RESEARCH ARTICLE

Alternatives to Heparin Anticoagulation for Cardiopulmonary Bypass and Extracorporeal Membrane Oxygenation

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Abstract:

Mechanical circulatory support devices such as extracorporeal membrane oxygenation (ECMO) and cardiopulmonary bypass (CPB) are increasingly used to support patients with severe cardiopulmonary organ dysfunction. Due to the thrombogenic and inflammatory nature of their circuits, patients ideally should be anticoagulated to avoid potential complications. Heparin is the most commonly used anticoagulant, given its ease of titration, predictable pharmacokinetics, bedside monitoring capability, and reliable reversal with protamine. However, a subset of patients is contraindicated to heparin, such as those with heparin induced thrombocytopenia, who present with additional challenges in management in this setting. The goal of this narrative review is to comprehensively discuss alternative strategies of anticoagulation in the setting of heparin contraindication. We will touch upon both pharmacologic and nonpharmacologic methods, each with their distinct advantages and disadvantages. Both established alternatives as well as cutting-edge, experimental ones will bue discussed. Due to the complex nature of these patients, it necessary for anesthesiologists, intensivists, and surgeons to be familiar with the alternative strategies in order to successful navigate their clinical care.

Introduction:

Cardiopulmonary bypass (CPB) and extracorporeal membrane oxygenation (ECMO) are both mechanical circulatory support technologies that augment the native heart and/or lung function. They involve drainage and reinfusion of blood while performing extracorporeal gas exchange.[1] In both devices, contact between patient blood and the non-endothelialized surface of the circuit triggers an inflammatory response and pro-coagulation cascade.[2–5] As a result, prophylactic anticoagulation is integral to prevent catastrophic thrombosis of the circuitry. In rare instances, there exist contraindications to heparin use, necessitating alternative management strategies.[6] In this review, we will examine heparin contraindications in mechanical circulatory support and summarize alternative approaches to anticoagulation in these circumstances.

Principles of Extracorporeal Circulation

Both ECMO and CPB allow external circulation of blood to maintain organ perfusion and gas exchange independent of cardiopulmonary function. However, their circuits differ in several important ways (Table 1). CPB utilizes a venous reservoir which introduces a blood-air interface, circuits are typically not heparin-bonded, and periods of low flow may be maintained during cardiac surgery. All of these features lead to a more pronounced inflammatory response than would typically be seen in an ECMO circuit, thus requiring greater levels of anticoagulation.[7,8] Furthermore, smaller priming volumes and pulsatile blood flow in ECMO may further decrease neutrophil activation and inflammatory response.[4]

Table 1: Differences between CPB and ECMO

	CPB	ECMO
Duration	Short term (minutes-hours)	Long-term (days-weeks)
Anticoagulation	High-dose; reversed at the end of the case	Low-dose; not reversed
Cardioplegia	Used	Not used
Pump flow rates	2-2.2 L/min/m^2, non-pulsatile	>4L/min, sometimes pulsatile
Hypothermia	Used for neuroprotection	Not used
Circuit components	Venous reservoir, arterial filter	No venous reservoir or arterial filter
Air-blood interface	Yes	No, closed circuit
Hemodilution	Yes	To a lesser degree

CPB: cardiopulmonary bypass; ECMO: extracorporeal membrane oxygenation

Limitations of Heparin and Protamine

Heparin works by binding to antithrombin III, enhancing its ability to inactivate thrombin (factor IIa) and factor Xa. Unfractionated heparin (UFH) is commonly used for both CPB and ECMO due to its rapid and predictable onset, low cost, ease of monitoring, and availability of a reversal agent.[6] Unfortunately, the use of heparin and its reversal agent, protamine, has its limitations. Clinical contraindications may preclude its use in mechanical circulatory support, resulting in the need for alternative anticoagulation strategies.

