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UNDERSTANDING THE DISEASE

Why we need safer anticoagulant strategies for patients on short-term percutaneous mechanical circulatory support

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The field of percutaneous mechanical circulatory support (pMCS) and by extension of critical care has evolved markedly over recent years. In particular, the use of extracorporeal membrane oxygenation (ECMO) of balloon pumps and more recently microaxial-flow pumps has become more reliable with steadily improving technology and increasing experience, reflected in its improving results. Also, the possible duration of MCS support has greatly increased (from days to weeks) due to improved oxygenators and better medical management in dedicated high-volume ECMO centres [1].

Mechanical complications of pMCS have decreased with introduction of centrifugal pumps, low-resistance membranes and modern coating surfaces. Nevertheless, complications are still frequent and often jeopardize the patient's outcome and survival. Critically ill pMCS patients often present with underlying renal and hepatic failure or sepsis, causing a pro-coagulant acute phase response [2]. Additionally, exposure of blood to the non-biologic (negatively charged) artificial surfaces of pMCS circuits causes a complex activation of the coagulation system, next to platelet and leucocyte activation. This ultimately leads to a systemic inflammatory response syndrome with further disruption of the normal coagulation system. All these factors are contributory to both thrombosis (especially neurological complications and limb ischaemia) and bleeding. Not surprising, the reported rates of ECMO-associated venous thromboembolism (VTE) range from 18 to 85% [3]. Therefore, antithrombotic therapy is needed to maintain the patency of the extracorporeal circuit and reduce the risk of thrombosis and consumption coagulopathy. On the other hand, minimizing the risk of haemorrhage is crucial, as bleeding complications are not only devastating by themselves, but also necessitate prompt discontinuation of the anticoagulation therapy, further jeopardizing pMCS [4]. Up to 16% of venoarterial ECMO patients develop intracranial haemorrhage and nearly 60% of the ECMO population develops major bleeding. This can be associated with bad outcome, even if the patient survived the ECMO treatment [5]. Therefore, the precarious balance between bleeding and thrombotic complications forms a daily struggle for critical care physicians and strongly influences MCS-induced morbidity and mortality [6].

Mechanical circulatory support and (anti) coagulation

Despite the rapid evolution of high-tech supportive ICU equipment, anticoagulation protocols worldwide are still based on unfractionated heparin (UFH), the oldest anticoagulant [7]. UFH has many advantages: it targets both the intrinsic and extrinsic system, has a short half-life, is easy to reverse by protamine, is not contra-indicated in renal failure (UFH is mainly excreted by the reticular–endothelial systems) and is inexpensive. Therefore, most ECMO centres have ample UFH experience. Nevertheless, UFH-monitoring can be very challenging and the UFH dose–response effect is unpredictable due to the indirect effect on the coagulation cascade via antithrombin (AT). Indeed, acquired AT deficiency is common in ICU patients due to either decreased production, increased losses or consumption by the pMCS. Although

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routinely AT supplementation is common practice in many ECMO centres, evidence from prospective trials is lacking and retrospective data have associated AT use with an increase in both thrombotic and haemorrhagic ECMO complications [7, 8]. The activated partial thromboplastin time (aPTT) is an easily available test that is commonly used for UFH monitoring. Nevertheless, it may not provide an accurate measure of UFH anticoagulant effect as a result of various confounding factors which are more marked in critically unwell patients (low fibrinogen, liver failure, inflammation). The anti-Xa assay is not as significantly affected by these confounding factors and has been proposed as a first-choice assay for monitoring UFH during pMCS, but may not be available in all centres [9]. The use of thromboelastography-guided UFH monitoring as an attempt to additionally include platelet effects and fibrinolysis has been studied, but needs further validation [10]. Another major concern during UFH therapy on ECMO is heparin-induced thrombocytopaenia (HIT). Although up to 70% of patients on cardiopulmonary bypass develop anti-PF4/heparin-antibodies, only 4% had proven HIT. Similarly, the incidence of HIT on ECMO is much lower as previously assumed (reported as 0.36% in 5797 VA-ECMO patients) [11]. Therefore, the validation of HIT by functional assays is strongly encouraged**.** Although direct thrombin inhibitors argatroban and bivalirudin are commonly used in patients with HIT (Table 1), only few centres use these anticoagulants in pMCS patients because of their renal and hepatic clearance, challenging monitoring and high cost [12].

A crucial question remains how extracorporeal circuits activate our coagulation system: is it mainly driven by the intrinsic (contact activation) or extrinsic (tissue factor) coagulation pathway, via platelet activation or shear stress-induced acquired von Willebrand abnormalities, or a combination as summarized in Fig. 1? Therefore, further unravelling the mechanism by which artificial surfaces activate the human coagulation system would allow us to design a pMCS-tailored antithrombotic strategy for this critically ill patient group, avoiding the devastating side effects of UFH.

