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Pathophysiology of Cardiopulmonary Bypass: Current Strategies for the Prevention and Treatment of Anemia, Coagulopathy, and Organ Dysfunction

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Abstract

The techniques and equipment of cardiopulmonary bypass (CPB) have evolved over the past 60 years, and numerous numbers of cardiac surgical procedures are conducted around the world using CPB. Despite more widespread applications of percutaneous coronary and valvular interventions, the need for cardiac surgery using CPB remains the standard approach for certain cardiac pathologies because some patients are ineligible for percutaneous procedures, or such procedures are unsuccessful in some. The ageing patient population for cardiac surgery poses a number of clinical challenges, including anemia, decreased cardiopulmonary reserve, chronic antithrombotic therapy, neurocognitive dysfunction, and renal insufficiency. The use of CPB is associated with inductions of systemic inflammatory responses involving both cellular and humoral interactions. Inflammatory pathways are complex and redundant, and thus, the reactions can be profoundly amplified to produce a multiorgan dysfunction that can manifest as capillary leak syndrome, coagulopathy, respiratory failure, myocardial dysfunction, renal insufficiency, and neurocognitive decline. In this review, pathophysiological aspects of CPB are considered from a practical point of view, and preventive strategies for hemodilutional anemia, coagulopathy, inflammation, metabolic derangement, and neurocognitive and renal dysfunction are discussed.

Keywords

cardiopulmonary bypass, heparin, hyperglycemia, coagulopathy, bivalirudin, anemia, neurological complications, renal dysfunction, reperfusion injury, inflammation

Introduction

Cardiopulmonary bypass (CPB) has been an essential technique of cardiac surgery for more than 60 years. The first successful cardiac operation for the closure of an atrial septal defect was performed on CPB in 1953 by John H Gibbon Jr, MD, at Jefferson University Hospital in Philadelphia, Pennsylvania.[1] Modern CPB techniques have immensely evolved from the earlier models through numerous failures and subsequent improvements of the CPB system.[2,3]

Separating the lung and heart for surgery of the cardiac chamber requires extracorporeal oxygenation and recirculation of the oxygenated blood into the patient. Both CPB and extracorporeal membrane oxygenation (ECMO) systems provide such cardiopulmonary support, but there are specific differences between CPB and ECMO.[4] First, CPB is equipped with a reservoir into which blood in the heart is drained, so that a bloodless surgical field can be obtained for valve and aortic operations. In contrast, the ECMO circuit does not contain a reservoir, so blood flow needs to be continuous. Second, CPB, but not ECMO, can be utilized in conjunction with air vent tubing, cardioplegia line for myocardial preservation, or cell salvage tubing.[5] Finally, the requirement for systemic anticoagulation with unfractionated heparin (hereinafter heparin) is less intense for ECMO because blood flow is continuous (ie, no blood stasis), and there is no blood-air space in the reservoir. Nevertheless, effective anticoagulation is crucial in preventing thrombus formation on the synthetic thrombogenic surface of CPB and ECMO.

In this review, we will primarily focus on the CPB system and associated pathophysiological phenomena, including hemodilution, coagulopathy, inflammation, and organ dysfunction. Second, we will review recent clinical data on the

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preventive measures and therapeutic interventions, which might mitigate CPB-related pathophysiological events.

CPB and Hemodilution

The extracorporeal circuit needs to be filled (i.e., priming) with a balanced electrolyte solution to avoid air embolism before it is connected to the patient. The priming volume is generally 30% of the adult blood volume, but it can be larger than the patient's blood volume in neonates and infants. Initial hemodilution on CPB is thus proportional to the ratio of the patient's blood volume to the priming volume. Mild hemodilution (MH) can reduce blood viscosity and increases the cerebral blood flow.[6] However, moderate to severe hemodilution can result in impaired oxygen-carrying capacity and tissue ischemia despite a decrease in the basal metabolic rate. The acceptable hematocrit levels during CPB vary in the range of <18% to 30% depending on the patient's age and comorbidities. The potential hazards of hemodilution on CPB have been suggested in the retrospective analyses of patients undergoing cardiac surgery on CPB.[7-10] Karkouti et al[8] retrospectively analyzed 9080 cardiac surgical patients for the incidence of acute renal failure (ARF) and its potential with hemodilution during CPB. The overall incidence of ARF was 1.5%, but the nadir hematocrit below 21% represented the (adjusted) odds ratio of 2.34 in the incidence of ARF requiring dialysis when compared with the nadir between 21% and 25%. The same group also retrospectively evaluated the incidence of persistent neurological deficit (stroke) within 30 days of cardiac surgical operations (n = 10 949). The overall incidence of stroke was 1.5%, but there were notable stroke risks associated with a nadir hematocrit below 21%. They estimated that each percentage drop in the nadir hematocrit was associated with a 10% increase in the odds of perioperative stroke.[9] In a prospective randomized study by Mathew et al,[11] the effect of hemodilution on cognition was evaluated in patients (n = 108) for coronary artery bypass grafting (CABG) using either MH (hematocrit >27%) or profound hemodilution (PH; hematocrit 15%-18%) on CPB. The target hematocrit was achieved in the PH patients by autologous blood collection with normovolemic hemodilution, and the blood was returned to the patient at the end of CPB. Although their study was prematurely stopped because of safety concerns and the incidence of cognitive deficit was statistically nonsignificant (37.5% in MH vs 42.5% in PH; $P = .65$), post hoc analyses demonstrated a significant interaction between hemodilution and age.[11] Thus, older patients (>85 years old) with PH experienced greater cognitive decline. In their retrospective analysis of 3003 CABG patients, Ranucci et al[12] concluded that the median lowest hematocrit values below 25% on CPB were associated with an increased major morbidity rate, whereas no increased morbidity was found when the lowest hematocrit was maintained above 28%. The association between hematocrit and mortality was not demonstrated.

