. Surg., vol. 102, no. 1, pp. 109–117, Jul. 2016, doi: 10.1016/J.ATHORACSUR.2016.01.006.

[11] J. A. Brown et al., "Long-Term Outcomes of Reoperation for Bleeding After Cardiac Surgery," Semin. Thorac. Cardiovasc. Surg., vol. 33, no. 3, pp. 764–773, Sep. 2021, doi: 10.1053/J.SEMTCVS.2020.11.013.

[12] R. H. Fu, A. L. Weinstein, M. M. Chang, M. Argenziano, J. A. Ascherman, and C. H. Rohde, "Risk factors of infected sternal wounds versus sterile wound dehiscence," J. Surg. Res., vol. 200, no. 1, pp. 400–407, Jan. 2016, doi: 10.1016/J.JSS.2015.07.045.

[13] M. E. Porter, "What Is Value in Health Care?," 2010.

[14] A. G. M. Van Boxtel, D. Van Veghel, M. A. S. Hamad, D. N. Schulz, P. S. Stepaniak, and A. H. M. Van Straten, "Use of an intraoperative checklist to decrease the incidence of re-exploration for postoperative bleeding after cardiac surgery," Interact. Cardiovasc. Thorac. Surg., vol. 25, no. 4, pp. 555–558, Oct. 2017, doi: 10.1093/ICVTS/IVX130.

[15] G. Loor et al., "Process improvement in cardiac surgery: Development and implementation of a reoperation for bleeding checklist," J. Thorac. Cardiovasc. Surg., vol. 146, no. 5, pp. 1028–1032, Nov. 2013, doi: 10.1016/J.JTCVS.2013.05.043.

[16] J. M. Ali, C. Gerrard, J. Clayton, and N. Moorjani, "Reduced re-exploration and blood product transfusion after the introduction of the Papworth haemostasis checklist," Eur. J. Cardio-Thoracic Surg., vol. 55, no. 4, pp. 729–736, Apr. 2019, doi: 10.1093/EJCTS/EZY362.

[17] L. B. Ohmes et al., "Incidence, risk factors, and prognostic impact of re-exploration for bleeding after cardiac surgery: A retrospective cohort study," Int. J. Surg., vol. 48, pp. 166–173, Dec. 2017, doi: 10.1016/J.IJSU.2017.10.073.

[18] T. Senage, C. Gerrard, N. Moorjani, D. P. Jenkins, and J. M. Ali, "Early postoperative bleeding impacts long-term survival following first-time on-pump coronary artery bypass grafting," J. Thorac. Dis., vol. 13, no. 10, p. 5670, Oct. 2021, doi: 10.21037/JTD-21-1241.

[19] R. S. Stephens and G. J. R. Whitman, "Postoperative critical care of the adult cardiac surgical patient. Part I: Routine postoperative care," Crit. Care Med., vol. 43, no. 7, pp. 1477–1497, Jul. 2015, doi: 10.1097/CCM.0000000000001059.

[20] B. L. Pearse et al., "Protocol guided bleeding management improves cardiac surgery patient outcomes," Vox Sang., vol. 109, no. 3, pp. 267–279, Oct. 2015, doi: 10.1111/VOX.12279.

[21] G. F. Serraino and G. J. Murphy, "Routine use of viscoelastic blood tests for diagnosis and treatment of coagulopathic bleeding in cardiac surgery: updated systematic review and meta-analysis," BJA Br. J. Anaesth., vol. 118, no. 6, pp. 823–833, Jun. 2017, doi: 10.1093/BJA/AEX100.

[22] C. Dyke et al., "Universal definition of perioperative bleeding in adult cardiac surgery," J. Thorac. Cardiovasc. Surg., vol. 147, no. 5, pp. 1458-1463.e1, May 2014, doi: 10.1016/J.JTCVS.2013.10.070.

[23] R. Mehran et al., "Standardized Bleeding Definitions for Cardiovascular Clinical Trials," Circulation, vol. 123, no. 23, pp. 2736–2747, Jun. 2011, doi: 10.1161/CIRCULATIONAHA.110.009449.

[24] R. Whitlock, M. A. Crowther, and H. J. Ng, "Bleeding in Cardiac Surgery: Its Prevention and Treatment—an Evidence-Based Review," Crit. Care Clin., vol. 21, no. 3, pp. 589–610, Jul. 2005, doi: 10.1016/J.CCC.2005.04.003.

[25] A. Affronti and M. Ruel, "Emergency surgery for iatrogenic injuries attributable to percutaneous coronary interventions: When planning and time matter," J. Am. Heart Assoc., vol. 8, no. 1, Jan. 2019, doi: 10.1161/JAHA.118.011525.