Table 1 Various anticoagulation strategies in the setting of mechanical circulatory support

Agent/therapy	Mechanism of action	Monitoring	Indications/remarks/comments
Heparin (UFH) [7]	Factor II/FXa inhibition via antithrombin	(ACT), aPTT Anti-Xa	Standard of care in MCS-treated patients (ELSO recommended); challenging to monitor, dose–response variability, indirect effect via antithrombin
Low molecular weight heparin [17]	FXa inhibition via antithrombin	Anti-Xa	Low anticoagulation VV-ECMO regimen; prophylactic dose. However, UFH is more preferable due to its shorter half-life
Bivalirudin [18]	Direct thrombin inhibition	aPTT	Valuable alternative to UFH; mainly in HIT patients/UFH resistance. Cleaved by thrombin in stagnant blood; short half-life; 20% renal excretion; no comparative trials vs. UFH
Argatroban [19]	Direct thrombin inhibition	aPTT	Valuable alternative to UFH; mainly in HIT patients/UFH resistance; Short half-life, no co-factors, hepatic metabolization, highly selective for thrombin; no comparative trials vs. UFH
Citrate [2]	Ca^{2+}-binding	pH, calcium ratio	Only data in animal models or in citrate-driven dialysis; high risk for citrate accumulation in ECMO since this would require high citrate volumes
Special cannula/oxygenator surfaces [20]	1. Biomimetic surfaces (UFH, NO) 2. Biopassive surfaces (albumin, perfluorocarbon, PPC, PMEA) 3. Endothelialization of surfaces	–	Covalently heparin-bound circuits are mostly standard of care; others are still under development
No anticoagulation [17]	–	–	Most evidence in literature for VV-ECMO with good results; indicated in patients with important haemorrhages (e.g. ICH); prophylactic dose of UFH should be considered
Dual antiplatelet therapy [21]	Platelet receptor inhibition	None	*Additional* therapy in patients with selected indications (recent PCI, AMI, stroke)

UFH unfractionated heparin, *ELSO* Extracorporeal Life Support Organization, *ACT* activated clotting time, *aPTT* activated partial thromboplastin time, *MCS* mechanical circulatory support, *VV-ECMO* venovenous extracorporeal membrane oxygenation, *HIT* heparin-induced thrombocytopaenia, *PCI* percutaneous coronary intervention, *AMI* acute myocardial infarction, *NO* nitric oxide, *ICH* intracranial haemorrhage, *PMEA* poly-2-methoxyethylacrylate, *PPC* phosphorylcholine