Carson et al[13] reported that the 30-day morbidity and mortality were 57.7% and 34.4%, respectively, among Jehovah's Witness patients whose hemoglobin levels were 4.1 to 5.0 g/dL after noncardiac and thoracic surgery, whereas morbidity of 9.4% and mortality of 0% were observed when postoperative hemoglobin levels were 7.1 to 8.0 g/dL.

Taken together, moderate anemia with hematocrit in the range of 21% to 25% is generally well tolerated in most cardiac surgical patients, but extreme anemia and hemodilution can be associated with organ injuries, particularly in the elderly.

Table 1. Hematological Effects of Washing of the Salvaged Blood by Cell Savers.[a]

	Unit	Prewash	Postwash
Hemoglobin	mg/dL	6.9	100
Leukocyte	$\times 10^9$/L	80-100	80-100
Platelet	$\times 10^9$/L	95	25
Fibrinogen	mg/dL	100	<50
tPA	ng/mL	12.4	0.6
TAT	μg/mL	110	21.8
Heparin	U/mL	6.3	0.3

Abbreviations: tPA, tissue plasminogen activator; TAT, thrombin-antithrombin complex.
[a]Data shown as median values (n = 49).[18]

Intraoperative Cell Salvage

Intraoperative cell salvaging is an important technique to collect shed blood and recover red blood cells (RBCs). The use of cell savers enables washing of the collected shed blood, which contains fat particles, cell debris, fibrin clot, cytokines, and activated complements.[14-17] However, platelets, coagulation protein, and inhibitors are progressively lost during the cell-saver washing (Table 1).[18] Djaiani et al[19] conducted a prospective, randomized study of cell-saver washing versus unprocessed reinfusion of shed blood in 226 patients (>60 years old) undergoing CPB for CABG.[19] Demographic and intraoperative (surgical) parameters were similar between the 2 groups. Incidence of cognitive dysfunction was observed 6 weeks after CABG in 6% of the cell-saver group versus 15% of the non–cell-saver controls ($P = .038$). Although major clinical outcomes, including the incidences of RBC transfusion, atrial fibrillation, myocardial infarction (MI), renal failure, stroke, and death were similar, plasma transfusion was notably higher in the cell-saver group than in controls (25% vs 14%; $P = .018$). Among patients who received cell-salvaged blood, the median volumes of cell salvage were 632 mL in those who subsequently received plasma, and 379 mL in those without plasma transfusion ($P < .0001$). These data indicate that

Table 2. Choice of Anticoagulant for Cardiac Surgery.[a]

Clinical Setting	Laboratory Profile		Recommended Anticoagulation for Surgery
	Platelet Count	Immunological Assay	
Remote HIT	Recovered	Negative	Use heparin
Subacute HIT	Recovered	Positive	1. Delay surgery, if possible until immunological assay is negative 2. Use bivalirudin if surgery cannot be delayed
Acute HIT	Thrombocytopenia	Positive	1. Delay surgery, if possible until PLT count is normal and immunological assay is negative 2. Use bivalirudin if surgery cannot be delayed 3. Case reports suggest repeated plasmapheresis may transiently reduce HIT antibody levels to allow a single heparin exposure

Abbreviation: HIT, heparin-induced thrombocytopenia.
[a]Recommendations by Cuker A, Crowther MA. Clinical practice guideline on the evaluation and management of adults with suspected heparin-induced thrombocytopenia. Quick Reference, American Society of Hematology 2013

blood loss managed by cell salvage can induce progressive plasma dilution despite the maintenance of hemoglobin levels. Plasma dilution that exceeds 45% is generally associated with preoperative risks (small body size, female gender, etc) as well as intraoperative risks (complex surgery, excess bleeding, prolonged CPB time, etc).[10,20] Multimodal strategies are necessary to address various risk factors that lead to excess hemodilution and potential organ failures after CPB.

Strategies to Minimize Hemodilution

Hemodilution is often caused by excess crystalloid and colloid infusions, and fluid restriction can be effective in reducing RBC transfusion.[21] The priming of CPB is another major contributor to hemodilution. Sakwa et al[22] conducted a prospective randomized study of a standard CPB circuit versus a minimized circuit (Medtronic Resting Heart Circuit; Medtronic, Minneapolis, MN) in 199 patients undergoing CABG. Shorter tubings and minimized circuit reduced the priming volume (0.9 L vs 1.8-2 L for a standard CPB). Demographic and surgical data were similar between the 2 groups, but total chest tube drainage was greater in the standard CPB group than in the minimized circuit group (1124 ± 647 vs 560 ± 214 mL; $P < .001$). The nadir hematocrit values (mean) were 25.5% versus 30.5% in the standard and minimized CPB, respectively ($P < .0001$). Platelet count was also higher in the minimized circuit group on intensive care unit (ICU) arrival; 117.4×10^9/L versus 186.4×10^9/L in the controls ($P < .0001$).[22] The overall rate of transfusion was significantly lowered in the minimized circuit group (16% vs 51% in the standard CPB; $P < .0001$). A mini-CPB circuit setup with a priming volume of 110 mL has been reported to minimize allogeneic transfusion in pediatric cardiac surgery.[23]

Heparin Anticoagulation

Extracorporeal circulation, including CPB, requires systemic anticoagulation to support endogenous anticoagulant proteins and minimize thrombin activation, and subsequent platelet activation and fibrin clot formation. Antithrombin (AT, formerly ATIII) is a major coagulation inhibitor that circulates in plasma at a high concentration (150 μg/mL), and its fraction is bound to endothelial surface heparan sulfate. Although AT itself is a relatively slow inhibitor of coagulation, heparan-bound AT is efficient in inhibiting circulating thrombin and activated factor X (FXa). For CPB, high concentrations of heparin (300-400 U/kg) are administered to turn circulating plasma AT into a rapid inhibitor of thrombin and FXa. Major advantages of heparin include a rapid onset after intravenous administration and reversibility using protamine sulfate. Conversely, shortcomings of heparin are the diminished efficacy in the presence of low AT levels (<60%) and incomplete inhibitions of clot-bound thrombin and FXa, particularly at a lower concentration (<2 U/mL).[24,25]