Heparin

Heparin-induced thrombocytopenia (HIT) is the most commonly encountered heparin contraindication. There are two major HIT types: Type 1 is non-immune

mediated, causes mild thrombocytopenia, and exhibits spontaneous platelet recovery despite continued heparin use.[6,9] Type 2 is an immune mediated process, in which heparin binds to platelet factor 4 (PF4) and triggers the formation of IgG auto-antibodies, which then bind to platelets. Continued activation leads to both platelet aggregate removal (causing thrombocytopenia) and procoagulant release (causing a prothrombotic state).[10] For the remainder of this discussion, HIT will be referred to as HIT type II.

CPB: Patients with acute or sub-acute HIT may present for cardiac surgery with CPB. Management depends on the urgency of the procedure and the presence of HIT antibodies.[11] If elective, one can employ a "wait-and-see" approach. HIT antibodies typically decline over approximately 80 days.[6] Once this occurs, there is a low likelihood of antibody recurrence in the presence of heparin, which may then be safely given during surgery.[12–15] If emergent, several options exist. One approach is to use plasmapheresis to reduce antibody titers by 50-84%, allowing safe heparin utilization in CPB.[15,16] IV immune globulin similarly decreases antibody titers and has been successfully used for vascular bypass surgery. However, experience with its use in CPB is limited to a single case report and it is not currently recommended.[17] There are additionally several case series describing the use of heparin in conjunction with platelet antagonists (tirofiban, ilioprost, cangrelor) for CPB (as discussed later in the review).[18–21] The most common approach is to select a direct thrombin inhibitor (DTI) as a heparin alternative for CPB.[11]

ECMO: In ECMO patients with confirmed HIT, discontinuation of heparin and selection of an alternative anticoagulant is recommended, though an optimal strategy for this has not yet been defined.[22] DTIs, including bivalirudin and argatroban, are the most thoroughly studied, although data is largely extrapolated from CPB literature.[22,23] Notably, as ECMO circuits typically include heparin-bonded components, there is a risk of ongoing HIT despite switching to an alternate coagulant, which could necessitate circuit exchange.[24] Previously, plasmapheresis has been utilized to reduce heparin-PF4 antibody burden in ECMO safely.[25–27] In clinical scenarios where safe alternatives are lacking, studies have demonstrated that interrupting anticoagulation for prolonged periods in these patients may be feasible, though current guidelines recommend the use of anticoagulation.[28–30] Lastly, heparin-PF4 antibodies can often be detected in subgroups of patients on CPB or ECMO without the development of clinical HIT.[31–38] The significance of this is currently unknown, as literature is equivocal on antibody presence and adverse outcomes.[31,34,37,39–43] Due to high prevalence of these antibodies especially in the critically ill, it is even more important to use robust criteria including functional studies (i.e. serotonin release assay or heparin-induced platelet aggregation assay) to prevent over-diagnosis of HIT.

Protamine

Protamine sulfate is a commonly used reversal agent for UFH. However, it can cause significant side effects including profound vasodilation, anaphylaxis, and acute pulmonary vasoconstriction leading to cor pulmonale. The incidence of protamine reaction in CPB ranges from 0.1% to 13%.[44,45] Patient risk factors include prior exposure, use of protamine-containing insulin, and possibly fish allergy and/or prior vasectomy.[45,46] Those who have experienced a protamine reaction are at increased risk of mortality.[44]

If a patient has a documented history of protamine reaction, alternative strategies

for heparin reversal should be pursued. The first option is to forgo reversal entirely and allow heparin activity to passively decline.[47] This takes time, and additional blood product administration may be necessary to correct coagulopathy. Another option is to utilize a heparin-coated circuit, which decreases the systemic heparinization requirement. Several studies have demonstrated successful CPB runs with target activated clotting times (ACT) of 180-250s versus the usual >400s using these circuits.[48,49] As a result, protamine use can be minimized or avoided altogether. Thirdly, heparin may be neutralized either by a heparin removal device or novel drugs such as heparinase and hexadimethrine, although these have not yet been widely adopted.[50–55] Finally, anticoagulation can be achieved using another drug in lieu of heparin, thus forgoing the need for reversal with protamine.

