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Coagulopathy and anticoagulation management in adult ECPR patients

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Abstract

Extracorporeal cardiopulmonary resuscitation (ECPR) has emerged as a lifesaving strategy for refractory cardiac arrest, restoring systemic perfusion when conventional cardiopulmonary resuscitation fails. However, ECPR profoundly disrupts haemostasis, driven by the combined effects of whole-body ischaemia–reperfusion injury, systemic inflammation, endothelial activation, platelet dysfunction, and blood contact with extracorporeal surfaces. Together, these processes create a highly dynamic and unstable thromboinflammatory milieu, marked by the simultaneous risk of thrombosis and life-threatening bleeding. Systemic anticoagulation is required to maintain circuit patency and prevent thromboembolic complications, yet optimal strategies remain uncertain. Haemostasis during ECPR is highly dynamic, shaped by the underlying aetiology of cardiac arrest, patient-specific characteristics, and circuit-related factors. This complexity underscores the limitations of fixed anticoagulation targets and the need for individualized, context-sensitive management guided by continuous clinical and laboratory assessment. Despite the increasing global adoption of ECPR, high-quality evidence to guide anticoagulation practices remains scarce. Current strategies are largely extrapolated from other extracorporeal life support populations, contributing to substantial inter-centre variability. This review synthesizes the available evidence on coagulopathy and anticoagulation in adult patients receiving ECPR and discusses emerging approaches to monitoring and anticoagulation management.

Keywords ECPR; ECMO; Anticoagulation, Resuscitation, CPR, Heparin, Extracorporeal, Coagulopathy

Introduction

Cardiac arrest is a leading cause of morbidity and mortality worldwide [1]. In addition to conventional resuscitation, extracorporeal cardiopulmonary resuscitation (ECPR) has emerged as an advance life-support strategy for patients with refractory cardiac arrest. It is defined as the initiation of veno-arterial extracorporeal membrane oxygenation (V-A ECMO), which can restore adequate systemic perfusion and tissue oxygenation when conventional cardiopulmonary resuscitation (CPR) fails [2]. As a relatively novel technology, evidence regarding the efficacy of ECPR continues to evolve; suggesting that ECPR may reduce mortality and improve neurological outcomes [3]. Accordingly, the International Liaison Committee on Resuscitation suggests that ECPR may be considered as a rescue therapy for selected patients, when appropriate institutional expertise and resources are available [4].

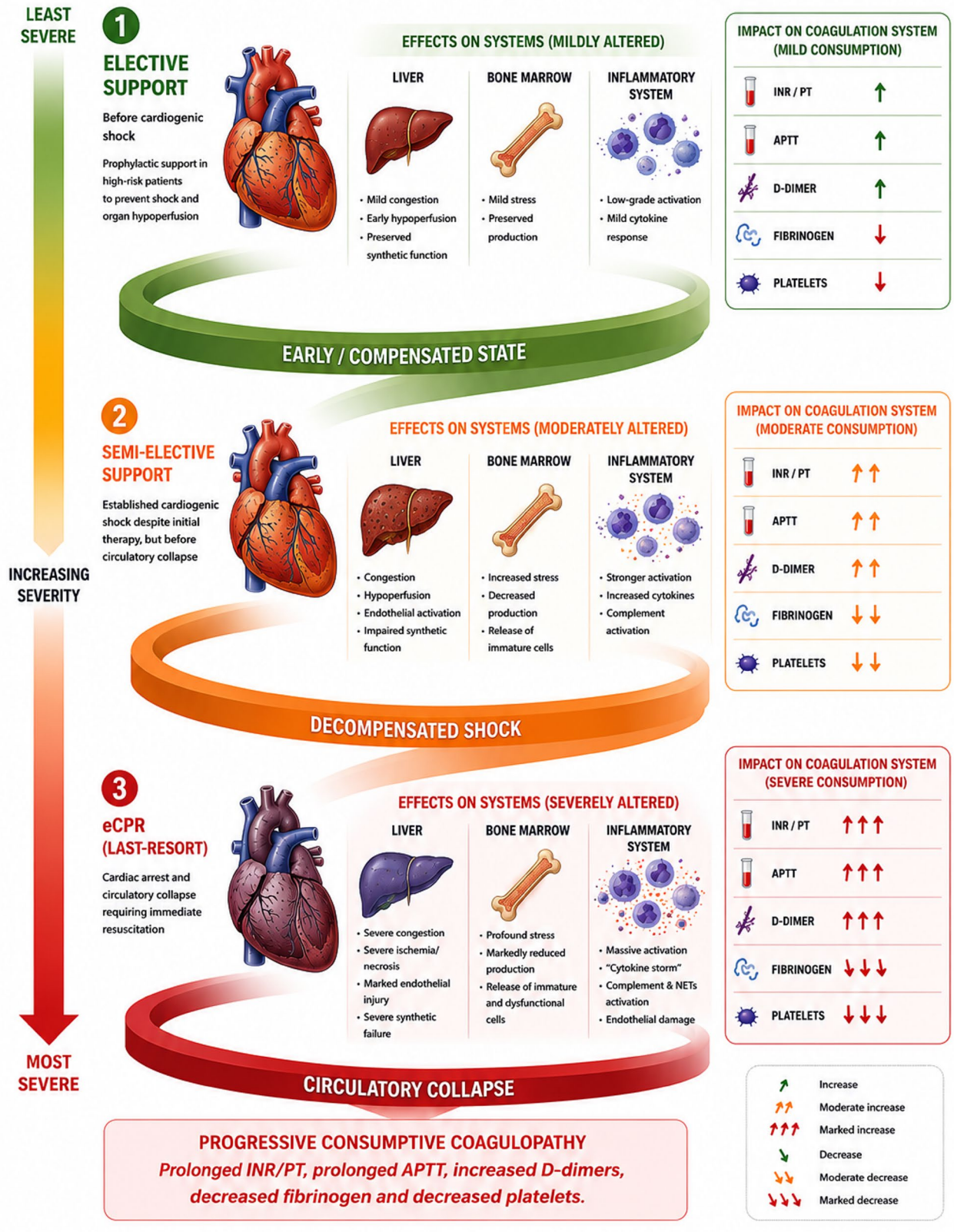
The initiation of ECMO is associated with profound haemostatic disruption, necessitating systemic anticoagulation to maintain circuit patency and to prevent

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Graphical abstract



thromboembolic complications and circuit components failure. Conversely, systemic anticoagulation is associated with an increased risk of haemorrhagic complications in ECMO patients, particularly among those receiving ECPR [5–10]. The coagulopathy observed in these patients is driven both by patient-related factors, such as cardiac arrest and ischaemia–reperfusion injury, and exposure to the ECMO circuit, and may manifest as either a prothrombotic or bleeding-prone state. This complex and evolving pathophysiology is one of the key determinants of clinical outcomes [11–15].