Platelet activation occurs during heparin-anticoagulated CPB, as demonstrated by the surge of platelet factor 4 (PF4) released from platelet α granules.[26] Heparin-induced thrombocytopenia and thrombosis (HITT) is another complication of heparin anticoagulation. The formation of IgG antibody against the complex of heparin-PF4 is causally associated with HITT. The Fc terminal of IgG antibodies can induce activation of platelets via FcγRIIa receptors, and immune-mediated and consumptive losses of platelets ensue, resulting in thrombocytopenia and a hypercoagulable state.[27] Heparin-PF4 IgG antibodies are found in up to 50% of post-CPB cardiac surgical patients, but only a fraction of patients (1%-3%) develop symptomatic HITT.[28] Heparin-induced thrombocytopenia (HIT) antibodies usually decline to undetectable levels in about 3 months, and there is no anamnestic response (immunological memory) against heparin-PF4.[29] In the patients who were previously positive for HIT antibodies but with no detectable antibody titers, heparin can be used for anticoagulation during CPB (Table 2).[30,31] However, it is prudent to avoid a repeated exposure to heparin by implementing heparin-less catheters and utilizing heparin alternatives for preoperative and postoperative anticoagulation in these patients.

Table 3. Clinical Doses of Argatroban and Bivalirudin.

	Initial Dosing	Monitoring
Argatroban	• Bolus: none • Continuous infusion: 2 μg/kg/min • Serum bilirubin >1.5 mg/dL: 0.5-1.2 μg/kg/min	Adjust dose to 1.5-3.0 times baseline aPTT; repeat aPTT q4h during dose titration
Bivalirudin		
HIT	• Bolus: none • Continuous infusion: 0.15 mg/kg/h • Reduced dose for renal insufficiency	Adjust dose to 1.5-2.5 times baseline aPTT
CPB	• Bolus: 0.75-1.5 mg/kg • CPB prime: 50 mg • Continuous infusion[a]: 0.75-1.0 mg/kg/h • Reduced dose for renal insufficiency	ACT 300-350 s (ECT 400-500 s)

Abbreviations: aPTT, activated partial thromboplastin time; HIT, heparin-induced thrombocytopenia; CPB, cardiopulmonary bypass; ACT, activated clotting time' ECT, ecarin clotting time.
[a]Stop infusion 15 minutes prior to the weaning from CPB.

Table 4. Novel Oral Anticoagulants.

Drug	Mechanism of Action	Indication	Tmax	Half-life	Renal Excretion	Protein Binding	Dose Reduction
Dabigatran	Anti-IIa	Prevention of stroke and VTE	1.25-3 hours	12-17 hours	80%	35%	CrCl < 30 mL/min
Apixaban	Anti-Xa	Prevention of Stroke and VTE	1-3 hours	8-15 hours	25%	87%	Not reported
Rivaroxaban	Anti-Xa	Prevention of stroke and VTE	2-4 hours	9 hours; 11-13 hours (elderly)	33%	>90%	Age >75 years; CrCl < 50 mL/min

Abbreviations: VTE, venous thromboembolism; CrCl, creatinine clearance.

Direct Thrombin Inhibitors (DTIs)

In the case of HIT, an alternative to heparin anticoagulation may be required, and this is usually achieved using a DTI—argatroban or bivalirudin (Table 3). Either one of the DTIs can be used in acute HIT cases, titrating the dose by activated partial thromboplastin time (aPTT). The lack of an antidote for any of the DTIs increases the risk of bleeding complications.[32-35] In patients with renal failure, half-lives of lepirudin and bivalirudin can be prolonged, whereas hepatobiliary metabolism of argatroban is not affected. The choice of DTIs is thus based on the clinical situation and on the pharmacokinetics of each agent. For anticoagulation in cardiac surgery, bivalirudin is most commonly used to manage CPB and off-pump cases (Table 3). Activated clotting time (ACT) remains the mainstay monitoring for bivalirudin during cardiac surgery because ecarin clotting time, which is more reliable in monitoring DTI, is not commercially available.[36] The target ACT value is generally set at 300 to 350 s (or at least 2.5 times the baseline ACT) by bolus infusion of 0.75 to 1.0 mg/kg bivalirudin followed by infusion at 1.75 to 2.5 mg/kg/h (lower value for off-pump and higher value for CPB cases).[37-39]

Novel Oral Anticoagulants (NOACs)

Several NOACs have been recently approved by the FDA for prevention of venous thromboembolism after knee or hip replacement, and stroke prevention in nonvalvular atrial fibrillation.[40] NOACs belong to direct factor Xa inhibitors (anti-Xa: apixaban and rivaroxaban) and DTIs (anti-IIa, dabigatran; Table 4). The advantages of new oral agents over warfarin include a rapid onset (1-3 hours), reliable pharmacokinetics without coagulation testing, and the lack of food restrictions. Bleeding complications of oral anti-Xa and anti-IIa agents are dose dependent, but the overall incidences of bleeding are similar to or decreased compared with warfarin. Nonetheless, there are potential concerns related to NOACs in cardiac surgical patients with multiple comorbidities. First, plasma half-life of dabigatran is increased in kidney dysfunction (creatinine clearance ≤50 mL/min) because 80% of dabigatran is excreted unchanged from the kidneys. About 60% of dabigatran can be removed after 2 hours of hemodialysis. Apixaban and rivaroxaban generally do not require dose reduction unless kidney function is severely impaired (creatinine clearance ≤30 mL/min), but they cannot be

removed by hemodialysis because they are highly protein bound. In general, bleeding risks with new anti-Xa and anti-IIa agents increase with age (>75 years old), coexisting renal or hepatic disease, and emergency surgery. Unlike warfarin, which can be rapidly reversed with prothrombin complex concentrate (PCC),[41] managing bleeding resulting from new oral anticoagulants is difficult because there is no direct antidote. Pharmacological agents such as recombinant activated factor VII (rFVIIa) and both activated and nonactivated PCCs have been considered as adjunct hemostatic agents, but there is no clinical evidence to support their efficacy.[33,42]