Alternatives to Heparin

When there is a contraindication to heparin for CPB or ECMO, DTIs (specifically bivalirudin) have the highest level of evidence as an alternative anticoagulation strategy (Class IIa). Other therapies including non-bivalirudin anticoagulants, plasmapheresis, non-thrombogenic circuits, and platelet inhibitors have been studied but currently carry only a Class IIb recommendation.[56] The remainder of this review will focus on heparin alternatives that have been studied and used off-label for mechanical circulatory support devices.

Direct Thrombin Inhibitors

Thrombin is the final factor in the coagulation cascade, thus serving as a potent target for anticoagulation.[57] DTIs such as lepirudin, bivalirudin, and argatroban are approved in the US for the treatment of HIT.[58] Although none are formally approved for CPB or ECMO, their use in these scenarios are supported by the Society of Cardiovascular Anesthesiologists (SCA) despite being considered off-label (Class IIa and Class IIb recommendations). A summary of DTIs is provided in Table 2.

DTIs are derived from hirudin, or *hirudo medicinalis,* which is produced from leech salivary glands.[59] The active molecule binds to thrombin bivalently and irreversibly. Hirudin itself is not commercially available, although several analogs are available and are discussed below.

Lepirudin

Lepirudin is a hirudin analog and the first DTI approved for HIT with thrombosis in both the US and Europe.[58] Similar to hirudin, lepirudin forms an almost irreversible, bivalent bond to both the active site and exosite 1 on the thrombin molecule. The drug is both metabolized and eliminated renally, and in patients with renal failure, its half-life may be extended up to 120 hours, as compared to its usual 40-80 minutes.[58]

The preferred monitoring modality for lepirudin is activated partial thromboplastin time (aPTT), with a goal of 1.5-2.5x the baseline or control.[60] Plasma levels can also be checked (goal 3.5-4.5 μg/mL), however this assay is more expensive and less readily available.[58] Of note, ecarin clotting time (ECT) was developed specifically for DTI monitoring, however, the device used was not widely available and is no longer manufactured.[58]

Table 2: Summary of direct thrombin inhibitors

Drug	Mechanism	Dose*	Half-life	Elimination	Reversal	Monitoring	Additional information
Bivalirudin	DTI via reversible bond	CPB: 1 mg/kg bolus + 50 mg added to circuit, 2.5 mg/kg/hr infusion and additional boluses of 0.1-0.5 mg/kg as needed (Koster et al., 2007) ECMO (wide variability): no loading dose + 0.028-0.05 mg/kg/hr OR 0.4-0.5 mg/kg loading dose + 0.05-0.5 mg/kg/hr	20-25 minutes	Plasma proteases with core temperature of 37-38 C prior to renal elimination	No antidote but dialyzable	ACT most commonly at a minimum of 2.5x baseline value OR Serum drug concentration 10-15 µg/mL	SCA: Class IIA recommendation for a patient with HIT who needs urgent surgery requiring CPB ELSO: Recommend for patients with HIT
Argatroban	DTI via reversible bond	CPB: 5-mg bolus + 5 µg/kg/min Hirasaki et al., 2019) ECMO: no loading dose + 0.1-0.3 mg/kg/min (Geli et al., 2021)	45-55 minutes	Hepatobiliary system, temperature independent	No antidote and not dialyzable	CPB: ACT goal >480 seconds, however difficulty achieving anticoagulation even with this goal ECMO: 43-70 and 60-100 seconds for aPTT and between 150-210 and 180-230 seconds for ACT	SCA: Class IIB recommendation for patients with renal failure and HIT who require CPB with the warning of increased bleeding risk. ELSO: Recommend for patients with HIT Delay in effect of 30 minutes and peak effect not reached for 2 hours.
Lepirudin	DTI via irreversible bond	CPB: loading dose of 0.25 mg/kg, 0.2 mg/kg added to priming solution and additional boluses of 5 mg as needed to extend CPB time (Riess et al., 2007) ECMO: very wide range	40-80 minutes, up to 120 hours in renal failure	Both degraded and eliminated renally	No antidote but dialyzable	Serum drug concentration 3-5 µg/mL using ECT OR aPTT with the goal of a value 1.5-2.5 times the patient's baseline or control	ELSO: Recommend for patients with HIT Risk of allergic reaction.