The purpose of this review is to provide a comprehensive overview of current evidence and clinical practice related to coagulopathy, anticoagulation strategies, and monitoring in adult patients receiving ECPR, Fig. 1.

Coagulopathy: pathophysiology and haemostasis

Cardiac arrest: *the patient*

Cardiac arrest is a state of prolonged, complete whole-body ischaemia during which the delivery of oxygen and metabolites ceases, and the products of metabolism are no longer removed, leading to global tissue and organ injury. The return of spontaneous circulation (ROSC) leads to a condition known as post-cardiac arrest syndrome, which is characterised by brain injury, myocardial dysfunction, a systemic ischemia–reperfusion response, and the persistence of the underlying pathology that precipitated the cardiac arrest [16–18]. From a clinical perspective, this temporal spectrum of progressive shock is reflected across three principal organ systems and key pathophysiological axes that warrant particular attention.

First, the liver - the primary site of synthesis for fibrinogen and nearly all plasma coagulation factors, is exquisitely vulnerable to the combined insult of reduced perfusion and venous congestion [19, 20]. While it performs multiple essential functions, the regulation of coagulation is often the first to deteriorate in the setting of liver failure or ischaemia. This early dysfunction is classically reflected by a prolongation of the international normalised ratio (INR), and by depletion of coagulation factors with short half-lives (such as factor VII, V, and protein C) as well as antithrombin, resulting in a complex bleeding–thrombotic phenotype. At a more advanced stage, impaired drug metabolism and disrupted glucose

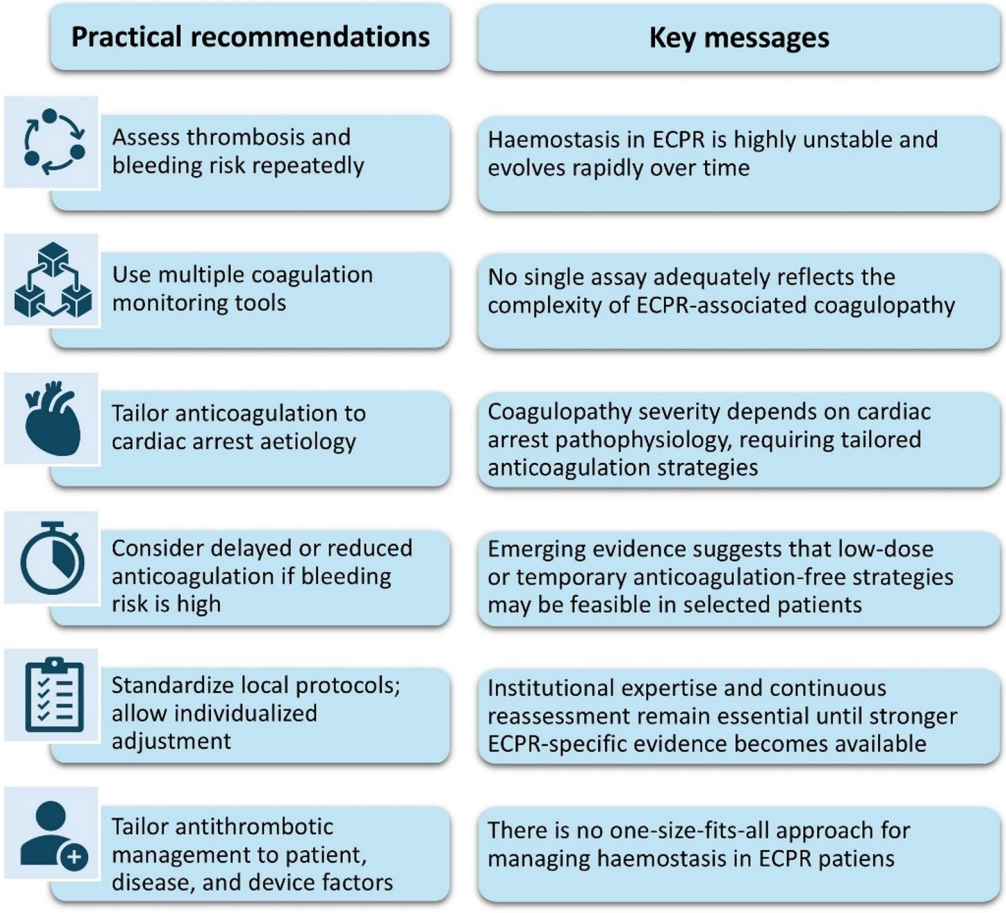


Fig. 1 Practical recommendations and key messages for anticoagulation management in adult ECPR patients. Abbreviations: ECPR, extracorporeal cardiopulmonary resuscitation

homeostasis can further complicate patient management [21–24].

Second, the bone marrow, which is responsible for the production of erythrocytes, leukocytes, platelets, and their precursors, is vulnerable to hypoperfusion-mediated suppression, resulting in impaired haematopoiesis, a decline in circulating blood cells, and consumptive thrombocytopenia driven by ongoing coagulation activation over the course of critical illness [25, 26]. This effect is exacerbated by systemic inflammation, haemodilution, and the catecholamine surge associated with resuscitation, all of which may worsen transient haematopoietic suppression and alter leukocyte and platelet kinetics [27]. Together, these mechanisms result in a profound imbalance between cellular production and peripheral consumption, thereby aggravating anaemia, leukopenia, and thrombocytopenia in the early post-resuscitation phase and contributing to haemostatic instability in ECPR patients.

Third, ischaemia–reperfusion injury triggers a systemic inflammatory response through the release of damage-associated molecular patterns (DAMPs), a process that is frequently accompanied by disseminated intravascular coagulation (DIC) [28–30]. Moreover, pressor-dependent haemodynamic instability, myocardial dysfunction, and microcirculatory failure may result in persistent inadequacy of oxygen delivery and utilisation. With increasing duration and severity of shock, as is often the case in patients undergoing ECPR, progressive activation and consumption of the coagulation system, together with accumulating oxygen debt, lead to depletion of critical haemostatic components and ultimately to DIC [16, 31].

This process is characterised by excessive thrombin generation, impairment of physiological anticoagulant pathways through depletion of antithrombin, protein C, and protein S, and suppression of fibrinolysis. These alterations promote widespread microvascular fibrin deposition, organ dysfunction, and microcirculatory reperfusion disorders [11, 12, 21, 32, 33]. Endogenous fibrinolytic activity depends on endothelial integrity and function, both of which may be markedly impaired following ischaemia–reperfusion injury [34–36].