[26] M. G. Hagag, M. S. Amar, A. A. E.-B. Emara, and I. I. Moheb, "Perioperative effect of acetylsalicylic acid stoppage duration before coronary artery bypass grafting," Menoufia Med. J., vol. 35, no. 2, p. 694, 2022, doi: 10.4103/MMJ.MMJ_187_21.

[27] P. J. Navin et al., "Periprocedural Major Bleeding Risk of Image-Guided Percutaneous Chest Tube Placement in Patients with an Elevated International Normalized Ratio," J. Vasc. Interv. Radiol., vol. 30, no. 11, pp. 1765–1768, Nov. 2019, doi: 10.1016/J.JVIR.2019.07.002.

[28] J. M. Bastida et al., "Molecular Diagnosis of Inherited Coagulation and Bleeding Disorders," Semin. Thromb. Hemost., vol. 45, no. 7, pp. 695–707, 2019, doi: 10.1055/S-0039-1687889/ID/JR02615-28.

[29] M. W. Besser, E. Ortmann, and A. A. Klein, "Haemostatic management of cardiac surgical haemorrhage," Anaesthesia, vol. 70, pp. 87-e31, Jan. 2015, doi: 10.1111/ANAE.12898.

[30] P. H. Colson et al., "Active Bleeding after Cardiac Surgery: A Prospective Observational Multicenter Study," PLoS One, vol. 11, no. 9, p. e0162396, Sep. 2016, doi: 10.1371/JOURNAL.PONE.0162396.

[31] J. Ichikawa, M. Kodaka, K. Nishiyama, Y. Hirasaki, M. Ozaki, and M. Komori, "Reappearance of Circulating Heparin in Whole Blood Heparin Concentration-Based Management Does Not Correlate With Postoperative Bleeding After Cardiac Surgery," J. Cardiothorac. Vasc. Anesth., vol. 28, no. 4, pp. 1003–1007, Aug. 2014, doi: 10.1053/J.JVCA.2013.10.010.

[32] A. Galeone et al., "Monitoring Incomplete Heparin Reversal and Heparin Rebound After Cardiac Surgery," J. Cardiothorac. Vasc. Anesth., vol. 27, no. 5, pp. 853–858, Oct. 2013, doi: 10.1053/J.JVCA.2012.10.020.

[33] M. I. Meesters et al., "Effect of high or low protamine dosing on postoperative bleeding following heparin anticoagulation in cardiac surgery a randomised clinical trial," Thromb. Haemost., vol. 116, no. 2, pp. 251–261, Aug. 2016, doi: 10.1160/TH16-02-0117/ID/JR0117-3.

[34] E. K. Adeli, S. M. Alavi, A. Alizadeh-Ghavidel, H. Bakhshandeh-Abkenar, and A. A. Pourfathollah, "Perioperative changes in platelet count and function in patients undergoing cardiac surgery," Med. J. Islam. Repub. Iran, vol. 31, no. 1, p. 37, 2017, doi: 10.14196/MJIRI.31.37.

[35] B. R. Griffin et al., "Thrombocytopenia After Cardiopulmonary Bypass Is Associated With Increased Morbidity and Mortality," Ann. Thorac. Surg., vol. 110, no. 1, pp. 50–57, Jul. 2020, doi: 10.1016/J.ATHORACSUR.2019.10.039.

[36] G. Kjellberg, M. Holm, G. Lindvall, G. Gryfelt, J. van der Linden, and A. Wikman, "Platelet function analysed by ROTEM platelet in cardiac surgery after cardiopulmonary bypass and platelet transfusion," Transfus. Med., vol. 30, no. 5, pp. 369–376, Oct. 2020, doi: 10.1111/TME.12678.

[37] E. R. Strauss, M. A. Mazzeffi, B. Williams, N. S. Key, and K. A. Tanaka, "Perioperative management of rare coagulation factor deficiency states in cardiac surgery," BJA Br. J. Anaesth., vol. 119, no. 3, pp. 354–368, Sep. 2017, doi: 10.1093/BJA/AEX198.

[38] D. Vetri et al., "A Case of Acquired Factor V Deficiency in Patient with Bleeding," TH Open, vol. 04, no. 02, pp. e77–e79, Apr. 2020, doi: 10.1055/S-0039-3402024.

[39] J. Bartoszko et al., "The association of thrombin generation with bleeding outcomes in cardiac surgery: a prospective observational study," Can. J. Anesth., vol. 69, no. 3, pp. 311–322, Mar. 2022, doi: 10.1007/S12630-021-02165-1/TABLES/3.

[40] D. Bolliger and K. A. Tanaka, "Point-of-Care Coagulation Testing in Cardiac Surgery," Semin. Thromb. Hemost., vol. 43, no. 4, pp. 386–396, Jun. 2017, doi: 10.1055/S-0037-1599153/ID/JR02425-27.