*Given that none of the drugs are FDA approved for CPB/ECMO, none of the drugs have a defined dose, the above are suggested doses from studies

DTI: Direct thrombin inhibitor; CPB: cardiopulmonary bypass; ECMO: extracorporeal membrane oxygenation; ACT: activated clotting time; SCA: Society of Cardiovascular Anesthesiologists; ELSO: Extracorporeal Life Support Organization; aPTT: activated partial thromboplastin clotting time; HIT: heparin induced thrombocytopenia; ECT: ecarin clotting time.

Lepirudin use presents several disadvantages. Firstly, there is no reversal agent in the event of excessive bleeding. Secondly, the elimination half-life can be unpredictable, making precise timing of an infusion difficult in cardiac surgery. If levels during CPB are elevated, hemofiltration may be used to facilitate its removal, though this adds expense and time.[58] Finally, lepirudin is composed of non-human proteins and can potentially lead to anti-hirudin antibody formation and anaphylaxis.[59]

While use of lepirudin has been successfully described in CPB, there are only two case reports of its use in ECMO.[61] The first was in a pediatric patient who developed HIT while on veno-venous (VV) ECMO. A lepirudin infusion was initiated and the ECMO circuit was maintained without any complications for 6 days, although the patient ultimately expired due to other causes.[62] The second discussed an adult patient with renal dysfunction who developed HIT while on VV ECMO and was successfully anticoagulated with a reduced-dose lepirudin infusion.[63]

Bivalirudin

Bivalirudin is a hirudin analog that forms a reversible bond with thrombin. It has a short half-life (20-25 minutes) and is metabolized by plasma proteases independent of renal or hepatic function.[64] A dose reduction is recommended in patients with renal failure due to impaired excretion.[58] The aPTT goal on CPB/ECMO is 1.5-2.5x the baseline or control, or plasma concentrations of 10-15 μg/mL.[64] Similar to lepirudin, there is no reversal agent. Hemofiltration prior to blood return to a patient on bypass could potentially be utilized to mitigate the risk of high therapeutic levels.[65]

Due to its short half-life and ease of use, bivalirudin is the most studied DTI for CPB/ECMO. As previously stated, the 2018 SCA guidelines recommend bivalirudin use in patients with acute HIT undergoing CPB (Class IIa).[11] There have been two landmark trials of bivalirudin used for CPB. The first was EVOLUTION-ON, a multicenter randomized controlled trial comparing bivalirudin versus heparin in patients without a diagnosis of HIT. The primary endpoint was procedural success, which was defined as survival, myocardial infarction, stroke, or repeat revascularization. These outcomes were similar between the two groups at 7 days, 30 days or 12 weeks. While the bivalirudin group did have slightly higher operative blood loss, there was no significant difference at 24 hours or in transfusion requirements.[66] The CHOOSE-ON trial was a prospective study that compared CPB patients with documented history or a current diagnosis of HIT while using bivalirudin against historical controls. The primary outcome was also procedural success. Again, there was no difference in outcomes, even in those patients with renal dysfunction (despite a lack of dose adjustments).[67]

To date, there have been no randomized controlled trials of bivalirudin use for ECMO. San Fillip et al performed a systematic review of case reports, case series, and retrospective studies of patients who had been successfully anticoagulated on ECMO using bivalirudin.[68] There were extensive variations in both dosing and monitoring techniques, suggesting that an optimal regimen has not yet been described. A retrospective review by Kaseer et al of 52 patients on veno-arterial ECMO showed no differences in rates of thrombosis, major bleeding, or in-hospital mortality compared to heparin.[69] Similarly, there are several smaller studies demonstrating the safety and efficacy of bivalirudin use for ECMO.[70,71]

Argatroban

Argatroban is another DTI that reversibly binds to the thrombin active site.