Bleeding Complications Associated With Nonheparin Anticoagulants

The lack of a specific antidote for any of the DTIs makes it difficult to manage bleeding complications. Koster et al[32] reported their clinical experience of lepirudin anticoagulation for CPB in 57 HIT patients. They found that 24-hour chest tube drainage volumes were 50 to 480 mL in uncomplicated surgery (n = 41) but 450 to 2200 mL in complicated surgery (n = 16). Transfused allogeneic blood products were about 2.5 U for both RBCs and plasma, but in patients with renal failure, the transfusion requirements were much higher (9-15 U for RBCs, and 9-18 U for plasma). Similarly, a marked variability in the 24-hour chest tube drainage was found in a prospective randomized study of bivalirudin (n = 98) versus heparin (n = 52) for non-HIT cardiac surgery on CPB. In the bivalirudin group, 3 patients had a 4- to 10-L blood loss over 24 hours, although the mean 24-hour blood loss was 1.1 L. Also, 6 patients (6.1%) in the bivalirudin group and one (1.9%) in the heparin group required reexploration for bleeding ($P = .67$).

Balancing hemostasis and thrombosis is difficult in complex cardiac surgery on CPB using bivalirudin. Apostolidou et al[33] described the case of a 59-year-old man with positive HIT who required a left-ventricular assist device. Bivalirudin was used as a 50-mg bolus (additional 50 mg in the CPB priming), followed by 2 mg/kg/h. Although bivalirudin was terminated 7 minutes before the weaning from CPB and ultrafiltration was used to remove 2.4 L of fluid, ACT remained at 605 s at 30 minutes off CPB. Severe coagulopathy persisted despite administration of multiple units of blood products (RBCs 15 U, plasma 10 U, apheresis platelets 6 U, and cryoprecipitate 12 U). rFVIIa was administered as a single bolus (90 μg/kg), and shortly after, multiple thrombi were observed in the left atrium and pulmonary veins, and fibrous strands were noticed in the inferior vena cava and hepatic veins. Fortunately, the patient survived this complication and received heart transplantation 7 months after left ventricular assist device (LVAD) under heparin anticoagulation.

In unstable post-CPB patients, hemodialysis is difficult, but the use of hemofiltration may facilitate the elimination of bivalirudin. In the experimental study of hemofiltration after bivalirudin anticoagulation for CABG in 35 non-HIT patients (creatinine clearance >30 mL/min), the elimination half-life of bivalirudin was 0.6 ± 0.11 hours, but a filtrate volume of 3 L with a constant flow of 300 mL/m^2 body surface area per minute reduced the half-life to 0.47 ± 0.11 hours.[43]

A major perioperative bleeding event has been reported for NOAC therapy (Table 4). A case of severe post-CPB bleeding was reported in a 79-year-old man (80 kg) on dabigatran 150 mg twice daily until 2 days before surgery.[44] This patient had renal insufficiency (creatinine clearance, 36 mL/min), and preoperative aPTT (normal = 22-35 s) and thrombin time (normal = 20-30 s) were both prolonged to 60 s and >150 s, respectively. After aortic valve replacement and a single-vessel CABG on CPB using heparin (total 35 000 U), bleeding persisted at >1500 mL/h despite protamine administration (400 mg) and antifibrinolytic therapy with tranexamic acid. Three doses of rFVIIa (2.4 mg or 30 μg/kg per dose) were administered but without any improvement of hemostasis. Two additional larger doses of rFVIIa (7.2 mg or 90 μg/kg per dose) in conjunction with massive transfusion (RBCs 26 U, plasma 22 U, platelets 5 U, and cryoprecipitate 50 U) reduced the bleeding to about 800 mL/h. Hemodialysis was initiated in the ICU, and hemostasis was normalized after 6 hours of hemodialysis. The authors later confirmed that plasma dabigatran concentration was therapeutic at 95 mg/mL after CPB, and it was decreased to 27 ng/mL after 6 hours of hemodialysis. This single case report highlights the need for adjusting preoperative discontinuation of dabigatran according to renal function (Table 4)[45] and the need for multimodal hemostatic therapy, including blood products, rFVIIa, and hemodialysis.

Besides rFVIIa, other hemostatic agents, including PCC, and activated PCC (factor VIII inhibitor bypassing agent [FEIBA]) have been suggested as potential reversal agents for DTIs and anti-Xa agents. In general, coagulation test results improve after dosing rFVIIa, PCC, or FEIBA; conflicting data have been reported on the hemostatic efficacy in vivo, using various nonhuman species and different bleeding models.[42] In the case of life-threatening bleeding, the off-label use of rFVIIa (90 μg/kg), PCC (25-50 IU/kg), or FEIBA (25 IU/kg) is considered to be a reasonable option.[46-48]

Antiplatelet Therapy

Dual antiplatelet therapy (DAPT) using ASA and clopidogrel is the current standard for the management of acute coronary syndrome, and for the prevention of ischemic events after percutaneous coronary intervention.[49] For

Table 5. Antiplatelet Agents.