Simultaneously, ischaemia, hypoxia, and catecholamine excess promote platelet activation and, together with the release of vWF-Ag/Factor VIII complex from activated endothelial cells, generate a pronounced thromboinflammatory state. This state is characterised by enhanced tissue factor expression, thrombin generation, and interleukin-1 release, further amplifying the coagulopathic phenotype of DIC [37, 38]. Moreover, platelet function may be impaired by acidosis and hypothermia [16]. The result is a complex platelet phenotype in which markers of activation coexist with functional impairment, increasing the risk of both microvascular thrombosis and bleeding complications.

In the early phases of shock, these hemostatic derangements may remain reversible with timely restoration of perfusion and targeted haemostatic resuscitation [28, 39]. However, with ongoing delay, the consumptive process becomes self-perpetuating and ultimately irreversible, resulting in severe haemorrhagic and thrombotic complications, Fig. 2 [16, 26, 40]. This pattern differs from that observed in other critically ill populations, including patients with trauma, sepsis, or thrombosis [35].

Beyond the complex activation of coagulation and the systemic inflammatory response following cardiac arrest, ECPR further amplifies these processes through blood exposure to the ECMO circuit [7].

Extracorporeal circuit: *the device*

In the setting of profoundly deranged homeostasis and haemostasis due to cardiac arrest and prolonged resuscitation, ECPR cannulation leads to blood contact with the non-endothelial surfaces of the circuit, triggering activation of factor XII to factor XIIa, Fig. 3. This initiates the *intrinsic coagulation pathway*, in which factor XIIa converts factor XI to XIa, which in turn activates factor IX to IXa. This cascade leads to activation of factor X, representing the first common step of the intrinsic and extrinsic pathways (24). Activated factor X (FXa) then converts prothrombin to thrombin, which cleaves fibrinogen to fibrin, ultimately resulting in clot formation. Thrombin, in turn, induces endothelial expression of P- and E-selectin and the production of platelet-activating factor (PAF), thereby enhancing neutrophil adhesion and activation [13, 29]. Furthermore, factor XIIa activates kallikrein and bradykinin, both potent mediators of coagulation and inflammation [15, 29, 41]. Kallikrein can directly activate neutrophils [42], while bradykinin stimulates the release of nitric oxide, tumour necrosis factor-α, and interleukin-10. The role of bradykinin in inflammation during ECPR may be particularly important because the lungs, the primary site of bradykinin inactivation, are partially bypassed during extracorporeal circulation [29]. Compared with other ECMO modalities, this process is further exacerbated in ECPR patients due to prolonged ischaemia, end-organ injury, pre-existing activation of inflammatory and coagulation pathways, and the underlying aetiology of cardiac arrest [43].

The *complement system*, a key component of innate host defence, is rapidly activated following cannulation, triggering a cascade involving more than 30 complement-related proteins that promote the clearance of foreign substances and generate proinflammatory anaphylatoxins [44]. Finally, there is considerable inter-individual variability in the inflammatory response to this trigger, the causes of which remain incompletely understood,

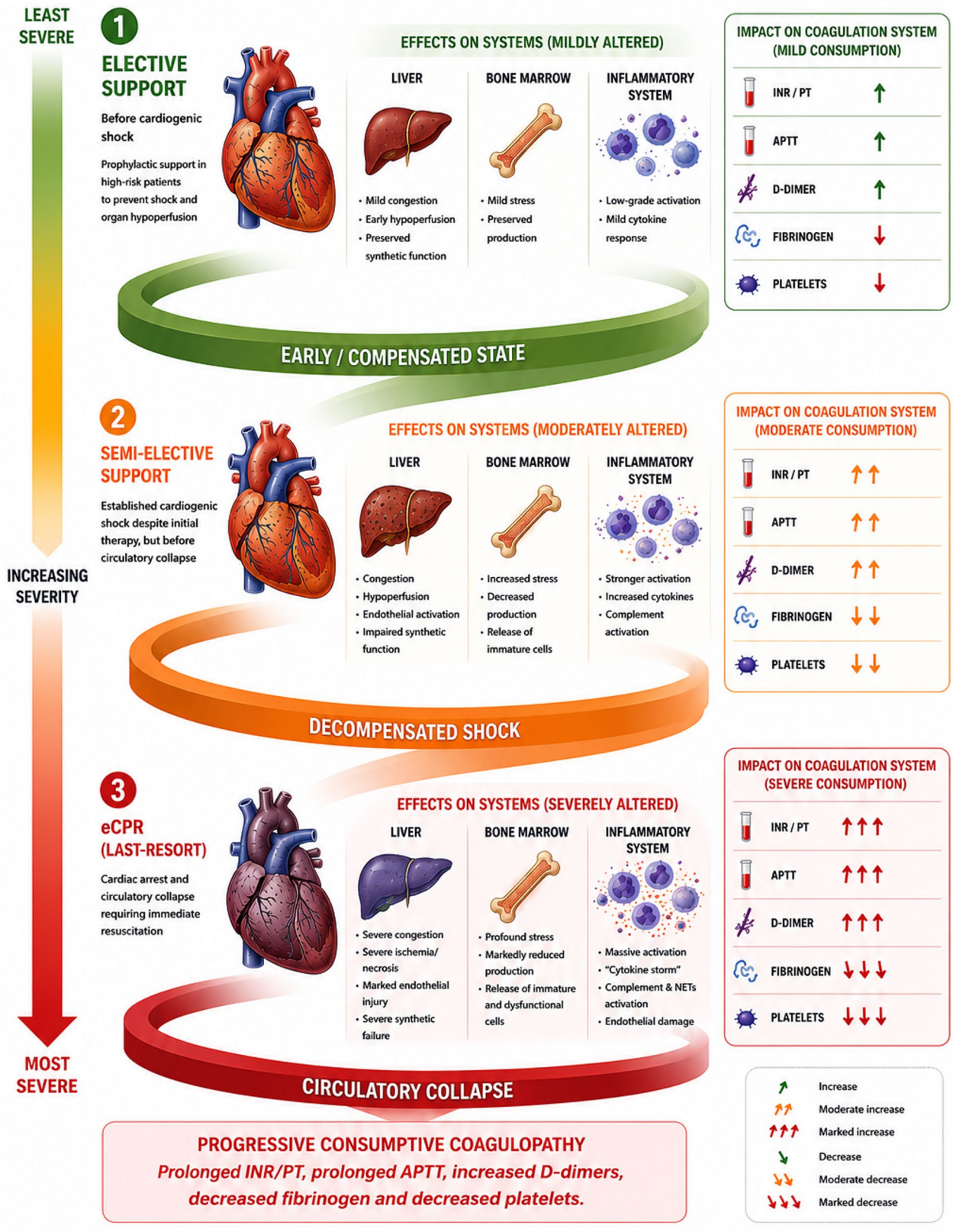


Fig. 2 The concept of the vicious cycle of cardiogenic shock and coagulation derangement. Progressive worsening and prolonged duration of shock result in escalating disturbances of the coagulation system, leading to severe consumptive coagulopathy. Abbreviations: ECPR, extracorporeal cardiopulmonary resuscitation; INR, international normalized ratio; PT, prothrombin time; aPTT, activated partial thromboplastin time; NETs, neutrophil extracellular traps