Its half-life is 45-55 minutes and it is eliminated via hepatobiliary excretion and cannot be dialyzed. Unlike bivalirudin, which requires a core temperature of 37-38°C for metabolism, argatroban is eliminated via a temperature-independent pathway, which is a useful feature in cardiac surgery.[72] Like other DTIs, there is no commonly used reversal agent. Additionally, there is a delay in onset of 30 minutes and peak effect is typically not reached for two hours.[73]

Case reports of argatroban use in CPB have noted difficulty in achieving adequate anticoagulation.[72,74,75] In one case report, CPB was established after a bolus of argatroban followed by continuous infusion to achieve an activated clotting time (ACT) > 480s.[74] However, the ACT response was found to be unpredictable, and the target ACT was difficult to maintain despite repeated boluses. In this case, anticoagulation was confirmed with rotational thromboelastometry.[74] Another report described the death of a 12 year-old patient undergoing heart transplantation due to a clot in the CPB circuit despite an ACT of > 800s.[75] A recent systematic review included four cohort studies and 9 case series totaling 307 patients with the use of argatroban during ECMO.[76] A continuous infusion without a loading dose was used in the majority of cases, although infusion rates varied widely. aPTT was most often used for monitoring but without consensus targets. Bleeding and thromboembolic complication rates were found to be comparable to those of patients who received UFH.[76] For argatroban, the SCA has issued a Class IIb recommendation for patients with renal failure and HIT who require CPB, with warning of increased bleeding risk.[11] Currently, the Extracorporeal Life Support Organization (ELSO) guidelines recommend consideration of the aforementioned three parenteral DTIs as alternative anticoagulants for patients with HIT.[30]

Dabigatran

Dabigatran was the first oral DTI to market. The half-life is 12 hours, but can be up to 24 hours in patients with renal failure.[64] Because of concerns for toxicity with the increased dosage necessary for CPB, it has not yet been used in humans for this purpose.[77] Dabigatran is also a substrate of p-glycoprotein, and can potentially be subject to interactions with p-glycoprotein inhibitors or inducers.[59] Recently, Nadtochiy et al performed a simulation of CPB using human blood and dabigatran and monitored anticoagulation response via TEG.[77] Bypass was maintained for 120 minutes followed by successful reversal with idarucizumab. Additional trials will be needed prior to clinical use.

Heparinoids (danaparoid)

Heparinoids like danaparoid are byproducts of UFH production. Like UFH, heparinoids work by inhibiting factor Xa activity. They can be monitored by measuring anti-Xa activity, though this is impractical in a cardiac surgical setting. They are renally eliminated and do not have reversal agents. At this time, appropriate dosing for their use in this context is not known.[58] Danaparoid is not available in the US and has not been widely studied. In one French study, four patients underwent CPB safely with danaparoid.[78] There have not yet been studies published on the use of danaparoid for ECMO.

Ancrod

Ancrod is derived from Malayan pit viper venom as a serine protease that abnormally cleaves fibrinogen. It is eliminated by the reticuloendothelial system. Though there is no rapid reversal agent, the use of fibrinogen concentrates, cryoprecipitate, or plasma can replenish fibrinogen. Unfortunately, the use of ancrod

is logistically difficult, as it requires early initiation (at least 12 hours) prior to surgery to achieve satisfactory anticoagulation, as well as a prolonged wait for liver synthesis to replenish fibrinogen levels postoperatively.[79] Additionally, ancrod does not inhibit thrombin production, thus increasing the risk of thrombotic events. For these reasons, production was discontinued in 2002.[64]

Factor XIIa Inhibitors

Thrombosis on artificial surfaces like ECMO and CPB circuits is triggered by factor XIIa activation as part of the clotting cascade.[80] It has been proposed that coating catheters with factor XIIa inhibitors can prolong their patency. Ixodes ricinus contact phase inhibitor (Ir-CPI) is expressed in ticks and inhibits factors XIIa and XIa. Pireaux et al successfully performed CPB on sheep using Ir-CPI. However, supplementation with UFH was also done, which would not be suitable for patients with HIT.[81] Thus far, there have been only preclinical studies on this new class of anticoagulant.