Drug	Mechanism of Action	Prodrug	Onset of Inhibition	Half-life	Recovery of PLTs[a]	Dose Reduction
Aspirin	COX-1 inhibition	No	0.7 hours	15-20 minutes	30% At 2 days	When used with ticagrelor[b]
Clopidogrel	$P2Y_{12}$ inhibition	Yes	2-5 hours	7-9 hours	40% At 3 days	
Prasugrel	$P2Y_{12}$ inhibition	Yes	0.5 hours	8 hours	2-3 days	Body weight < 60 kg[c]
Ticagrelor	$P2Y_{12}$ inhibition	No	1.5 hours	6-12 hours	57% at 24 hours	Avoid if history of ICH
Abciximab	GPIIb/IIIa inhibition	No	Immediate	10-15 min	12 hours	Body weight ≤ 75 kg
Eptifibatide	GPIIb/IIIa inhibition	No	Immediate	2.5 hours	4-6 hours	CrCl < 50 mL/min
Tirofiban	GPIIb/IIIa inhibition	No	Immediate	2 hours	4-8 hours	CrCl < 30 mL/min

Abbreviations: PLT, platelets; COX, cyclo-oxygenase; ICH, intracranial hemorrhage; GP, glycoprotein; CrCl, creatinine clearance.
[a]Recovery time for platelet function after drug withdrawal.
[b]Aspirin >100 mg/d reduces the efficacy of ticagrelor.
[c]Avoid if age >75 years old or history of ICH.

elective surgery in the patients on DAPT, aspirin is continued while clopidogrel is usually discontinued five days before surgery (Table 5).[50-52] Clopidogrel is a prodrug, and its active form inhibits $P2Y_{12}$ adenosine diphosphate receptor on platelets. Less than 10% of clopidogrel becomes an active metabolite through a 2-step hepatic cytochrome P-450 dependent oxidation process, whereas the remainder is hydrolyzed and inactive. There is a significant interindividual variability demonstrated as residual platelet aggregation in response to adenosine diphosphate[53] because of an interaction of clopidogrel with proton pump inhibitors and genetic polymorphisms of intestinal transport proteins and the P-450 system.[54-57] Uninterrupted DAPT before CABG appears to pose higher risks of major bleeding, reexploration, and allogeneic blood transfusion, as demonstrated in the meta-analysis of 23 studies involving 3505 patients exposed to clopidogrel within 7 days before CABG.[58] Testing of platelet responsiveness to clopidogrel can be useful in shortening the preoperative discontinuation to 1 to 3 days according to the residual platelet aggregability.[59,60]

The newer $P2Y_{12}$ inhibitors, prasugrel and ticagrelor (Table 5), are superior to clopidogrel with regard to the faster onset, greater platelet inhibition with less interindividual variability, and fewer drug-to-drug interactions. In the subgroup of patients who underwent CABG during a head-to-head comparison of prasugrel and clopidogrel, greater 12-hour chest tube drainage and increased platelet transfusion were demonstrated in the prasugrel group, particularly when the last dose was within five days of surgery.[61] The bleeding risk associated with ticagrelor was found to be similar to clopidogrel in relation to CABG, but more episodes of intracranial bleeds unrelated to CABG were reported with ticagrelor relative to clopidogrel.[62] It is currently recommended to stop prasugrel 7 days, and ticagrelor 5 days, prior to the invasive procedure.[50-52]

Platelet glycoprotein IIb/IIIa inhibitors (Table 5) are intravenous agents that are used in conjunction with heparin in the setting of acute coronary syndrome and percutaneous coronary intervention.[49] Tirofiban (half-life = 2 hours) has been used as a "bridging therapy" to sustain platelet inhibition while clopidogrel is being weaned off.[63] This approach is not mentioned in the recent American College of Cardiology Foundation/American Heart Association guidelines, but European and Australia/New Zealand guidelines recommend it for patients at high risk for cardiovascular events as a result of recently placed drug-eluting stents.[64,65] Tirofiban infusion is started on the day after clopidogrel is stopped, using a bolus of 12 μg/kg followed by a maintenance dose of 0.1 μg/kg/min until 4 hours before surgery. The dose is reduced by 50% and the infusion is stopped 8 hours before surgery if creatinine clearance is below 30 mL/min.[66] This regimen can be resumed after hemostasis is established (eg, 2 hours after surgery) and continued until clopidogrel is resumed. The case series (n = 30) of bridging therapy using tirofiban reported no major increases in bleeding, MI, or death while clopidogrel was temporarily suspended.[63] Furthermore, the combination of heparin and tirofiban (10 μg/kg bolus, followed by 0.15 μg/kg/min) has been suggested as an alternative anticoagulation strategy for CPB in patients with HIT who are at high risk for DTI-associated bleeding (ie, impaired renal function). No major bleeding or need for reexploration was reported in a small case series (n = 10) when tirofiban infusion was terminated 1 hour prior to the CPB weaning. The use of tirofiban during CPB is not recommended by the manufacturer because it is considered off-label.

Cangrelor is an ultra-short-acting (half-life of 3-6 minutes) intravenous $P2Y_{12}$ inhibitor, which is planned to be used as a bridging therapy, but this agent has not been approved by the FDA.[67]

Management of severe bleeding associated with platelet inhibitors involves platelet transfusion. The efficacy of platelet transfusion can be affected by residual platelet aggregability of the recipient, quality of transfused platelets, and circulating platelet inhibitors. In general, platelets administered within 6 hours from the last drug intake are highly likely to be inhibited by active metabolites of the

$P2Y_{12}$ inhibitor,[68,69] but platelet transfusion after 6 to 12 hours should be less affected.[70,71]

Fibrinolysis and CPB

The profibrinolytic state triggered by CPB is attributed to several mechanisms, including elevated tissue plasminogen activator (tPA) levels as a result of stress during surgery and CPB, and contact activation involving FXII and kallikrein.[72,73] It has been long postulated that aprotinin, a broad-spectrum serine protease inhibitor, exerts hemostatic and anti-inflammatory effects by inhibiting kallikrein in addition to plasmin. However, the major role of kallikrein activation as a cause of coagulopathy was refuted in the recent clinical trial of ecallantide, a synthetic kallikrein inhibitor, in cardiac surgery on CPB.[74] Ecallantide lacks plasmin inhibitory activity, but it inhibits bradykinin-mediated capillary leak, and it has been approved by the FDA for the treatment of hereditary angioedema. The prospective randomized study of ecallantide versus tranexamic acid on CPB was prematurely terminated after 109 patients were enrolled in each group because 30-day mortality was higher with ecallantide compared with tranexamic acid (12% vs 4%; $P = .041$).[74] The median RBC transfusion was also increased with ecallantide compared with tranexamic acid (900 vs 300 mL; $P < .001$). The lack of contact activation in the deficiency of high-molecular kininogen (a cofactor in the activation of kallikrein and FXII) was also shown to have normal thrombin generation and profibrinolytic activation during CPB.[75]