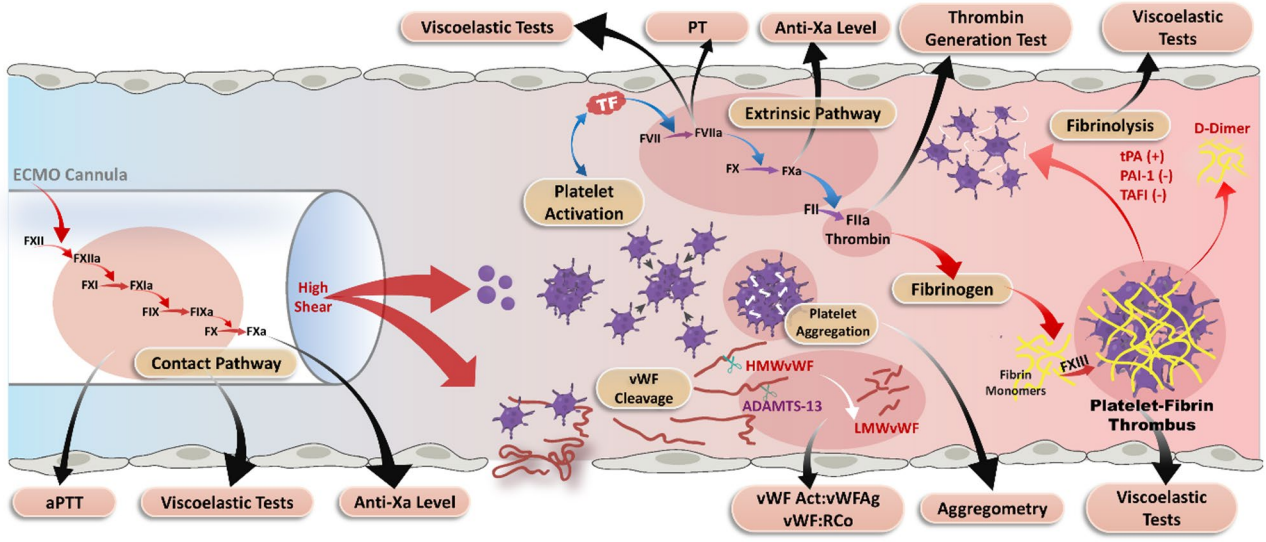


Fig. 3 Pathophysiology of coagulopathy and available monitoring tests. The figure illustrates the presence of ECMO cannulae within the blood vessel. Contact between blood and the non-endothelial surfaces of the extracorporeal circuit leads to activation of the coagulation cascade, while platelet activation is further promoted by exposure to the non-endothelial surfaces and high shear stress conditions. Together, these processes contribute to platelet aggregation and thrombus formation. ECMO support, characterized by continuous (non-pulsatile) flow, promotes cleavage of HMW of vWF, resulting in the development of aVWS and increased susceptibility to haemorrhage. Endogenous fibrinolysis, mediated predominantly by t-PA, PAI-1 and TAFI, plays a key role in preventing persistent thrombotic occlusion; however, when enhanced, it may further increase bleeding risk. Abbreviations: ECMO, extracorporeal membrane oxygenation; aVWS, acquired von Willebrand syndrome; HMW, high-molecular-weight; UFH, unfractionated heparin; vWF, von Willebrand factor; t-PA, tissue-activated plasminogen activator; PAI-1, plasminogen activator inhibitor-1; TAFI, thrombin-activatable fibrinolysis inhibitor; aPTT, activated partial thromboplastin time; PT, prothrombin time; TF, tissue factor

particularly given the difficulty in distinguishing the respective contributions of cardiac arrest and the extracorporeal circuit.

Consequently, the haemostatic alterations observed during ECPR reflect the combined effects of the primary pathology, ischaemia–reperfusion injury, and circuit-induced inflammation. Understanding this multifactorial origin of coagulation activation is essential for balancing thrombosis prevention against bleeding risk, which remains one of the central challenges in the care of patients undergoing ECPR [45].

What fundamentally distinguishes ECPR from elective or semi-elective V-A ECMO cannulation in evolving cardiogenic shock is the degree of hemodynamic compromise at the time of initiation, Table 1. Cardiogenic shock represents a clinical spectrum in which time is the critical determinant of outcome, and in ECPR, shock has, by definition, already progressed to its most advanced stage (SCAI E) [40, 46–49]. This profound circulatory collapse directly determines the severity and duration of end-organ hypoperfusion and, consequently, the extent of initially reversible versus ultimately irreversible organ injury [3, 40]. The central therapeutic imperative is to restore systemic perfusion before the threshold of irreversible organ damage is reached [48, 50].

Anticoagulation in ECPR

Given the dynamic haemostatic alterations, systemic anticoagulation remains a key intervention to preserve circuit function and mitigate thrombotic risk.

The timing of systemic anticoagulation

The timing of systemic anticoagulation during ECPR represents a complex and high-stakes clinical decision. Most contemporary ECPR protocols incorporate administration of unfractionated heparin (UFH) at the time of vascular access, particularly during arterial cannulation, to mitigate the risk of thrombus formation on intravascular guidewires. This practice is supported by decades of interventional and surgical non-ECPR experience demonstrating rapid thrombus generation on wires introduced into the arterial circulation, with the potential for cerebral and systemic embolization [52]. Early procedural anticoagulation during cannulation is therefore widely accepted as a critical preventive measure, despite guidewire times in ECPR being significantly shorter than those in percutaneous coronary interventions.

