Weber et al. | Frontiers in Medicine 2026 | Perspective

UFH Monitoring in ECMO & Cardiac Surgery

The search for a valid reference standard

Anti-Xa is useful - but not a universal reference standard

Extracorporeal circulation creates a moving target: PF4, protamine, assay design and clinical context can all change what the number means.

WHY THIS MATTERS

UFH remains the standard anticoagulant for cardiopulmonary bypass (CPB) and ECMO, where both under- and over-anticoagulation can have serious consequences.

- CPB: high-dose UFH
- ECMO: lower-dose, prolonged
- Post-protamine: residual UFH?

3 KEY POINTS

1 The reference standard is missing

ACT and aPTT are rapid and familiar, but they lack heparin specificity and standardisation. VET adds whole-blood context, but contact-pathway activation and limited CPB/ECMO validation mean it is not yet a reference standard.

Key insight: a more specific assay is not automatically a validated reference method.

2 Anti-Xa is assay-dependent

Dextran sulphate (DS) changes what anti-Xa can see; the same sample may read differently depending on reagent design, PF4 release, sample handling and protamine.

WITH DS

PF4 + UFH + PROT → **May overestimate**

DS may release bound heparin in vitro, creating an apparent high anti-Xa value.

WITHOUT DS

PF4 + UFH → **May underestimate**

PF4 released during sample handling can neutralise heparin before analysis.

Bottom line: anti-Xa assays are not automatically interchangeable across sites or studies.

3 Context changes interpretation

Monitoring is not one problem. Standard IV UFH, high-dose CPB, low/moderate ECMO and post-protamine residual UFH are distinct analytical scenarios.

- IV UFH without bypass
- High-dose CPB
- Low/moderate ECMO
- After protamine

Story of the science: the assay, reagent, sample path and clinical phase all shape the result.

Clinician takeaway

- Know your anti-Xa configuration: with or without dextran sulfate, and how samples are handled.
- Be cautious after protamine and during ECMO, where PF4/protamine complexes may distort anti-Xa results.
- Do not treat ACT, aPTT, VET or anti-Xa as a universal truth; interpret with patient context and local validation.

Ideas for further research

- Define an appropriate reference method for biologically active UFH in CPB/ECMO.
- Set acceptance criteria linked to thrombotic and hemorrhagic outcomes.
- Validate candidate lab and point-of-care assays in multicenter CPB/ECMO cohorts.
- Test CTAD/no-DS strategies and low residual UFH measurement after protamine.

TAKE-HOME MESSAGE

No single assay is currently a universally validated reference standard for biologically active UFH in CPB/ECMO. Monitoring needs scenario-specific validation.

Source: Weber CF, Zacharowski K, Calatzis A, Lindner ML. Monitoring unfractionated heparin in ECMO and cardiac surgery: the search for a valid reference standard. Frontiers in Medicine. 2026;13:1818646.