Another paradox related to the profibrinolytic state and CPB is that the initial peak tPA level occurs early (30-60 minutes) during CPB,[72,76,77] whereas D-dimer levels rise toward the end of CPB in cases where no antifibrinolytic agent was administered.[77,78] It is important to recognize that tPA is a weak activator of plasmin in the absence of fibrin, and free tPA is rapidly inhibited by plasminogen activator inhibitor-1 (PAI-1).[76,77] Conversely, fibrin formation steadily increased toward the end of CPB as a result of the incomplete suppression of thrombin generation by heparin-AT.[72,77] Indeed, elevations of prothrombin fragment 1.2 (F1.2) and thrombin-AT complex precede the increase of D-dimer.[78]

Lysine analogues (ε-aminocaproic acid and tranexamic acid) are routinely administered as antifibrinolytic therapy in CPB cases. As they exert antifibrinolytic activity by preventing the binding of plasminogen to fibrin, their hemostatic efficacies are diminished in the deficiency of fibrin (eg, hypofibrinogenemia). Minimizing hemodilution during CPB preserves endogenous antifibrinolytic proteins, including α_2-plasmin inhibitor, PAI-1, and thrombin activatable fibrinolysis inhibitor, as well as clot formation (ie, platelet, fibrinogen and procoagulant factors).[79,80]

Allogeneic Blood Transfusion

Major concerns relating to allogeneic blood transfusion have conventionally focused on pathogen transmissions, but the recent advances in donor testing and blood banking dramatically reduced the rate of infectious complications.[81] Perioperative anemia has been considered to be an important modulator of clinical outcomes[8,9,82-87] but treating anemia with RBC transfusion is also increasingly scrutinized for affecting morbidity and mortality after cardiovascular surgery. A recent report by Surgenor et al[88] demonstrated that (1) hemodilutional anemia was an independent predictor of low-output heart failure (ie, the need for IABP, return to CPB after initial separation, or treatment with ≥ 2 inotropes at 48 hours of surgery) and (2) treating low hemoglobin with RBC transfusion was associated with a 27% increased risk of low-output failure irrespective of the extent of anemia. Increased 30-day and long-term mortality have also been demonstrated by other retrospective studies.[89-93]

The optimal hemoglobin trigger for RBC transfusion has been evaluated in 1 prospective randomized trial in cardiac surgery (Transfusion Requirements After Cardiac Surgery; TRACS).[94] A total of 502 CPB patients were assigned to either a restrictive (maintain hematocrit ≥24%) or a liberal (maintain hematocrit ≥30%) strategy. The primary outcomes of 30-day mortality and in-hospital major morbidity were comparable between the 2 transfusion strategies. RBC transfusion was given to a lesser percentage of patients in the restrictive group than in the liberal group (47% vs 78%), which amounted to a 60% reduction in the number of transfused RBCs in the former group. Regardless of the transfusion strategy, RBC transfusion itself was found to be an independent risk factor for 30-day mortality. Transfusing stored RBCs has been considered a potential hazard[95] partly because stored RBCs are less deformable and are adherent to endothelium in the capillaries.[96] The depletion of ATP and 2,3-DPG from stored RBCs also contribute to reduced capability to improve oxygen delivery to peripheral tissues.[96] There is an ongoing randomized clinical trial of RBCs stored for <10 days versus ≥21 days in cardiac surgical patients (NCT00991341).[97] The results of this study and others (NCT00458783) are eagerly awaited to clarify the controversy related to stored-RBC lesions.[97]

Metabolic Derangement

The perturbation of glucose metabolism is a well-known phenomenon during CPB in patients with and without diabetes. Hyperglycemia, hypoinsulinemia, and insulin resistance are common during hypothermic nonpulsatile CPB.[98,99] A marked increase in plasma epinephrine concentration during CPB also contributes to hyperglycemia.[100] Hyperglycemia is presumed to adversely affect cellular and immune functions,

The potential harms of a postoperative hyperglycemic state attracted major attention after Van den Berghe et al[101] conducted a single-center, randomized trial (n = 1548) comparing intensive insulin therapy (IIT) with conventional management. The target blood glucose (BG) was set at 80 to 110 mg/dL in the IIT group and 180 to 200 mg/dL in the control group. The IIT group had reduced in-hospital mortality, infection, ARF, and RBC transfusion and shorter lengths of mechanical ventilation and ICU stay. More hypoglycemic events (BG < 40 mg/dL) were observed in the IIT group, but it was not associated with mortality. After this landmark trial, several retrospective data analyses in cardiac surgical patients reported that high intraoperative glucose levels were associated with higher morbidity and mortality.[102-104] However, the definitions of hyperglycemia were variable in these retrospective studies, and the optimal glucose range and the safety of IIT could not be determined for cardiac surgical patients. To address these questions, Gandhi et al[105] prospectively randomized 400 adult cardiac surgical patients to either IIT (target BG 80-100 mg/dL) or conventional therapy (insulin for BG >200 mg/dL). Both groups received the same insulin regimen, targeting BG of 80 to 100 mg/dL in the ICU. The authors found that intraoperative hyperglycemia (BG >250 mg/dL) was less (0 vs 7; $P = .015$) in the IIT group than in the control group, with no increases in hypoglycemia (BG < 60 mg/dL). However, they found more deaths (4 vs 0; $P = .061$) and more strokes (8 vs 1; $P = .02$) in the IIT group.