The subsequent decision regarding the initiation and intensity of continuous anticoagulation is more nuanced and is necessary to reduce the risk of circuit thrombosis, oxygenator dysfunction, and thromboembolic events during low-flow or nonpulsatile states [53]. Moreover, caution is warranted regarding the risk of left ventricular thrombosis, particularly in situations of severely reduced

Table 1 Expected clinical and hemostatic profile across the V-A ECMO spectrum

Parameter	Elective V-A ECMO	Semi-Elective V-A ECMO	ECPR
Clinical context (SCAI shock stage)	Planned support, stable haemodynamic (A–B)	Evolving shock, escalating support (C–D)	Cardiac arrest, no cardiac output (D–E)
Pathophysiological aspects	Stable haemodynamic, with less severe end-organ damage and a more stable baseline coagulation and inflammatory profile at cannulation	Low cardiac output with evolving end-organ hypoperfusion and progressive inflammation and coagulation disturbance prior to cannulation	Whole-body ischaemia–reperfusion injury, with profound metabolic acidosis, systemic inflammation, and early consumptive coagulopathy preceding cannulation
Time sensitivity	Elective	Variable (hours)	Extreme (rapid deployment)
Hepatic synthetic function	Preserved	Early impairment (↑INR, ↓albumin)	Acute cardiogenic liver injury
Bone marrow output	Normal	Stressed (early suppression possible)	Suppressed (hypoperfusion)
Endothelial activation	Minimal	Moderate (↑syndecan-1, ↑sTM)	Severe endotheliopathy (possible SHINE)
Dominant haemostatic phenotype	Compensated	Early consumptive	Overt post-arrest DIC / consumptive coagulopathy
ISTH DIC score	0–2 (no DIC)	3–4 (non-overt DIC)	≥ 5 (overt DIC possible)
Haemorrhagic diathesis	Minimal baseline haemorrhagic diathesis at initiation, with bleeding risk mainly iatrogenic (cannulation, anticoagulation-related)	Moderate haemorrhagic diathesis driven by evolving shock-induced coagulopathy, hepatic dysfunction, and inflammation	Severe, with occult resuscitation-related bleeding, diffuse alveolar haemorrhage, thorax trauma, cannulation site bleeding, and other
Reversibility of coagulopathy	Highly reversible	Potentially reversible	Potentially reversible, only if perfusion restored rapidly
Platelets	Mild consumption	Moderate consumption	Severe consumption
Fibrinogen	Normal/near-normal	Declining	Critically depleted, possible hyperfibrinolysis
D-dimer	Normal to mildly elevated	Moderately elevated	Markedly elevated
PT / INR	Normal	Prolonged	Markedly prolonged
aPTT	Normal (or heparin effect)	Prolonged (or heparin effect)	Markedly prolonged
Lactate (mmol/L)	< 2	2–5	> 5
Anticoagulation	Therapeutic systemic anticoagulation is usually initiated early at cannulation	Anticoagulation is typically initiated early and titrated to predefined targets according to bleeding risk	Individualised approach based on cardiac arrest aetiology, with minimised or delayed anticoagulation in cases of high bleeding risk

Adapted from the main text and [1, 10, 16, 19, 25, 28, 30, 31, 37, 40, 46, 50, 51]. Abbreviations: aPTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; ECPR, extracorporeal cardiopulmonary resuscitation; INR, international normalized ratio; ISTH, International Society on Thrombosis and Haemostasis; PT, prothrombin time; SCAI, Society for Cardiovascular Angiography and Interventions; SHINE, shock-induced endotheliopathy; sTM, soluble thrombomodulin; V-A ECMO, veno-arterial extracorporeal membrane oxygenation

ejection fraction or a completely akinetic ventricle, as reported in clinical experience with V-A ECMO. In such conditions, blood stagnation within the left ventricle (the so-called "smoke sign") may lead to rapid thrombus formation, representing a potentially serious complication [54, 55].

Early anticoagulation strategies may be favoured in clinical scenarios in which thrombotic risk predominates, and bleeding risk is relatively controlled. These include cardiac arrest secondary to massive pulmonary embolism, acute myocardial infarction requiring percutaneous coronary intervention, or profound left ventricular dysfunction with ongoing intracardiac stasis [56, 57]. However, early anticoagulation requires careful balancing against a substantial haemorrhagic risk in patients with CPR-related injuries, such as thorax trauma from mechanical chest compression devices, vascular injury related to cannulation, or unrecognised intracranial haemorrhage.

A contemporary decision-making framework emphasizes individualised and dynamic assessment rather than rigid timing thresholds [53, 56–58]. This approach integrates initial coagulation profiling with arrest aetiology, thrombotic burden and bleeding risk. Serial reassessment of coagulation status and haemorrhagic risk is essential, recognising that the balance between thrombosis and bleeding may evolve rapidly during the early hours of ECPR support [25].

Anticoagulants

Heparin products

Unfractionated heparin remains the primary anticoagulant used during ECPR and ECMO support owing to its rapid onset and potential for immediate reversal [7, 53, 59–61]. The Extracorporeal Life Support Organization (ELSO) anticoagulation guidelines recommend an initial bolus at the time of cannulation (50–100 IU/kg), followed by continuous intravenous infusion throughout the ECMO course (typically 5–20 IU/kg/h), without specific differentiation between ECMO indications or modalities. However, in patients with severe coagulopathy or active bleeding, the UFH bolus can be adjusted, and the

initiation of continuous systemic anticoagulation may be delayed [53].

In a sub-study of the Reduced Anticoagulation Targets in Extracorporeal Life Support (RATE), a multicentre, 3-arm, randomized, non-inferiority trial conducted in the Netherlands (NCT04536272) [62], including 37 ECPR patients, the authors concluded that both low-dose UFH (aPTT 1.5–2.0× baseline) and therapeutic low-molecular-weight heparin (LMWH) had comparable haemorrhagic complication rates to standard-dose UFH (target aPTT 2.0–2.5× baseline), with no thromboembolic events observed and no differences in six-month mortality. These findings may suggest that low-dose, rather than therapeutic, anticoagulation is theoretically feasible in the context of ECPR; however, larger prospective studies including a greater number of ECPR patients are needed to provide definitive evidence.

Direct thrombin inhibitors

Direct thrombin inhibitors (DTIs) directly bind to the active site of thrombin, inhibiting both circulating and fibrin-bound thrombin. Compared with heparin, they show less plasma protein binding, resulting in more predictable pharmacokinetics and antithrombin-independent anticoagulation [7, 63]. Argatroban is a synthetic DTI characterized by rapid hepatic metabolism and a short half-life of approximately 45 min, features that may be particularly advantageous in ECPR patients at high risk of bleeding [63]. It is also considered a safe anticoagulation option in patients with heparin-induced thrombocytopenia (HIT) and renal failure [64]. Its limitations include the lack of a specific antidote, limited availability of specific laboratory monitoring, limited clinical experience, and high cost [65]. A recent pilot randomised controlled trial including 19 ECPR and 21 V-V ECMO patients compared UFH with argatroban and found no differences in clinically relevant outcomes according to the anticoagulant used [66].

Bivalirudin is a synthetic bivalent polypeptide DTI that reversibly binds both the active site and exosite-1 of thrombin, with a half-life of approximately 25 min. It is primarily cleared from plasma through proteolytic cleavage, while a smaller proportion is eliminated renally, occasionally requiring dose adjustments in patients with renal impairment [65]. Although bivalirudin has not been extensively studied in the ECPR population, data from other ECMO cohorts suggest potential clinical benefits [67]. While high-quality evidence remains limited, DTIs could be considered the treatment of choice for ECPR patients with contraindications to UFH [64, 66, 68, 69].

