Heparin-Induced Thrombocytopenia: An Iceberg Rising

To paraphrase William Thomson (1824-1907), we know what we can measure. For translational and biomedical researchers, this aphorism continually reasserts itself. Heparin-induced thrombocytopenia (HIT) was first recognized by Weismann and Tobin1 almost 50 years ago, but at that time, they did not measure the platelet count and did not associate the thrombocytopenia with the thrombotic complications. Instead, they described heparin-associated arterial emboli that had an unusual flesh- or salmon-colored gross appearance and, on microscopic analysis, were virtually devoid of red blood cells. Their original observations were quickly followed by a series of case reports documenting that the platelet count decreased at the time of the thrombosis. Particular credit should go to Rhodes et al2 who, in 1973, suggested an immunological cause for the disorder. These investigators laid the groundwork for testing for HIT when they observed that serum from patients with HIT could cause aggregation of platelets. However, the ability to confirm the diagnosis serologically would not occur until 1986 when Sheridan et al3 developed a diagnostic test for HIT. This biological assay measures heparin-dependent activation of platelets across a series of heparin concentrations. Refinements in this test followed, but it continues to be the gold standard for diagnosing HIT with an exceptionally high sensitivity (some say 100%) but a lower specificity.

The ability to diagnose HIT in a routine clinical laboratory followed the work of Amiral et al.4 These researchers identified that the target of the antibody was platelet factor 4 (PF4), an observation that led to a rapid enzyme immunoassay to diagnose the disorder. To borrow again from Thomson, when scientists could “measure” HIT, the knowledge regarding the disorder expanded rapidly. It was no longer thought to be a rare disorder characterized by pearly white or “salmon-colored” arterial clots.1,5 Studies quickly indicated that HIT was a common and intensely prothrombotic disorder with venous thrombi dominating over arterial thrombi and the localization of the thrombus being related to the site of underlying vascular damage or stasis.6,8 Serologic tests also led to clarification of the pathophysiology of thrombotic complications of HIT: IgG-PF4-heparin immune complexes bind to platelet Fc receptors, which release intensely procoagulant platelet microparticles.9

The wide availability of assays for HIT both enlightened and confounded. The major confounding factor was a series of interlocking observations from several laboratories.10-15 These observations can be summarized as follows: (1) virtually every patient with HIT has a positive serologic test result for HIT; (2) the frequency of HIT is related to the type of heparin preparation (unfractionated being greater than low-molecular-weight heparin) and the clinical situation (orthopedic surgery has a higher risk of HIT than many other surgical/heparin exposures); and (3) patient populations exposed to heparin will have differing frequencies of positive serology: invariably there are more patients with a positive serology and no decrease in the platelet count (possible false-positive test) than patients with a positive serology and a decrease in the platelet count with or without thrombosis (HIT).

About 10 years ago, these observations led us to propose an “iceberg” model of HIT. We conceptualized HIT as an iceberg with most of the iceberg being submerged below the water. The largest component of the iceberg represented patients with a positive serologic test result for HIT but no decrease in platelet count or clinical evidence of HIT. We postulated that such patients did not have clinical HIT. A smaller proportion of the iceberg (conceptualized as that being above the water) represented patients who had a decrease in platelet count plus positive serology but no thrombotic complications. The tip of the iceberg was composed of patients with positive serology, a decrease in the platelet count, and thrombotic complications (sometimes termed heparin-induced thrombocytopenia and thrombotic syndrome).

Our iceberg model implicitly suggested that most patients who develop positive serology without a decrease in platelet count would remain well. Hence, the positive serology in these patients was false-positive for a clinically important event. Intuitive reasons support such a hypothesis. For example, we and others have observed variability in the frequency of “false-positive” serology. About 30% to 50% of patients who undergo coronary artery bypass grafting (CABG) will develop positive serology,14,15 yet most of these patients will not have a decrease in the platelet count, other than the CABG-induced thrombocytopenia, and most do not have thrombosis. Although the relative ratio of false-positive serology is lower in patients undergoing orthopedic surgery treated with heparin, the same general observation occurs: more patients will have a false-positive than a true-positive serologic assay for HIT.14

Address correspondence to John G. Kelton, MD, McMaster University, 1200 Main St W, Rm 2E1, Hamilton, Ontario, Canada L8N 3Z5 (e-mail: keltonj@mcmaster.ca).