Taken together, currently available clinical evidence suggests that high BG levels of more than 270 to 360 mg/dL should be avoided, but the treatment target of BG should be in the range of 140 to 180 mg/dL rather than <110 mg/dL during cardiac surgery.[102-106]

Inflammatory Responses

The use of CPB is associated with the activation of multiple inflammatory pathways involving both cellular elements (RBCs, platelets, and white blood cells) and soluble proteins. The activation of complements is triggered in virtually all surgical procedures, but the response is higher in cardiac surgical procedures under CPB. The magnitude of complement activation is proportional to the duration of CPB.[107] Although the blood contact with CPB circuits can trigger a classical complement pathway via C_1 activation by FXIIa,[108] alternate complement pathways appear to predominate in the formation of anaphylatoxins (C_{3a}, C_{5a}) and terminal (membrane attack) complex ($C_{5b\text{-}9}$).[109] Neutrophil activation caused by anaphylatoxins and kallikreins leads to the release of lytic enzymes (eg, elastase) and oxygen-free radicals, both of which can cause tissue damage and organ dysfunction.[110] Cytokines are also increased from complement activation and neutrophil activation during CPB.[111] Interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor are a few proinflammatory cytokines that are elevated in response to tissue injury and endotoxic challenge and are involved in the pathogenesis of post-CPB inflammatory syndrome and sepsis.[112,113]

Critically ill patients have a limited reserve to counterbalance inflammatory responses, and they are at increased risk for extensive endothelial damage and capillary leak syndrome. All organs are susceptible to increased tissue edema, but the lungs, brain, kidneys, and myocardium are particularly vulnerable. Post-CPB syndrome can present as noncardiogenic pulmonary edema, myocardial dysfunction, severe vasoplegia, hemodynamic instability, and renal dysfunction and, in severe cases, as multiorgan failure.[114]

Therapeutic strategies for the established post-pump organ dysfunction are limited to supporting a failing organ, and thus, the research studies have been focused on preventive therapies for inflammatory responses to CPB.[115] However, no solid therapeutic strategy has been developed to date, and there are several explanations for it. First, there is no uniform reporting of inflammatory measures and clinical outcomes.[116] Cardiopulmonary equipment, anesthetic techniques, and other significant confounders such as transfusion protocols were not standardized. Second, experimental studies showing beneficial effects of any single drug or a nonpharmacological approach on inflammation could not be translated in clinical studies because of the multifactorial nature of the inflammatory response.[117] Finally, most of the past clinical trials were lacking adequate power as a result of the low event rate.

Despite the above-mentioned limitations, it may be useful to describe some evidence for a few practical strategies to mitigate inflammation and organ dysfunction during CPB. Corticosteroids (steroids) are commonly utilized for their anti-inflammatory effects in cardiac surgery but with different studies showing conflicting results. Dieleman et al[118] in a large randomized placebo-controlled trial (n = 4494) studied the effect of a single administration of high-dose dexamethasone (1 mg/kg) on 30- day mortality and organ dysfunction after cardiac surgery. No difference could be shown in their primary outcome, but dexamethasone lowered the risk of postoperative respiratory failure, shortened the times for ventilator weaning, and reduced risk of pneumonia during postoperative hospitalization. This could be explored further in future clinical trials. Preliminary results of another prospective, randomized trial (Steroids In caRdiac Surgery Trial; SIRS; NCT00427388) involving 7507 patients to evaluate the potential benefit of methylprednisolone (250 mg at anesthetic induction and 250 mg on CPB) vs. placebo failed to improve 30-day morbidity and mortality, but increased the incidence of MI (13.5% vs. 11.2%; $P = 0.001$) (http://www.cardiosource.org/Science-And-Quality/Clinical-Trials/S/SIRS.aspx).

The inhibition of complement activation has also been considered as a major therapeutic strategy in cardiac surgery. Pexelizumab is a recombinant monoclonal antibody that inhibits the conversion of C_5 to C_{5a} and $C_{5b\text{-}9}$.[119] This agent has been studied in several experimental animals and in clinical studies. The incidence of cognitive dysfunction was not decreased by pexelizumab in a large randomized multicenter and placebo-controlled trial in CABG patients.[120] Similarly, another randomized placebo-controlled trial in CABG or CABG-valve surgery showed no difference between the groups in the primary composite outcome (cardiac and neurological dysfunction in 30 days). However, a post hoc, subgroup analysis showed a lower incidence of non-Q-wave MI and also a reduction in the composite 30-day outcomes (MI and death) in patients treated with pexelizumab (bolus plus 24-hour infusion).[121] Additional large-scale studies (Pexelizumab for Reduction in Infarction and Mortality in Coronary Artery Bypass Graft Surgery; PRIMO-CABG I and II) have shown beneficial effects of pexelizumab in reducing MI or mortality after high-risk cardiac surgery.[114] These results suggest that the complement inhibition can be part of a multimodal anti-inflammatory strategy for high-risk cardiac surgical patients, but further investigations are required for its exact indication and cost-effectiveness.

Statins are another group of drugs that show a wide array of beneficial anti-inflammatory effects called pleiotropic effects.[122] In patients receiving statins, it is advisable to continue statins because they appear to decrease perioperative morbidity and mortality. However, in patients who were not on statins before surgery, it is not clear if perioperative statin therapy offers any benefit. Phosphodiesterase inhibitors, methylene blue, levosimendan, and insulin are a few other anti-inflammatory drugs, but there is no clear-cut evidence for their benefits on perioperative morbidity and mortality.[115]

Ischemia and Reperfusion Injury

The myocardium is prone to tissue injuries from ischemia and reperfusion during cardiac surgery with CPB because the blood supply is interrupted to achieve a quiescent, bloodless surgical field.[123] Ischemic injury is related to the depletion of energy source, and therefore. cardioplegic solutions are used to protect the myocardium during the ischemic period of CPB. Even if myocardial protection is successful, the subsequent reperfusion of the myocardium can result in the injury as a result of intracellular calcium trapping, inflammatory mediators, oxygen-free radical generation, and neutrophil-endothelial interactions.[123] A number of strategies are combined to prevent reperfusion injury, and such clinical practices include controlled aortic reperfusion with mean arterial pressure <70 mm Hg, warm hyperkalemic cardioplegia at reperfusion (hot shot), avoidance of ventricular distension and aggressive treatment of ventricular fibrillation during reperfusion, and extensive deairing to avoid coronary emboli.[124] Calcium channel blockers added to cardioplegic[125] or hypocalcemic cardioplegia[126] seem to produce better myocardial recovery. Adding free radical scavengers (catalase, superoxide dismutase, glutathione, *N*-acetyl cysteine, and allopurinol) remains controversial because blood cardioplegia provides naturally occurring free radical scavengers (vitamin C, superoxide dismutase, catalase, and glutathione).[127]