[41] A. M. Pishko and A. Cuker, "Heparin-Induced Thrombocytopenia in Cardiac Surgery Patients," Semin. Thromb. Hemost., vol. 43, no. 7, pp. 691–698, Oct. 2017, doi: 10.1055/S-0037-1602664/ID/JR02451-26.

[42] BRIDGE Study Investigators, "Bridging Anticoagulation," Circulation, vol. 125, no. 12, Mar. 2012, doi: 10.1161/CIRCULATIONAHA.111.084517.

[43] D. J. Angiolillo et al., "Bridging Antiplatelet Therapy With Cangrelor in Patients Undergoing Cardiac Surgery: A Randomized Controlled Trial," JAMA, vol. 307, no. 3, pp. 265–274, Jan. 2012, doi: 10.1001/JAMA.2011.2002.

[44] A. Tanaka et al., "Unfractionated Heparin during the Interruption of Antiplatelet Therapy for Non-cardiac Surgery after Drug-eluting Stent Implantation," Intern. Med., vol. 55, no. 4, pp. 333–337, Feb. 2016, doi: 10.2169/INTERNALMEDICINE.55.5495.

[45] W. Li et al., "Benefits may not outweigh risks of low molecular weight heparin (LMWH) in early postoperative thromboprophylaxis following minimally invasive cardiac surgery: a propensity score-matched analysis," J. Thorac. Dis., vol. 11, no. 12, p. 5266, Dec. 2019, doi: 10.21037/JTD.2019.11.56.

[46] P. S. Myles et al., "Stopping vs. Continuing Aspirin before Coronary Artery Surgery," N. Engl. J. Med., vol. 374, no. 8, pp. 728–737, Feb. 2016, doi: 10.1056/NEJMOA1507688/SUPPL_FILE/NEJMOA1507688_DISCLOSURES.PDF.

[47] L. M. Willemsen et al., "Blood loss after coronary artery bypass by aspirin responsiveness assessed with preoperative VerifyNow aspirin testing," Res. Pract. Thromb. Haemost., vol. 5, no. 8, p. e12623, Dec. 2021, doi: 10.1002/RTH2.12623.

[48] A. T. Mokhtar, A. Baghaffar, S. D. Jackson, and D. Horne, "When is the optimal time to discontinue clopidogrel before in-hospital coronary bypass surgery? A closer look at the current literature," J. Card. Surg., vol. 35, no. 2, pp. 413–421, Feb. 2020, doi: 10.1111/JOCS.14371.

[49] B. Huo, G. M. Hirsch, S. Doucette, C. R. Herman, R. Gainer, and A. T. Mokhtar, "Impact of Clopidogrel Stop Interval on Major Adverse Bleeding Events in Cardiac Surgery," CJC Open, vol. 4, no. 1, pp. 12–19, Jan. 2022, doi: 10.1016/J.CJCO.2021.08.006.

[50] M. Vlachou, M. Didagelos, A. Kouparanis, H. Karvounis, and A. Ziakas, "Bridging with Tirofiban During Temporary Withdrawal of Oral Antiplatelets for Two Major Surgical Procedures in High Ischaemic Risk Patients," Open Cardiovasc. Med. J., vol. 13, no. 1, pp. 1–4, Feb. 2019, doi: 10.2174/1874192401913010001.

[51] Domenico Pagano, Michael I. Meesters, Umberto Benedetto, and Christian von Heymann., "2017 EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery," Eur. J. Cardio-Thoracic Surg. , pp. 79–111, 2018, doi: 10.1093/ejcts/ezx325.

[52] S. De Hert, A. Ouattara, D. Royston, J. van der Linden, and K. Zacharowski, "Use and safety of aprotinin in routine clinical practice," Eur. J. Anaesthesiol., vol. 39, no. 8, pp. 685–694, Aug. 2022, doi: 10.1097/EJA.0000000000001710.

[53] E. R. Strauss et al., "A Pharmacokinetic and Pharmacodynamic Investigation of an ε-Aminocaproic Acid Regimen Designed for Cardiac Surgery With Cardiopulmonary Bypass," J. Cardiothorac. Vasc. Anesth., vol. 35, no. 2, pp. 406–417, Feb. 2021, doi: 10.1053/J.JVCA.2020.07.048.

[54] J. Shi et al., "Effect of High- vs Low-Dose Tranexamic Acid Infusion on Need for Red Blood Cell Transfusion and Adverse Events in Patients Undergoing Cardiac Surgery: The OPTIMAL Randomized Clinical Trial," JAMA, vol. 328, no. 4, pp. 336–347, Jul. 2022, doi: 10.1001/JAMA.2022.10725.