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In general, this model has proved true. Again, reflecting on the iceberg metaphor, positive serology without a decrease in platelet count (the iceberg below the waterline) was not clinically relevant. But, like a true iceberg (in which the submerged portion is the largest and most dangerous), this analogy can be challenged. For example, Williams et al reported, in a prospective study, that patients with acute coronary syndrome who had anti-PF4-heparin antibodies had a greater 30-day risk of death or myocardial infarction (odds ratio, 4.0; 95% confidence interval, 1.4-11.3; \( P = .0093 \)) and myocardial infarction (odds ratio, 4.6; 95% confidence interval, 1.4-15.0; \( P = .0108 \)) compared with patients who did not have antibodies.

In the current issue of *Mayo Clinic Proceedings*, Peña de la Vega et al extend these observations. These researchers performed a prospective study in patients undergoing hemodialysis who had frequent exposures to heparin. Only 1 of 57 patients (1.8%) developed clinical HIT, which is consistent with other investigators who found a similar low frequency of HIT in such patient populations. However, the study by Peña de la Vega et al is noteworthy for the observation that patients in the highest tertile of HIT antibodies but with no decrease in platelet count (what traditionally would have been termed a *false-positive test*) had a 2.5-fold greater risk of death during follow-up (median, 798 days) than those in the lower tertiles (\( P = .03 \)).

The study by Peña de la Vega et al also highlights some of the intricacies of the laboratory diagnosis of HIT. They used an enzyme-linked immunosorbent assay (GTI-PF4) that will detect IgG, IgA, and IgM antibodies to immobilized PF4-polyanionic heparin substitute complexes; however, only the G subclass is thought to be pathogenic. As a result, this assay will often detect antibodies that are not implicated in HIT, thus lowering the specificity of the test. In addition, a heparin inhibition step is generally required to confirm that the antibody detected is specific for PF4-heparin; without this confirmatory step, the specificity of the test is reduced even further.

The titer of PF4-heparin antibodies may provide useful diagnostic information. Patients with high titers of antibody more often have a positive platelet activation assay and a greater likelihood of actually having HIT. The presence of PF4-heparin antibodies has been shown to correlate with thrombotic complications and in vivo activation of the coagulation and fibrinolytic systems in patients with suspected HIT. The corollary to high-titer antibodies is “subclinical HIT,” that is, PF4-heparin antibodies found in isolation, usually in low titers. Increasing evidence suggests that such antibodies might cause disease. Finally, HIT antibodies may be more or less likely to cause HIT, depending on the patient population. Cardiac surgical patients are far more likely to develop HIT antibodies than orthopedic surgical patients; however, orthopedic patients are more likely to develop clinical HIT. Perhaps the importance of isolated HIT antibodies also depends on the population, and patients with end-stage renal disease undergoing hemodialysis may be particularly prone to the clinical sequelae because of increased inflammation, endothelial dysfunction, and increased platelet activation.

The study by Peña de la Vega et al adds to the evidence that HIT antibodies, even in the absence of overt HIT, may be pathogenic. However, these conclusions must be interpreted with caution because they are derived from results obtained outside of the test’s reference range, and important confounders such as chronic inflammation have not been excluded. In any event, perhaps the HIT “iceberg” is starting to rise and what was previously thought to be a false-positive HIT test result could, in certain patient populations, cause thrombosis—or perhaps the water is still too murky for us to see clearly below the surface.

Donald M. Arnold, MD
John G. Kelton, MD
Department of Medicine
Michael G. DeGroote School of Medicine
McMaster University
Hamilton, Ontario