Beyond these studies, comparative data on anticoagulation intensity and agent selection in ECPR remain limited. Future research should prioritize prospective, strategy-based comparisons of anticoagulation approaches. Particular focus should be placed on DTIs and LMWH, given their potential advantages over UFH. In addition, defining optimal anticoagulation intensity and integrating multimodal monitoring into patient-tailored strategies remain key research priorities.

Anti-aggregant therapy

In ECPR patients with ischemia-triggered cardiac arrest, dual antiplatelet therapy is indicated after percutaneous coronary intervention. As in conventional CPR, hypothermia, reduced gut perfusion/function, and opioid use can impair absorption of oral platelet inhibitors [70], potentially reducing the efficacy of ticagrelor, clopidogrel, and prasugrel and leading to high on-treatment platelet reactivity. Small studies have reported the feasibility of intravenous P2Y12 inhibition with cangrelor in patients receiving different types of mechanical circulatory support [56, 71, 72]. Moreover, initial studies evaluating cangrelor suggest that, in patients with cardiogenic shock, its administration during percutaneous coronary intervention is associated with a reduced risk of both major adverse cardiovascular events and all-cause mortality. In contrast, among patients with cardiac arrest, no such benefit has been demonstrated, and an increased risk of major bleeding has been observed. Whether these findings translate to patients undergoing ECPR, particularly given the additional bleeding risk, remains uncertain owing to limited evidence [73–75].

Anticoagulation monitoring

The most important caveat in anticoagulation monitoring is understanding *what* is actually being measured and avoiding treatment based solely on test results. Instead, clinical decisions should be guided by the overall clinical condition of the patient, as no single test provides a comprehensive assessment of the whole coagulation system and its dynamic nature [6, 25].

The available monitoring modalities include clotting time–dependent methods such as activated clotting time (ACT), activated partial thromboplastin time (aPTT), prothrombin time (PT), and INR, as well as viscoelastic assays and anti-factor Xa (anti-Xa) measurement [76]. Clotting time–dependent and viscoelastic methods provide a broader assessment of the coagulation system, whereas anti-Xa represents a specific measure of heparin activity, Fig. 3 [53, 59, 76–80].

Clotting time-dependent methods

Activated clotting time has a particular role in anticoagulation monitoring in ECPR patients as a point-of-care test that provides results within minutes, uses whole blood, and assesses the intrinsic and common coagulation pathways. It has traditionally been the primary method for monitoring UFH anticoagulation, particularly in the

presence of high heparin concentrations [76]. Its widespread availability, low cost, and rapid turnaround make it useful as an initial screening tool while awaiting more comprehensive coagulation testing. However, despite incorporating the contribution of platelets and other components involved in clot formation, its clinical utility is limited by a weak correlation with heparin blood concentrations and anti-Xa activity [77]. Furthermore, ACT results may be affected by factors commonly present during the early phase of ECPR, including haemodilution, hypothermia, elevated D-dimer levels, hypofibrinogenaemia, quantitative and qualitative platelet abnormalities, platelet inhibitors, and other coagulation disturbances [31, 45, 81].

Currently, no specific recommendations exist regarding the use of ACT in ECPR patients. However, the International Society on Thrombosis and Haemostasis (ISTH) recommends ACT as an alternative to anti-Xa monitoring, proposing a therapeutic range of 180–220 s for ECMO patients, without differentiating between ECMO modalities or patient populations (respiratory failure, cardiac failure, or cardiac arrest) [65]. The guidelines further highlight the limited evidence supporting this target range. Due to the superior performance of aPTT and anti-Xa assays in low-range anticoagulation monitoring, ACT is increasingly being replaced in ECMO patients, independent of indication [76, 82].

The aPTT measures the intrinsic and common coagulation pathways in citrated plasma and is widely used to monitor heparin therapy. It is readily available, supported by extensive clinical experience, and can be used to monitor both UFH and DTIs, making it a commonly used method for anticoagulation monitoring in ECMO. The main limitations relate to alterations in coagulation factor levels due to bleeding, thrombosis, or liver injury, all of which are frequently encountered in the post-resuscitation period and specially in ECPR patients [45]. In addition, aPTT may be falsely prolonged in the presence of lupus anticoagulant (reported in up to one-third of ECMO patients) or deficiencies of factor XII or XI, commonly observed in ECPR and other ECMO patient populations [83–85]. Moreover, aPTT may be markedly altered in the presence of elevated acute-phase proteins. Notably, these proteins may also exhibit heparin-binding capacity, thereby reducing effective circulating heparin levels in vivo and further highlighting the need for assays capable of directly assessing the effect of heparin [76].

The suggested therapeutic range for ECMO patients is 2.0 to 2.5 times the patient's baseline aPTT; however, this target remains to be validated in well-powered trials in this population, including ECPR patients [7, 65]. Multiple studies have demonstrated significant discordance between aPTT and UFH concentrations, as well as between aPTT and anti-factor Xa levels or viscoelastic assays, indicating poor correlation between monitoring modalities [86–88]. However, the available evidence is derived predominantly from studies including V-A and V-V ECMO populations, with only a small proportion of ECPR patients represented, Supplementary Table 1.

Anti-factor Xa assay

The anti-Xa assay measures the inhibition of factor Xa by heparin rather than heparin concentration itself and is increasingly used for anticoagulation monitoring due to its superior correlation with heparin levels compared with time-dependent tests [89–93]. The suggested target range is 0.3–0.5 U/mL, irrespective of ECMO support modality [65, 89, 91].

Its main limitations include the presence of haemolysis (free haemoglobin concentrations ≥ 50–70 mg/dL) and hyperbilirubinaemia (> 16 mg/dL conditions frequently encountered in ECPR patients that may result in falsely low anti-factor Xa levels [94–96]. Moreover, in the setting of overlapping anticoagulant therapy—for example, prior use of DTIs and UFH use during cannulation with subsequent anticoagulation—anti-Xa levels may be falsely elevated. Finally, as with other plasma-based assays, anti-Xa testing does not account for platelet function or the contribution of fibrinogen and other factors to clot formation.

Given its limited ability to identify causes of coagulopathy unrelated to anticoagulation therapy, anti-Xa assays should be complemented with additional tests that assess global haemostatic function.

Viscoelastic methods

Viscoelastic methods may serve as useful tools for rapid coagulation assessment in the ECPR setting and may help guide haemostatic product replacement. They were originally developed to assess global haemostatic function, including cellular components of coagulation, thereby providing a complementary perspective on coagulation assessment. Viscoelastic methods offer the advantages of point-of-care use and rapid result availability; however, their role in anticoagulation monitoring remains limited due to insufficient validation as standalone tools and only poor to moderate correlation with conventional coagulation assays, with limited evidence in ECPR patients [86, 94, 97].

