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LETTER TO THE EDITOR

"Defining Heparin Resistance: Communication from the ISTH SSC Subcommittee of Perioperative and Critical Care Thrombosis and Hemostasis": comment from Gouin-Thibault et al.

We would like to greet the International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Committee (SSC) Subcommittee of Perioperative and Critical Care Thrombosis and Hemostasis communication titled "Defining Heparin Resistance" [1] in an attempt to clarify the issue and to briefly comment on a few selected aspects that we think deserve a deepening approach.

It does not come as a surprise that the survey found various definitions of "heparin resistance." However, do we need a threshold of unfractionated heparin (UFH) dose when one should carefully analyze the poor response to heparin to find the way to overcome it? As a matter of fact, when using a nomogram, whenever an increase in the dose is considered, one should ask oneself whether there is an actionable cause of poor response, making it possible to render UFH infusion more active.

Do we need to call "heparin resistance" an inadequate effect despite high doses of UFH? (which should be more specifically called resistance to UFH).

First of all, we are badly in need of a definition of "inadequate effect" (in the laboratory) and of "high dose." Historically, Levine et al. [2] considered that it could be problematic to increase UFH dose beyond 35 000 IU/d, notwithstanding body weight, because of the potential bleeding risk. The 35 000 IU/d threshold, widely used (see the Table in the study by Levy et al. [1]), has not been the basis of other prospective interventional studies. When activated partial thromboplastin time (APTT) was deemed insufficiently prolonged, the authors prospectively studied a switch to resorting to an anti-Xa assay (specifically Stachrom, Stago) and pointed out that the switch reduced, to some extent, heparin dosage escalation. The specific type of anti-Xa assay is not a trivial point since not all anti-Xa assays are equal [3]. Stachrom is a 2-stage assay (first, inhibition of added Xa, second, measurement of residual Xa) that is nowadays seldom used due to practical and cost issues; however, there are theoretical considerations for it being a better approach than widely used 1-stage, so-called competitive assays (competition for Xa between heparin-boosted antithrombin and the synthetic, chromogenic substrate of Xa).

More specifically, regarding the crucial point of laboratory response, it is important to understand the differences and limitations (both shared and specific) of laboratory tests for monitoring therapeutic heparin. We focus here on APTT and anti-Xa assays (both of which should be plural since there are many variations of them). Hence, the survey's single question about how therapeutic UFH is monitored in the laboratory nowadays is too restrictive to precisely and usefully depict the actual current practices and why they are so variable, being poorly supported by strong evidence and sound guidance. Here as well, it does not come as a surprise that respondents were roughly equally divided between APTT and anti-Xa assays; some of them using both without any explanations, while it could be the reasonable approach. To fully appreciate the differences between the 2 kinds of tests, the least here would be to point out that "resistance" is much less frequent when resorting to an anti-Xa assay [2] and more so if it is performed with dextran sulfate and to explain why it is so. It remains to be proven, however, that this is the best clinical option. The issue of the shortcomings of currently available tools to monitor heparin therapy in the laboratory deserves a thorough document duly updated [4]. We need in-depth and worldwide information, as soon as possible, on that point, including the following: (i) the status of knowledge by the persons in charge of the differences among anti-Xa assays and of the way the 0.3 to 0.7 IU/mL therapeutic range was elaborated and (ii) the way the specific assay was chosen locally and how it was successfully implemented in daily practice, depending on the heterogeneous clinical settings (acute venous thromboembolism, acute limb ischemia, acute coronary syndrome, mechanical circulatory support [extracorporeal membrane oxygenation and left ventricular assist device], endovascular/intracardiac procedures, and cardiovascular surgery).

Second, the concept of resistance must be challenged. *Stricto sensu* resistance would mean that the drug could not act on its very target in

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coagulation, which for heparins is antithrombin (with great amplification of its inhibitory power against thrombin); in that case, little or even nothing could be expected by increasing the dose. Such resistance simply does not exist, even when antithrombin is (partially) deficient, whatever the cause of the deficiency. An attenuation of anticoagulation is very plausible, although it can be overcome by increasing the dose of UFH. Thus, resorting to supplementation with antithrombin or to a direct (not antithrombin-mediated) inhibitor of thrombin should not, in our opinion, be the obligatory solution when facing such a scenario.

