What's new in anticoagulation on the ICU:

A future for contact pathway inhibition?

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Background

Bleeding and thrombotic complications are the main cause of morbidity and mortality in critically ill patients on the intensive care unit (ICU), receiving short-term percutaneous mechanical circulatory support (pMCS) by extracorporeal membrane oxygenation (ECMO), balloon pumps or microaxial flow pumps.[1] This is due to a bidirectional interplay of various factors influencing the haemostatic balance, including coagulopathy during critical illness, sepsis/inflammation, platelet consumption, hyperfibrinolysis, shear-induced acquired von Willebrand syndrome and direct contact pathway activation by the artificial surface of the pMCS-device.[2] To prevent thrombotic complications and device-induced localized intravascular coagulopathy (LIC), anticoagulation is indicated. Unfortunately, all currently available anticoagulants carry an increased bleeding risk, further jeopardizing patients' outcomes.[3] Therefore, the search for safer anticoagulants continues: the *holy grail* for the treatment of patients on pMCS – and by extension, all patients on anticoagulation – is to prevent thrombosis without affecting haemostasis, thus lowering the bleeding risk.[1]

The new kids on the block

Anticoagulant drug development started with the discovery of heparin and warfarin in the early 20th century. In recent decades, different parenteral and oral anticoagulants became available, almost all targeting the common pathway via effects on factor (F)IIa or FXa (except for citrate, which works through calcium chelation and pH alterations).[1, 4] Unfortunately, all anticoagulants are limited by their associated bleeding risk. Recently, new kids on the block have appeared, as contact pathway inhibitors targeting FXI and FXII made their entrance, endorsed by epidemiological data from genetic disorders concerning these coagulation factors.[4] Individuals with congenital FXI-deficiency rarely exhibit spontaneous major bleeding and have a lower risk of venous thromboembolism (VTE) and possibly acute myocardial infarction (AMI). They however, might exhibit a higher risk of minor bleeding after trauma or surgery, especially when the trauma involves mucosal tissues rich in fibrinolytic activity, such as the oropharynx/nasopharynx and genitourinary tract.[5] Particularly in individuals with severe (<1%) FXI-deficiency, a bleeding tendency due to reduced clot formation and increased susceptibility to fibrinolysis is demonstrated.[6] The latter may explain the usefulness of antifibrinolytic agents such as tranexamic acid here. While FXI-inhibition reduces (pathological) thrombus formation, the optimal percentage of FXI-inhibition should be sought, to counteract the risk for mucosal bleeds after trauma/instrumentation. Alternatively, patients with FXII-deficiency do not have a distinct clinical bleeding phenotype.[7] In both groups, the activated partial thromboplastin time (APTT) is markedly prolonged, whereas the prothrombin time (PT) is

not affected. The underlying mechanism by which FXI- and FXII-inhibition uncouples arterial and venous thrombosis from haemostasis in response to vascular injury, is that vascular injury does not necessarily involve amplification of thrombin generation via the contact/intrinsic pathway. Consequently, a contact pathway inhibitor could prevent thrombosis, without interfering with haemostasis.[4, 8] On the ICU, contact pathway inhibition could even be a double-win, given the fact that FXI and FXII are strongly activated by the negatively charged plastic surfaces of non-biological materials such as catheters, cannulas or devices, which are omnipresent in critically ill. Especially in patients on pMCS, contact pathway inhibition could be a real game changer, as it might tackle LIC and device-related thrombosis, without the increased major bleeding risk that accompanies other anticoagulants (Figure 1).[8]

The present and the future

Currently, three different classes of FXI- and FXII-inhibitors are under investigation in clinical trials: (I) FXI-antisense oligonucleotides (ASOs), leading to reduction in plasma levels of FXI by binding to messenger RNA and preventing translation; (II) monoclonal antibodies and (III) small molecules, both operating via binding of FXI/FXII. Additionally, natural inhibitors (derived from animals such as ticks) and aptamers are under development in a pre-clinical phase.[8] Promising data from phase-2 clinical trials have further supported the hypothesis that FXI-inhibition could reduce bleeding events in several clinical conditions including thromboprophylaxis in orthopaedic surgery, atrial fibrillation (AF), post-stroke, post-AMI and during haemodialysis.[9, 10] Importantly, these phase 2 studies were designed to assess safety (no increased bleeding risk), rather than efficacy (thromboprotection) and results are currently investigated in several phase-3 trials in VTE prophylaxis, AF, stroke and AMI.[8, 9]