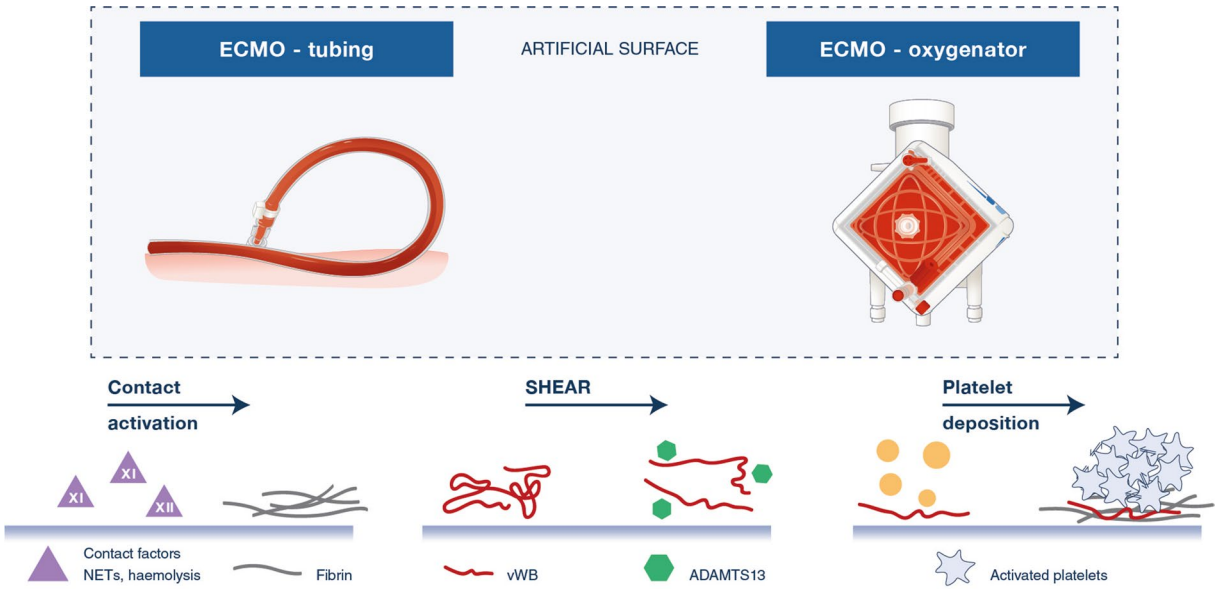

Fig. 1 During extracorporeal membrane oxygenation therapy, blood is continuously exposed to foreign body material (plastic surfaces in tubing and especially in the oxygenator); this causes a complex process of thrombus formation and consumptive coagulopathy due to contact activation resulting in fibrin deposition, high shear stress and von Willebrand deposition and platelet deposition/activation. *ECMO* extracorporeal membrane oxygenation, *vWB* von Willebrand molecule, *NET* neutrophil-extracellular-traps, *ADAMTS13* a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13

The ideal ICU anticoagulant should be administered parenterally, is short-acting and/or readily reversible, has a predictable effect in critically ill patients including those with (severe) renal function impairment, is easy to monitor and is of low-cost. Next to UFH, other antithrombotic strategies have previously been used in pMCS (Table 1). Anticoagulation in pMCS is mostly based on experience, rather than on evidence: prospective trials comparing UFH with other anticoagulants or (additional) anti-platelet therapies (e.g. acetylsalicylic acid, P2Y12-inhibitors or both) are lacking. Although pulmonary support strategies (venovenous ECMO) are generally run on prophylactic heparin levels whereas cardiac support (microaxial-flow pump, balloon pump, venoarterial ECMO) mostly on therapeutic levels, prospective trials assessing these optimal UFH levels are again non-existent [4, 13, 14]. Therefore, we strongly emphasize the need for further research towards identifying new anticoagulant molecules, tailored on the specific needs of an ICU patient and on the device itself. Also, we should move from a "one-size-fits-all" model to a more personalized approach (e.g. pharmacogenomic testing for clopidogrel versus newer antiplatelet agents) to substantially improve ICU patient care [15]. This would allow us to tackle an important hurdle in optimizing the safety and efficacy of pMCS therapy in critically ill patients.

The Holy Grail for patients on MCS is attenuating thrombosis without affecting haemostasis. Recent interest has focused on the contact pathway, particularly factor XII and XI, as potential new targets since both are strongly activated by highly negatively charged plastic surfaces. Experimental and clinical data illustrate the potential of FXII/XI inhibition to prevent thrombosis without increasing bleeding risk [16]. These findings identify FXII/FXI as interesting targets for the ICU population, but only if research and development for contact pathway-blocking agents would focus on intravenous molecules with short half-life and non-complex, linear pharmacokinetics.

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The author(s) declare that they have no conflict of interest.