The lungs are particularly prone to inflammatory damages and reperfusion injury after CPB, and therefore, protective ventilation strategies have been the focus of research. Low tidal volume protective ventilation strategy has attracted the attention of anesthesiologists because high tidal volumes have been shown to exacerbate lung injury after CPB.[128] Tutun et al[129] have reported that low tidal volume ventilation lowered malondialdehyde, myeloperoxidase, and lactate levels after beating heart (off-pump) mitral surgery.[129] Inflammatory mediators (IL-6 and IL-8) were higher in the high-tidal-volume/low-PEEP (positive end-expiratory pressure) group compared to the low-tidal-volume/low-PEEP group after 6 hours of mechanical ventilation during cardiac surgery with CPB.[130] Sundar et al[131] have reported that low tidal volume ventilation reduced the number of patients requiring ventilation at 6 hours and reintubation after cardiac surgery. Additional clinical trials are warranted to confirm the beneficial effects of protective ventilation strategies in cardiac surgical patients. Other lung protective methods described in the literature include vital capacity maneuvers, hyperoxic therapy, and continuing ventilation and perfusion during CPB.[132] The transfusion of RBCs and plasma is a modulator of inflammation and appears to be a risk factor for post-CPB pulmonary complication, but the relative risk contribution of each product remains unclear.[133]

Neurological Complications of CPB

Devastating complications to the neurological system, such as cerebral infarction and hemorrhage, are the most feared complications of CPB. Nonspecific neurocognitive decline is frequently observed after cardiac surgery.[134] The pathomechanism of neurological complications after CPB remains complex and multifactorial. As discussed earlier, severe anemia during CPB can contribute to cerebral ischemia and neurocognitive dysfunction in older people.[11] Endothelial and tissue damage caused by microemboli[135] and systemic inflammatory responses[136] are regarded as additional insults to the neurological system.

The American College of Cardiology and The American Heart Association describes 2 types of neurological injury.[137] Type I is less common but includes fatal cerebral injuries, coma, and stroke. Type II is frequent but is more

vaguely defined as postoperative cognitive decline of memory and delirium. The incidence of neurocognitive dysfunction at discharge for patients requring CPB has been consistently found to be present in greater than or equal to 50%.. Newman et al[138] found the incidence of subtle neurocognitive dysfunction in 36% and 24% of patients at 6 weeks and 6 months postoperatively, respectively, whereas the current incidence of stroke following CABG with CPB is 1% to 3%.[9] Modifiable factors, including the perfusion pressure and flow rate of CPB, acid-base management, and temperature management (rapid vs slow rewarming) have been suggested, but optimal values and techniques for cerebral protection remain controversial.[139-141]

Renal Complications of CPB

ARF after CABG with CPB is a major risk factor for mortality. Renal dysfunction without the need for dialysis occurred in 6.3%, and dysfunction requiring dialysis occurred in 1.4% in an observational study of 2222 CABG patients.[142] The postoperative mortality of patients without renal dysfunction was 0.9%, but it was increased to 19% and 63%, respectively, by non-dialysis- and dialysis-dependent renal dysfunction. Preoperative risk factors for ARF include age (70 years old), congestive heart failure, diabetes, and chronic renal insufficiency (creatinine >1.6 mg/dL), but procedural risks such as the duration of CPB, hemodilution, and complexity of surgery (reoperation) are significant contributors as well.[8,142-144] The risks of anemia,[8] ischemia caused by microemboli and macroemboli,[145] inflammations of the kidney parenchyma,[146] and nephrotoxic effects of free hemoglobin from hemolysis[147] are considerably higher in high-risk surgery.

Optimizing blood flow and oxygen delivery to the kidney during CPB has been hypothesized to provide renoprotective effects, but vasodilator therapies, including dopamine[148,149] and fenoldopam,[150] did not result in consistently improved renal outcomes. In a recent prospective randomized trial comparing recombinant human B-type natriuretic peptide (nesiritide) and placebo in CABG patients with low ejection (≤40%; n = 272), a peak creatinine elevation was attenuated (+0.15 vs +0.34 mg/dL in the controls; $P < .001$), and a greater urine output were observed in the group with nesiritide.[151] The 180-day mortality rate was also decreased (6.6% vs 14.7% in the controls; $P < .046$).[151] The maintenance of pulsatile flow to the kidney has been another consideration for renal protection.[152] This would be a theoretical advantage of off-pump coronary bypass grafting surgery to minimize CPB-related ARF, but two retrospective studies comparing off-pump and CPB CABG failed to demonstrate any difference in terms of the incidence of postoperative renal dysfunction.[153,154]

Conclusion

The safety of the CPB system has immensely evolved over 60 years, and many less-invasive forms of cardiopulmonary supports (ECMO) can be provided to critically ill medical and surgical patients. Understanding the perturbations of physiological functions of various organs is pivotal in preventing and treating potential complications associated with such extracorporeal supports. Most organ complications related to CPB have multiple causes, and it is unlikely that these events can be avoided by the use of a single intraoperative "magic potion." Preoperative factors, including comorbidities (eg, anemia) and intraoperative factors (eg, hemodilution), are clearly interconnected, and it is necessary to approach these problems in a multidisciplinary fashion. Future research should be directed at finding a unique combination of biological agents and therapeutic pathways that would result in improved outcomes. This is likely to be a significant challenge in the time of health care cost containment, but it is a shared responsibility of academia, industries, and governmental agencies around the world.

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