Similarly, pre-clinical data exploring contact pathway inhibition as a strategy for anticoagulation during pMCS have shown promising results.[7] In particular, three FXII-targeted agents (two antibodies (3F7 [11] and 5C12 [12]) and one small molecule (FXII900 [13, 14]) seemed effective in thromboprotection in pre-clinical animal ECMO models (rabbits, mice and baboons). One small molecule FXI-inhibitor (EP-7041[15]) prevented increases in oxygenator resistance without impairing haemostasis in a canine ECMO model. Likewise, in a recent study, Tweddell and colleagues showed that FXI- or FXI-depletion using ASOs prolonged ECMO lifespan, limited thrombotic complications and prevented fibrinogen consumption in a rabbit model.[16] Interestingly, in this study, FXII-depletion also appeared to mitigate lung edema and haemorrhage while FXI-depletion did not. This might be due to the particular position of FXII at a crossroads between haemostasis and inflammation as it also activates

prekallikrein into kallikrein, resulting in complement activation and activation of the bradykinin pathway. Moreover, the authors showed in a series of *in-vitro* experiments that membrane oxygenator fibres could drive significant thrombin generation in a FXII- and FXI-dependent manner and that these ECMO-fibres increase thrombin generation triggered by tissue factor (TF). However, only FXI- and not FXII-elimination could completely prevent the thrombin generation by ECMO-fibres in presence of high concentrations of TF, suggesting that thrombin-mediated activation of FXI may overshadow the role of FXII in ECMO when TF levels are high (as is the case in critical illness or post-surgery). This highlights the important potential differences between FXI- and FXII-inhibition in the setting of ECMO. However, more studies are needed to better define the clinical implications of (combination of) therapies targeting FXI and/or FXII. [7]

Evidently, this promising (pre-)clinical evidence underscores the potential of this new strategy and has boosted the development and testing of new molecules in other settings such as end-stage renal disease or renal impairment and cancer.[8, 9] However, on the ICU, we need to step up our game. Indeed, currently, there are no reported planned or ongoing trials on FXII- or FXI-inhibition in the context of mechanical device associated thrombosis. This despite the additional theoretical advantages of contact pathway inhibition to combat against plastic surface induced consumption coagulopathy in this patient population with a huge bleeding phenotype, further endorsed by pre-clinical evidence. Particularly, on the ICU, intravenous agents are needed that are short-acting and have a predictable effect in critically ill patients with renal/hepatic disfunction. This makes several of the FXI- and/or FXII-targeted molecules that are currently under investigation not useful in the ICU due to a long onset time (e.g., ASO's) or prolonged effect (e.g., abelacimab). Therefore, this plea from the ICU-community to researchers and industry leaders in our field: let's move forward with research on FXI- and FXII-inhibition in the critically ill, since otherwise, we risk remaining stuck in the past, with the usage of heparin; and our patients, those at the highest risk, will not reap the potential important benefits.