The Extracorporeal Life Support and Modification of Hemostasis (ELMOH) trial reported on early haemostatic changes in a predominantly cardiac arrest population within a V-A ECMO cohort. It demonstrated a hypocoagulable profile during the initial phase, characterised by prolonged clotting and clot formation times, together with reduced clot firmness amplitude at 10 min. These abnormalities normalised after 48 h, highlighting

the importance of close monitoring and timely correction of coagulopathy [25].

In conclusion, combining multiple monitoring modalities acknowledges the heterogeneity of ECPR patients with complex thrombotic and bleeding profiles; however, it increases complexity and requires substantial education and governance for implementation [6].

Heparin resistance and antithrombin deficiency

A clinically relevant challenge is an unexpectedly poor response to UFH, a phenomenon historically referred to as *heparin resistance* [98]. Heparin resistance is often defined as the inability to achieve or maintain anticoagulation targets despite escalating UFH doses [99]. As heparin exerts its major antithrombotic effect through complex formation with antithrombin, antithrombin deficiency is a commonly implicated cause of heparin resistance [99]. Acquired antithrombin deficiency is frequently encountered in a range of clinical settings, including liver failure, inflammation, increased consumption during bleeding or DIC, and the use of extracorporeal systems, all of which are commonly present in ECPR patients [100].

In many cases, poor response to UFH reflects limitations of the monitoring assays described above or binding of heparin to acute-phase proteins rather than true resistance [101]. However, once these confounding factors have been excluded, optimal management remains controversial, as it is unclear whether antithrombin supplementation should be initiated below a specific threshold, UFH dosing simply escalated, or anticoagulation switched to another agent [102]. This is particularly important in fragile ECPR patients with a high risk of bleeding and the potential for falsely low anticoagulation monitoring results. Evidence demonstrating that antithrombin monitoring or supplementation improves outcomes in ECMO patients remains lacking, and no isolated data are currently available for ECPR patients [31, 53, 99, 102, 103].

Anticoagulation-free approach

The management of ECMO without anticoagulation has been described in trauma patients [104]. Several case reports and retrospective observational studies have suggested the potential safety of reduced or delayed UFH administration for the first 72 h in selected cases [105, 106]. Moreover, in cases of diffuse alveolar haemorrhage during V-V ECMO, very low-dose UFH anticoagulation has been maintained for several days [104, 107]. A recent retrospective study comparing 51 ECPR patients receiving anticoagulation with 50 patients managed without anticoagulation concluded that an anticoagulation-free strategy during the first 24 h may be feasible, with a reduced risk of bleeding and no significant increase in thrombotic complications [108].

Based on these observations, in ECPR patients at high risk of bleeding, delayed anticoagulation may be considered until completion of essential diagnostic evaluations or until an appropriate time point has been reached to minimise bleeding complications (e.g., pulmonary haemorrhage or thorax trauma related to prolonged mechanical chest compressions). We suggest that the decision to delay anticoagulation should be made on an individual basis and guided by the aetiology of cardiac arrest, clinical circumstances, and a careful risk–benefit evaluation, bearing in mind that the available evidence originates from retrospective studies with small numbers of patients. Particular caution should be exercised in the setting of intracardiac stasis, myocardial infarction, massive pulmonary embolism, or other prothrombotic conditions. In the absence of prospective clinical data and randomised studies, the concept of anticoagulation-free ECMO remains controversial, and further research evaluating strategies with minimal or low systemic anticoagulation is warranted.

ECPR in special circumstances

In certain contexts, such as trauma, hypothermia, intoxication, or submersion, pre-existing or arrest-related coagulopathy may further tip the balance between thrombosis and bleeding. As a result, the risk of haemorrhage is heightened, and anticoagulation should be carefully tailored and closely monitored until haemostasis is restored [109]. Across all scenarios, anticoagulation should be guided by the clinical context, coagulation monitoring, and continuous reassessment of the evolving risks of bleeding and thrombosis [109].

Trauma patients

Traumatic cardiac arrest is commonly considered as a contraindication for ECPR, particularly in the presence of traumatic brain injury [110]. Nevertheless, ECPR is occasionally employed in highly selected cases, including trauma patients with potentially reversible causes of cardiac arrest of non-traumatic (medical) aetiology [105, 111].

Initial management in these patients often involves delayed, reduced (low fixed-dose), or anticoagulation-free strategies, with close monitoring [58, 112, 113]. Correction of coagulopathy due to mass transfusion protocols, damage control surgery and/or interventional haemorrhage control is prioritized to ensure safe and stable ECMO run in ECPR patients [25, 110].

Accidental hypothermia

Severe hypothermia affects coagulation through impaired enzymatic activity of clotting factors, platelet

dysfunction, haemolysis, and altered fibrinolysis [114]. Standard laboratory coagulation tests performed under normothermic conditions may underestimate the severity of coagulopathy in hypothermic patients. Despite laboratory findings suggestive of hypocoagulability, hypothermia is also associated with an increased thrombotic risk upon rewarming [115]. Anticoagulation should be reduced or withheld during the initial phase of ECMO, particularly at core temperatures below 30 °C. As controlled rewarming progresses and haemostasis is restored, anticoagulation may be introduced or escalated [115].

Intoxication

In cardiac arrest secondary to intoxications, certain toxins may directly impair haemostasis, while others exert indirect effects through hepatic dysfunction, metabolic acidosis, or rhabdomyolysis [116, 117]. In this context, ECPR may serve as a bridge to toxin clearance, hepatic recovery, or extracorporeal detoxification, necessitating ongoing reassessment of coagulation status [118, 119]. Importantly, in patients exposed to direct oral anticoagulants (DOAC), anticoagulation monitoring is only feasible using specific DOAC-calibrated assays or anti-Xa measurements. These patients may remain at high risk of bleeding despite often normal aPTT or INR values [76].

Pulmonary embolism

Acute pulmonary embolism is a potentially reversible cause of cardiac arrest. Several systematic reviews evaluating ECMO for pulmonary embolism report survival rates exceeding 60%, with multiple studies suggesting a potential benefit of ECPR in this population [57, 120, 121]. Moreover, ECMO itself may contribute to thrombus resolution through anticoagulation, shear stress, acquired von Willebrand syndrome, and other mechanisms associated with extracorporeal circuit–induced coagulopathy. By restoring systemic perfusion and oxygen delivery, ECPR can serve as a bridge to definitive treatment and organ recovery [120, 122].