Nafamostat

Nafamostat mesylate is a synthetic serine protease inhibitor that inhibits many procoagulant factors, including thrombin, plasmin, trypsin, kallikrein, factors XIIa and Xa, and complements C1r and C1s.[82] It has an extremely short half-life of only 8 minutes and is currently used in acute pancreatitis, shock, hemodialysis, and plasmapheresis, in order to reduce thrombotic complications.[83] A case series by Ota et al showed nafamostat can be safely used in patients on CPB for whom traditional anticoagulation would be prohibitively risky, including those with infectious endocarditis and intracranial hemorrhage.[82] There is some evidence nafamostat can be used safely for ECMO, including one case series of 13 patients with high bleeding risk.[84] Lim et al retrospectively reviewed heparin vs. nafamostat for ECMO and found a higher bleeding risk in the nafamostat group.[85] One adverse effect of nafamostat is its potential to cause hyperkalemia, as it inhibits amiloride-sensitive sodium channels.[23] Further studies are needed to determine the optimal dosing and safety profile of this drug.

Nonthrombogenic Circuits

Non-thrombogenic circuits for use in CPB and ECMO machines have been sought for decades with limited success. Heparin coated circuits do exist but unfortunately are contraindicated in patients with HIT.[64] Other options include biomaterial coatings having both antithrombin and antiplatelet properties. Several different types of surfaces have been studied in animal models, but none have undergone human trials. One potential surface studied by Yu et al is composed of argatroban linked to a polyurethane-silicone polymer, CarboSil®. These circuits would be ideal for patients with HIT and could potentially eliminate the need for systemic anticoagulation, but further study is needed.[86]

Platelet Inhibitors

There are several small studies demonstrating the safe use of platelet inhibitors in conjunction with UFH for HIT patients undergoing CPB. Tirofiban is a competitive GPIIb/IIIa inhibitor with a short half-life of 2 hours and primarily undergoes biliary excretion. In a study of 47 patients with HIT, Koster et al demonstrated the safe use of tirofiban in conjunction with UFH for CPB.[18,87]

Iloprost is a prostacyclin analogue that competitively inhibits platelets and has a short half-life of 30 minutes. In a study of three HIT patients undergoing CPB, continuous infusions of iloprost were started 1 hour before heparinization and continued until 15 minutes post protamine administration. Platelet counts remained stable and no excess blood loss was noted.[19]

Palatianos et al studied 10 patients with HIT undergoing CPB and showed that iloprost used in conjunction with heparin was associated with similar rates of thrombocytopenia, blood loss, and morbidity as in non-HIT patients.[20]

Epoprostenol is a prostaglandin (PGI_2) used to reduce pulmonary vasoconstriction in pulmonary hypertension patients. In addition to its vasodilatory properties, it also inhibits platelets. In a case series of 6 patients with HIT undergoing CPB, anticoagulation was achieved with epoprostenol and UFH without causing significant decline in platelet counts or excessive bleeding.[78] Notably, epoprostenol caused hypotension, which was successfully treated with norepinephrine infusions.

Finally, cangrelor is a P2Y12 ADP receptor inhibitor that blocks ADP-dependent platelet activation and aggregation. Cangrelor has a rapid onset of action (2 minutes), short half-life (3-6 minutes), and quick offset time (60 minutes). Its effects can be monitored by a point-of-care P2Y12 reaction unit (PRU) assay, unlike iloprost and tirofiban. A case series in which cangrelor was used alongside systemic heparinization for CPB demonstrated that this regimen was generally well tolerated in this patient population.[21]

Conclusion

Mechanical circulatory devices are increasingly used to support patients with severe cardiopulmonary derangement through their critical illnesses. Anticoagulation is necessary due to the thrombogenic and inflammatory nature of the extracorporeal circuit, most often achieved with heparin. In a subset of patients with contraindication to heparin use, a variety of alternative methods both pharmacologic and nonpharmacologic can be used to achieve anticoagulation as well, albeit each has its own advantages and disadvantages. Therefore, it necessary for anesthesiologists, intensivists, and surgeons caring for these patients to be familiar with the alternative strategies in order to successful navigate this complex clinical scenario.

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