The debate on whether the variability in the response to aspirin could result in genuine resistance eventually ended after long discussions and a lot of confusion [5]. Resistance was dismissed since no sequence variations in *COX-1* that could hinder the acetylation of the COX-1 enzyme encoded by that gene were ever identified [5]. By analogy with aspirin, when facing a poor laboratory response to UFH despite adequate increases in dose, it would be useful to have a simple *in vitro* test to check the individual response to spiked UFH and to dissect out the mechanisms.

Meanwhile, a systematic analysis of factors of poor response should be both logical and practical. In short, pharmacokinetics should be considered first, followed by pharmacodynamics as follows.

PHARMACOKINETIC CAUSES

Does UFH readily reach its target? Particular attention should be paid to platelet factor 4 since its large pool in the platelet alpha-granules can efficiently neutralize heparin. Platelet factor 4 can be released *in vivo* in case of intense platelet activation, for example, cardiac surgery, heparin-induced thrombocytopenia, or *in vitro*, from the very beginning of blood collection to the time of testing. To address that vital point, one should consider ways to prevent it, such as resorting to citrate-theophylline-adenosine-dipyridamole tubes—the theophylline-adenosine-dipyridamole mixture opposes platelet activation [6]. The citrate-theophylline-adenosine-dipyridamole tubes were ignored in the SSC communication, while it could have been a starting point for further collaborative studies about the interest of such tubes. Moreover, checking the preparation of the UFH diluted solution for infusion and the intravenous access lines as well as potential drug–drug deleterious interactions (eg, andexanet, which was cited in a former good review [7] on the topic by 2 of the authors of the ISTH communication) that deviate heparin from antithrombin is good clinical practice.

PHARMACODYNAMIC CAUSES

What makes the coagulation system poorly sensitive to an adequate acceleration of antithrombin action on thrombin? This refers to the issue of hypercoagulability and inflammation.—of note, this can be suspected only if APTT is (also) performed (a cause of dissociation between the 2 assays: anti-Xa levels are in the therapeutic range, but APTT is not sufficiently prolonged) [8].

At last but not at least, poor laboratory response should not be confused with clinical failure: worsening of thrombosis, pulmonary embolism, and early recurrence are not necessarily linked to or fully explained by poor laboratory response. The clinical outcome is not solely determined by the pharmacodynamic response to UFH as assessed by currently available tools, and this highlights the shortcomings of laboratory tests, more so for the anti-Xa assays since they focus in a very artificial manner on the target, antithrombin, without taking into account the whole process of the coagulation system.

Of note, 3 colleagues among the authors of the ISTH SSC communication recently acknowledged they totally differed in their appraisal of the scenario of "heparin resistance" [9]. Notwithstanding, they kept using the concept of "heparin resistance," albeit somewhat reluctantly in the ISTH communication, to advocate for prompt consideration of switching to a direct thrombin inhibitor, a proposal we consider both quite erroneous (see above about antithrombin) and dangerous—how many physicians are familiar and at ease with its use and laboratory monitoring?

We fully agree on the following points of the ISTH SSC Subcommittee of Perioperative and Critical Care Thrombosis and Hemostasis communication: (i) the term "heparin resistance" is commonly used without a specific definition or clarity; (ii) neither the 2016 nor 2021 updates of the American College of Clinical Pharmacy guidelines mention "heparin resistance"; (iii) future publications addressing the issue of "poor laboratory response" to UFH should include weight-based definitions, monitoring assay, and target level.

In brief, we believe that there is no need to search for a consensus definition of something that does not exist, but rather one should vigorously promote weight-adjusted nomograms [10], update those already available, and expand their validation; this should be the goal of ISTH and national professional groups (specialists in laboratory medicine and clinicians together).

With the use of a weight-based nomogram, prompt recognition of a dimed response to UFH is possible and should promptly lead to a systematic analysis in order to identify the root cause or the causes (since there are often more than one) and decide whether or not the dose should be (further) increased, complemented if deemed appropriate with an additional bolus, in order to expedite the achievement of the desired anticoagulation.

AUTHOR CONTRIBUTIONS

T.L. wrote the first draft of the manuscript. I.G.-T. and F.M. performed extensive critical revision, reviewed the manuscript, and approved the submitted version.

DECLARATION OF COMPETING INTERESTS

There are no competing interests to disclose.

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