Anticoagulation remains a cornerstone of management in ECPR patients with pulmonary embolism, with UFH as the most commonly used agent, providing both circuit anticoagulation and therapeutic benefit through prevention of further thrombus propagation. However, following systemic thrombolysis or invasive reperfusion procedures, many centres adopt a cautious anticoagulation approach until bleeding risk has been reassessed. Clinical management therefore requires frequent evaluation of coagulation parameters and adjustment of anticoagulation intensity to balance the risks of circuit thrombosis, recurrent embolism, and major bleeding [120, 123, 124].

Outlook and future developments

Extracorporeal circuit innovations and anticoagulants

Modern circuit design increasingly incorporates biocompatible surface coatings that reduce contact activation and platelet adhesion by mimicking the antithrombotic properties of the endothelium, thereby reducing the need for intensive systemic anticoagulation [7, 14, 125, 126]. In parallel, further technical developments in extracorporeal devices and circuit components, such as centrifugal pumps with optimized flow dynamics, smaller priming volumes, and improved oxygenator membranes have helped reduce blood stasis and shear stress, thereby potentially lowering the risk of thrombosis [127]. Although systemic anticoagulation remains standard practice, continued technological progress may shift practice toward lower-intensity anticoagulation in the ECPR setting [62].

Recent research on contact pathway inhibitors targeting FXI and FXII suggests a promising strategy to reduce bleeding risk without increasing thrombosis [128], as individuals with congenital FXI deficiency rarely experience spontaneous major bleeding yet have a lower risk of venous thromboembolism and potentially acute myocardial infarction. In contrast, patients with FXII deficiency do not exhibit a distinct clinical bleeding phenotype [41, 76]. As a result, contact pathway inhibitors may have the potential to prevent thrombosis without compromising normal haemostasis [41].

Future guidelines for anticoagulation in ECPR

Existing ECPR anticoagulation recommendations are largely extrapolated from non-cardiac arrest populations and fail to adequately reflect unique risks in ECPR. In this context, anticoagulation strategies must account for arrest aetiology, the degree of ischaemia–reperfusion injury, and the rapidly evolving nature of coagulation abnormalities over time, necessitating pragmatic guidance that prioritises patient safety over rigid adherence to unvalidated targets.

Pending further prospective data, an approach to anticoagulation in ECPR is the standardisation of practice within institutions, coupled with outcome-driven adjustment. Future guidelines should define core principles rather than prescriptive algorithms. Unfractionated heparin is likely to remain the standard anticoagulant, with guidance focusing on dosing ranges, staged initiation in patients at high risk of bleeding, and criteria for escalation or interruption. Monitoring strategies should permit the use of conventional coagulation assays alone or in combination with viscoelastic testing, recognising that introducing unfamiliar testing modalities may increase management errors and variability. Flexible frameworks that accommodate goal-directed or standardised approaches, grounded in local experience, staffing, and

laboratory infrastructure, are therefore essential. Guidelines should also outline structured responses to haemorrhagic and thrombotic complications, including safe re-initiation of anticoagulation, and identify research priorities such as prospective ECPR-specific trials, standardised definitions of bleeding and thrombosis, and registry-based evaluation.

We propose that the future of anticoagulation in ECPR should move toward patient- and disease-tailored strategies rather than a *one-size-fits-all* approach [25]. Careful assessment and "mapping" of each patient's coagulation status are crucial to guide individualized anticoagulation, balancing the competing risks of thrombosis and bleeding [53, 58]. Research focusing on the integration of dynamic coagulation monitoring into clinical practice is warranted, with the goal of enabling truly personalized anticoagulation strategies that optimize both safety and outcomes in this high-risk population.

Limitations

This work has several limitations. As a narrative review, it does not follow a systematic methodology for literature identification, selection, or appraisal and may therefore be subject to selection bias and incomplete representation of the available evidence. Although efforts were made to incorporate relevant and contemporary literature, some studies may not have been captured. However, to address the clinical complexity of coagulopathy and anticoagulation management in adult ECPR patients, we performed a focused literature search covering key concepts in this field. Searches were conducted in MEDLINE and Scopus, with additional screening of reference lists from relevant studies. Grey literature and Google Scholar were also consulted to identify further relevant publications. Moreover, the proposed framework was developed through iterative expert discussions rather than a formal consensus process (e.g., Delphi methodology), which may limit its reproducibility and generalisability.

As ECPR remains an evolving technology, data on ECPR patients have frequently been reported within broader V-A ECMO cohorts, with subgroup analyses for patients experiencing cardiac arrest performed only in some studies. Consequently, some recommendations in this review are extrapolated from other ECMO populations following careful consideration of whether the underlying pathophysiological mechanisms may be applicable to ECPR patients. To enhance transparency, the supplementary Table 1 provides details of the included studies, including cohort composition and the number of ECPR patients represented in each study.

Conclusion

Anticoagulation during ECPR remains a fundamental yet unresolved challenge in refractory cardiac arrest. The haemostatic environment is shaped by complex and rapidly evolving pathophysiological processes, resulting in a fragile balance between thrombosis and bleeding. In this context, anticoagulation is best conceptualised as a dynamic process shaped by the aetiology of cardiac arrest, the severity of ischaemia–reperfusion injury, circuit-related factors, and the patient's evolving coagulation profile. Despite the rapid global expansion of ECPR, high-quality evidence to guide anticoagulation remains limited, and current strategies are largely extrapolated from other ECMO populations. Until more robust evidence emerges, clinicians must rely on physiological reasoning, vigilance, and clinical judgement within a narrow therapeutic window.

Abbreviations

ECMO	Extracorporeal membrane oxygenation
ECPR	Extracorporeal cardiopulmonary resuscitation
V-A ECMO	Veno-arterial extracorporeal membrane oxygenation
ROSC	Return of spontaneous circulation
aVWS	Acquired von Willebrand syndrome
HMW	High-molecular-weight
UFH	Unfractionated heparin
vWF	Von Willebrand factor
t-PA	Tissue-activated plasminogen activator
PAI-1	Plasminogen activator inhibitor-1
TAFI	Thrombin-activatable fibrinolysis inhibitor
aPTT	Activated partial thromboplastin time
PT	Prothrombin time
TF	Tissue factor
ILCOR	International Liaison Committee on Resuscitation
DIC	Disseminated intravascular coagulation
PAF	Platelet-activating factor
ACT	Activated clotting time
aPTT	Activated partial thromboplastin time
INR	International normalised ratio
ELSO	Extracorporeal Life Support Organization
LMWH	Low-molecular-weight heparin
DTIs	Direct thrombin inhibitors

Supplementary Information

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Supplementary Material 1

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Disclaimer
The statements contained in this work are intended for informational and educational purposes only and do not constitute medical advice or legally binding standards of care. While every effort has been made to ensure accuracy, the authors assume no liability for decisions made on the basis of its content. Responsibility for clinical decisions rests solely with the treating team. Large language models were used for language editing.

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