Figures

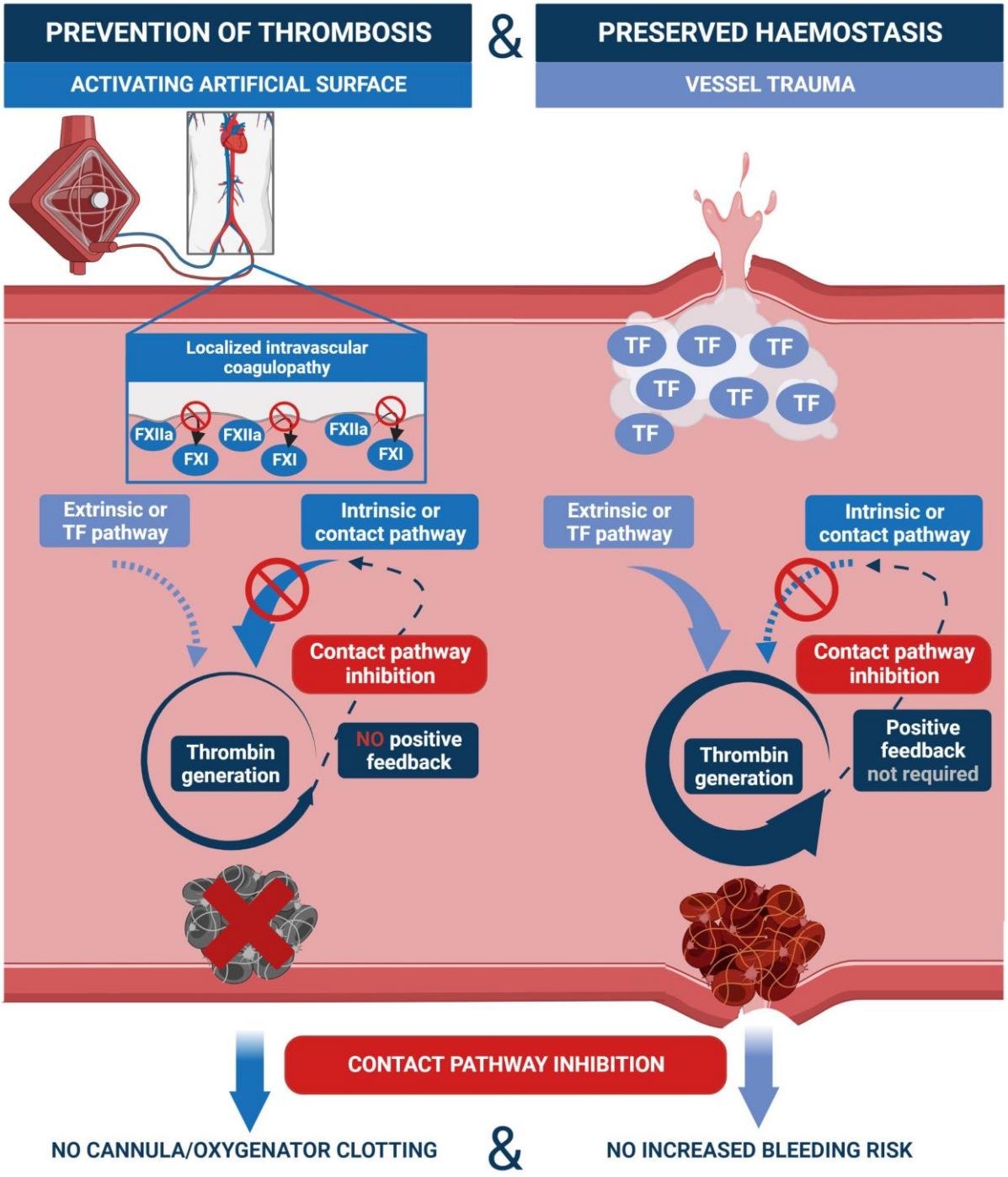

Fig. 1 Contact pathway inhibition is a promising target to interfere with pathological thrombus formation in the pMCS circuit, without affecting haemostasis Left part: Exposure of blood to artificial surfaces, such as catheters, haemodialysis or ECMO circuits in patients on the ICU, leads to extensive contact pathway activation and, consequently, thrombin generation and thrombus formation (localized intravascular coagulopathy (LIC). Right part: In case of vessel trauma, a large tissue factor and thrombin burst results in plug formation. Amplification via the contact pathway is not required and therefore contact pathway inhibition does not interfere with haemostasis. Consequently, contact pathway inhibition seems a logical approach to prevent clotting in this context, without interference with haemostasis.