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References

1. Abrams D, Garan AR, Abdelbary A, Bacchetta M, Bartlett RH, Beck J, Belohlavek J, Chen YS, Fan E, Ferguson ND, Fowles JA, Fraser J, Gong M, Hassan IF, Hodgson C, Hou X, Hryniewicz K, Ichiba S, Jakobleff WA, Lorusso R, MacLaren G, McGuinness S, Mueller T, Park PK, Peek G, Pellegrino V, Price S, Rosenzweig EB, Sakamoto T, Salazar L, Schmidt M, Slutsky AS, Spaulding C, Takayama H, Takeda K, Vuylsteke A, Combes A, Brodie D, International EN, The Extracorporeal Life Support O (2018) Position paper for the organization of ECMO programs for cardiac failure in adults. Intensive Care Med 44:717–729
2. Husain-Syed F, Ricci Z, Brodie D, Vincent JL, Ranieri VM, Slutsky AS, Taccone FS, Gattinoni L, Ronco C (2018) Extracorporeal organ support (ECOS) in critical illness and acute kidney injury: from native to artificial organ crosstalk. Intensive Care Med 44:1447–1459
3. Fisser C, Reichenbacher C, Muller T, Schneckenpointner R, Malfertheiner MV, Philipp A, Foltan M, Lunz D, Zeman F, Lubnow M (2019) Incidence and risk factors for cannula-related venous thrombosis after venovenous extracorporeal membrane oxygenation in adult patients with acute respiratory failure. Crit Care Med 47:e332–e339
4. Annich GM (2015) Extracorporeal life support: the precarious balance of hemostasis. J Thromb Haemost 13(Suppl 1):S336–342
5. Luyt CE, Brechot N, Demondion P, Jovanovic T, Hekimian G, Lebreton G, Nieszkowska A, Schmidt M, Trouillet JL, Leprince P, Chastre J, Combes A (2016) Brain injury during venovenous extracorporeal membrane oxygenation. Intensive Care Med 42:897–907
6. Cheng R, Hachamovitch R, Kittleson M, Patel J, Arabia F, Moriguchi J, Esmailian F, Azarbal B (2014) Complications of extracorporeal membrane oxygenation for treatment of cardiogenic shock and cardiac arrest: a meta-analysis of 1866 adult patients. Ann Thorac Surg 97:610–616
7. Protti A, Iapichino GE, Di Nardo M, Panigada M, Gattinoni L, (2019) Anticoagulation management and antithrombin supplementation practice during veno-venous extracorporeal membrane oxygenation: a worldwide survey. Anesthesiology.
8. Wong TE, Nguyen T, Shah SS, Brogan TV, Witmer CM (2016) Antithrombin concentrate use in pediatric extracorporeal membrane oxygenation: a multicenter cohort study. Pediatr Crit Care Med 17:1170–1178
9. Arnouk S, Altshuler D, Lewis TC, Merchan C, Smith DE, 3rd, Toy B, Zakhary B, Papadopoulos J (2019) Evaluation of anti-xa and activated partial thromboplastin time monitoring of heparin in adult patients receiving extracorporeal membrane oxygenation support. ASAIO J. https://doi.org/10.1097/MAT.0000000000001004
10. Panigada M, Iapichino GE, Brioni M, Panarello G, Protti A, Grasselli G, Occhipinti G, Novembrino C, Consonni D, Arcadipane A, Gattinoni L, Pesenti A (2018) Thromboelastography-based anticoagulation management during extracorporeal membrane oxygenation: a safety and feasibility pilot study. Ann Intensive Care 8:7
11. Kimmoun A, Oulehri W, Sonneville R, Grisot PH, Zogheib E, Amour J, Aissaoui N, Megarbane B, Mongardon N, Renou A, Schmidt M, Besnier E, Delmas C, Dessertaine G, Guidon C, Nesseler N, Labro G, Rozec B, Pierrot M, Helms J, Bougon D, Chardonnal L, Medard A, Ouattara A, Girerd N, Lamiral Z, Borie M, Ajzenberg N, Levy B (2018) Prevalence and outcome of heparin-induced thrombocytopenia diagnosed under veno-arterial extracorporeal membrane oxygenation: a retrospective nationwide study. Intensive Care Med 44:1460–1469
12. Selleng S, Selleng K (2016) Heparin-induced thrombocytopenia in cardiac surgery and critically ill patients. Thromb Haemost 116:843–851
13. Bein T, Zimmermann M, Philipp A, Ramming M, Sinner B, Schmid C, Muller T, Graf B, Schlitt HJ, Weber-Carstens S (2011) Addition of acetylsalicylic acid to heparin for anticoagulation management during pumpless extracorporeal lung assist. ASAIO J 57:164–168
14. Schellongowski P, Combes A, Moller MH (2018) Focus on extracorporeal life support. Intensive Care Med 44:2251–2253
15. Beitelshees AL, Voora D, Lewis JP (2015) Personalized antiplatelet and anticoagulation therapy: applications and significance of pharmacogenomics. Pharmgenomics Pers Med 8:43–61
16. Weitz JI (2016) Factor XI and factor XII as targets for new anticoagulants. Thromb Res 141(Suppl 2):S40–45
17. Krueger K, Schmutz A, Zieger B, Kalbhenn J (2017) Venovenous extracorporeal membrane oxygenation with prophylactic subcutaneous anticoagulation only: an observational study in more than 60 patients. Artif Organs 41:186–192
18. Sanfilippo F, Asmussen S, Maybauer DM, Santonocito C, Fraser JF, Erdoes G, Maybauer MO (2017) Bivalirudin for alternative anticoagulation in extracorporeal membrane oxygenation: a systematic review. J Intensive Care Med 32:312–319
19. Rouge A, Pelen F, Durand M, Schwebel C (2017) Argatroban for an alternative anticoagulant in HIT during ECMO. J Intensive Care 5:39
20. Ontaneda A, Annich GM (2018) Novel surfaces in extracorporeal membrane oxygenation circuits. Front Med (Lausanne) 5:321
21. Staudacher DL, Biever PM, Benk C, Ahrens I, Bode C, Wengenmayer T (2016) Dual Antiplatelet Therapy (DAPT) versus no antiplatelet therapy and incidence of major bleeding in patients on venoarterial extracorporeal membrane oxygenation. PLoS ONE 11:e0159973