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LETTER TO THE EDITOR

"Finding a common definition of heparin resistance in adult cardiac surgery: Communication from the ISTH SSC Subcommittee on Perioperative and Critical Care Thrombosis and Hemostasis": comment from Mansour et al.

Dear Editor,

We commend the authors of the recent International Society on Thrombosis and Haemostasis Scientific and Standardization Committee Subcommittee on Perioperative and Critical Care Thrombosis and Hemostasis publication entitled "Finding a common definition of heparin resistance in adult cardiac surgery" for addressing the critical issue of heparin responsiveness specifically in cardiac surgery [1]. However, we question the significance and utility of this definition of "heparin resistance."

As Gouin-Thibault et al. [2] recently discussed, the term "heparin resistance," despite its widespread use in clinical practice, does not accurately describe the phenomenon of decreased heparin responsiveness. Beyond the general case of therapeutic dose unfractionated heparin (UFH), the anticoagulation for cardiopulmonary bypass (CPB), as currently practiced, involves 2 specific considerations: the use of high doses of heparin and the need to quickly achieve effective anticoagulation to align with surgical procedure timelines. While scenarios of decreased heparin responsiveness are frequently encountered during cardiac surgery with CPB, genuine heparin resistance, which would correspond to the failure of the drug to act on its target, simply does not exist [3]. We will first address the applicability of the proposed definition and will further discuss the concept of decreased heparin responsiveness later in this text.

The proposal to generalize a definition of decreased heparin responsiveness or heparin resistance, as outlined in this publication, not only seems challenging to implement but also lacks justification with robust data, beyond its arbitrary application in studies evaluating antithrombin supplementation.

First, as the authors described, the activated clotting time (ACT) target during CPB is poorly documented. This leads to several issues: 1) there is a high variability in practice among centers, with ACT targets ranging from 480 seconds down to 300 seconds; 2) using an ACT target of ≥480 seconds has not been linked to any proven clinical benefit; and 3) this target does not guarantee effective *in vivo* anticoagulation, as ACT above that target may be associated with markers of thrombin generation (such as thrombin–antithrombin complexes and fibrin degradation products) [4].

Second, ACT measurement is subject to significant biases, resulting in a poor correlation with heparin levels during CPB and potentially leading to divergent medical decisions regarding per-procedure heparinization, thereby questioning its very use in CPB [5]. In particular, significant variations in ACT results are observed depending on the devices used. A recent study evaluated 4 devices (Werfen Hemochron Signature Elite, Medtronic HMS Plus, Abbott i-STAT, and Helena Laboratories Cascade Abrazo) during CPB and demonstrated poor agreement, with up to 13% bias [6]. These measurement biases make the generalization of the proposed definition impossible, particularly in clinical research, where comparability between studies is crucial.

Third, the pharmaceutical formulation of UFH used (variability in chain lengths and proportion of molecules containing the AT-binding pentasaccharide sequence) also influences this definition. Significant variations in anticoagulation potency between different heparin brands have been demonstrated both *in vitro* and in clinical studies [7]. Again, this factor directly impacts the comparability between different centers.

Beyond the issue of the applicability of the proposed definition (ACT threshold not validated, different ACT devices used, and different heparin formulations administered), we wish to highlight the unresolved issues pertaining to decreased heparin responsiveness in the cardiac surgery setting. This phenomenon, often independent of antithrombin (AT) levels as noted by the authors, is frequently observed in complex perioperative settings involving inflammation, infection, or preoperative UFH use [8]. Consequently, discerning the direct causal effect of decreased heparin responsiveness on postoperative outcomes through observational studies is exceedingly challenging. Moreover, interventional data on heparin resistance primarily originate from randomized controlled trials assessing the

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benefit of AT supplementation on heparin responsiveness assessed by the ACT or total UFH dose administered, whereas:

1. As mentioned earlier, there is currently no evidence indicating that reaching a specific ACT target ensures clinical or biological effectiveness of anticoagulation. In addition, it remains unclear whether a decreased heparin responsiveness measured using ACT reflects inadequate *in vivo* anticoagulation. Shore-Lesserson et al. [9] found that during CPB, the occurrence of decreased heparin responsiveness measured by ACT response did not correlate with higher levels of thrombin generation markers (thrombin–antithrombin complexes and fibrin monomers) and went undetected by an alternative test to ACT, namely, the high-dose thrombin time.
2. Aside from increasing ACT values during CPB, AT supplementation has neither demonstrated clinical superiority nor improved anticoagulant effectiveness *in vivo* [10]. Aiming to increase the ACT response to heparin alone might therefore be of no clinical relevance.
3. Apart from the acknowledged importance of the time required for cannulation and initiation of CPB, the decision to increase UFH dosage to achieve a target ACT is often perceived as potentially risky. However, to date, there is no unbiased evidence to support those concerns, particularly regarding complex preoperative situations associated with decreased heparin responsiveness. For instance, the reality of heparin "rebound" and its potential risk of postoperative bleeding remains unproven. Conversely, some randomized controlled trials of AT supplementation have even suggested an increased risk of bleeding, despite being associated with the use of lower UFH dosage [10].

In conclusion, there is an urgent need for coordinated, high-quality research on heparin responsiveness and its management in cardiac surgery. The definition proposed by the authors is a step forward, yet it requires clinical validation taking into account the ACT device and activator used, UFH formulation administered, UFH levels effectively reached, and the effective control of coagulation activation as evidenced by markers of *in vivo* thrombin generation (eg, thrombin–antithrombin complexes and fibrin monomers), or, even better, an improvement in significant clinical outcomes (such as postoperative blood products use and surgical revisions for bleeding or intensive care unit length of stay). Furthermore, upcoming randomized controlled trials aimed at improving UFH responsiveness (eg, through AT supplementation) or evaluating nonheparin anticoagulation (such as direct thrombin inhibitors or factor XI/XII inhibitors) should include well-defined, up-to-date patient blood management and perioperative hemostasis protocols, along with a consensus on outcome measures. In this effort, the collaboration between anesthesiologist-intensivists and specialists in laboratory medicine is crucial.

AUTHOR CONTRIBUTIONS

All authors contributed to the drafting of the manuscript, approved the final work, and agree to be accountable for all aspects of the work.

DECLARATION OF COMPETING INTERESTS

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