[55] R. A. Henderson et al., "Hematologic evaluation of intraoperative autologous blood collection and allogeneic transfusion in cardiac surgery," Transfusion, vol. 61, no. 3, pp. 788–798, Mar. 2021, doi: 10.1111/TRF.16259.

[56] Q. Zhai, Y. Wang, Z. Yuan, R. Zhang, and A. Tian, "Effects of platelet-rich plasmapheresis during cardiovascular surgery: A meta-analysis of randomized controlled clinical trials," J. Clin. Anesth., vol. 56, pp. 88–97, Sep. 2019, doi: 10.1016/J.JCLINANE.2019.01.018.

[57] N. B. Hensley et al., "Retrograde Autologous Priming in Cardiac Surgery: Results From a Systematic Review and Meta-analysis," Anesth. Analg., vol. 132, no. 1, pp. 100–107, Jan. 2021, doi: 10.1213/ANE.0000000000005151.

[58] J. Raphael et al., "Society of Cardiovascular Anesthesiologists Clinical Practice Improvement Advisory for Management of Perioperative Bleeding and Hemostasis in Cardiac Surgery Patients," J. Cardiothorac. Vasc. Anesth., vol. 33, no. 11, pp. 2887–2899, Nov. 2019, doi: 10.1053/J.JVCA.2019.04.003.

[59] M. C. Christensen, F. Dziewior, A. Kempel, and C. Von Heymann, "Increased Chest Tube Drainage Is Independently Associated With Adverse Outcome After Cardiac Surgery," J. Cardiothorac. Vasc. Anesth., vol. 26, no. 1, pp. 46–51, Feb. 2012, doi: 10.1053/J.JVCA.2011.09.021.

[60] E. J. Pantin, J. L. Kraidin, S. H. Ginsberg, J. T. Denny, M. B. Anderson, and A. R. Solina, "The Swan-Ganz catheter as a teaching tool for the anesthesiologist learning minimally invasive cardiac surgery," Innov. Technol. Tech. Cardiothorac. Vasc. Surg., vol. 7, no. 3, pp. 204–207, May 2012, doi: 10.1097/IMI.0b013e31826521fe.

[61] F. J. Gómez-Romero et al., "Intra-operative temperature monitoring with two non-invasive devices (3M Spoton® and Dräger Tcore®) in comparison with the Swan-Ganz catheter," Cirugía Cardiovasc., vol. 26, no. 4, pp. 191–196, Jul. 2019, doi: 10.1016/J.CIRCV.2019.06.002.

[62] T. S. Metkus et al., "Transesophageal Echocardiography in Patients Undergoing Coronary Artery Bypass Graft Surgery," J. Am. Coll. Cardiol., vol. 78, no. 2, pp. 112–122, Jul. 2021, doi: 10.1016/J.JACC.2021.04.064.

[63] J. M. Harris, K. Sheehan, C. A. Rogers, T. Murphy, M. Caputo, and A. D. Mumford, "Prediction of Bleeding in Pediatric Cardiac Surgery Using Clinical Characteristics and Prospective Coagulation Test Results," Semin. Thorac. Cardiovasc. Surg., vol. 34, no. 1, pp. 277–288, Mar. 2022, doi: 10.1053/J.SEMTCVS.2021.01.006.

[64] J. M. Ali, C. Gerrard, J. Clayton, and N. Moorjani, "Hemostasis Checklist Reduces Bleeding and Blood Product Consumption After Cardiac Surgery," Ann. Thorac. Surg., vol. 111, no. 5, pp. 1570–1577, May 2021, doi: 10.1016/J.ATHORACSUR.2020.07.016.

[65] Y. Kawahara et al., "Use of laboratory testing for prediction of postoperative bleeding volume in cardiovascular surgery," Thromb. J., vol. 19, no. 1, pp. 1–6, Dec. 2021, doi: 10.1186/S12959-021-00324-4/FIGURES/3.

[66] E. A. Vlot et al., "Association of Plasma Fibrinogen and Thromboelastography With Blood Loss in Complex Cardiac Surgery," Clin. Appl. Thromb., vol. 27, May 2021, doi: 10.1177/10760296211016541.

[67] M. VANDENHEUVEL et al., "Comparison of coagulation monitoring using ROTEM and Sonoclot devices in cardiac surgery: a single-center prospective observational study.," Minerva Anestesiol., vol. 88, no. 9, pp. 680–689, Mar. 2022, doi: 10.23736/S0375-9393.22.16119-5.

[68] R. M. Bojar and R. M. Bojar, "Manual of perioperative care in adult cardiac surgery," p. 630, 2005.