References

1. Vandenbriele C, Vanassche T, Price S (2020) Why we need safer anticoagulant strategies for patients on short-term percutaneous mechanical circulatory support. Intensive Care Med 46:771–774. https://doi.org/10.1007/s00134-019-05897-3
2. Van Edom C et al (2023) In Press. Management of bleeding and hemolysis during percutaneous microaxial flow pump support: a practical approach. JACC Cardiovasc Interv
3. Vandenbriele C, Arachchillage DJ, Frederiks P, et al (2022) Anticoagulation for Percutaneous Ventricular Assist Device-Supported Cardiogenic Shock: JACC Review Topic of the Week. J Am Coll Cardiol 79:1949–1962. https://doi.org/10.1016/j.jacc.2022.02.052
4. Muscente F, De Caterina R (2023) The new in anticoagulation: factor XI inhibitors. European Heart Journal Supplements 25:B65–B68. https://doi.org/10.1093/eurheartjsupp/suad070
5. Gailani D, Bane CE, Gruber A (2015) Factor XI and contact activation as targets for antithrombotic therapy. J Thromb Haemost 13:1383–1395. https://doi.org/10.1111/jth.13005
6. Zucker M, Seligsohn U, Salomon O, Wolberg AS (2014) Abnormal plasma clot structure and stability distinguish bleeding risk in patients with severe factor XI deficiency. J Thromb Haemost 12:1121–1130. https://doi.org/10.1111/jth.12600
7. Goel A, Tathireddy H, Wang S-H, et al (2023) Targeting the Contact Pathway of Coagulation for the Prevention and Management of Medical Device-Associated Thrombosis. Semin Thromb Hemost. https://doi.org/10.1055/s-0043-57011
8. De Caterina R, Prisco D, Eikelboom JW (2023) Factor XI inhibitors: cardiovascular perspectives. Eur Heart J 44:280–292. https://doi.org/10.1093/eurheartj/ehac464
9. Harrington J, Piccini JP, Alexander JH, et al (2023) Clinical Evaluation of Factor XIa Inhibitor Drugs: JACC Review Topic of the Week. J Am Coll Cardiol 81:771–779. https://doi.org/10.1016/j.jacc.2022.11.057
10. Lorentz CU, Tucker EI, Verbout NG, et al (2021) The contact activation inhibitor AB023 in heparin-free hemodialysis: results of a randomized phase 2 clinical trial. Blood 138:2173–2184. https://doi.org/10.1182/blood.2021011725
11. Larsson M, Rayzman V, Nolte MW, et al (2014) A Factor XIIa Inhibitory Antibody Provides Thromboprotection in Extracorporeal Circulation Without Increasing Bleeding Risk. Sci Transl Med 6:1–13. https://doi.org/10.1126/scitranslmed.3006804
12. Wallisch M, Lorentz CU, Lakshmanan HHS, et al (2020) Antibody inhibition of contact factor XII reduces platelet deposition in a model of extracorporeal membrane oxygenator perfusion in nonhuman primates. Res Pract Thromb Haemost 4:205–216. https://doi.org/10.1002/rth2.12309
13. Wilbs J, Kong XD, Middendorp SJ, et al (2020) Cyclic peptide FXII inhibitor provides safe anticoagulation in a thrombosis model and in artificial lungs. Nat Commun 11:. https://doi.org/10.1038/s41467-020-17648-w
14. Naito N, Ukita R, Wilbs J, et al (2021) Combination of polycarboxybetaine coating and factor XII inhibitor reduces clot formation while preserving normal tissue coagulation during extracorporeal life support. Biomaterials 272. https://doi.org/10.1016/j.biomaterials.2021.120778
15. Pollack C V., Kurz MA, Hayward NJ (2020) EP-7041, a Factor XIa Inhibitor as a Potential Antithrombotic Strategy in Extracorporeal Membrane Oxygenation: A Brief Report. Crit Care Explor 2:e0196. https://doi.org/10.1097/cce.0000000000000196
16. Tweddell JS, Kharnaf M, Zafar F, et al (2023) Targeting the contact system in a rabbit model of extracorporeal membrane oxygenation. Blood Adv 7:1404–1417. https://doi.org/10.1182/bloodadvances.2022007586