Thoracic and Cardiovascular Surgery

Clinical Presentation and Laboratory Diagnosis of Heparin-Induced Thrombocytopenia

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Heparin-induced thrombocytopenia (HIT) type II is an immune mediated reaction in which pathologic antibodies develop to a complex composed of heparin and the platelet-derived alpha granule protein, platelet factor 4 (PF4). HIT must be recognized quickly so as to eliminate all heparin exposure from a patient's clinical care. Thrombosis (HITT) may accompany thrombocytopenia resulting in limb and life-threatening complications. Despite a higher incidence of subclinically detectable heparin-PF4 antibody formation in the cardiac care setting, the development of the full clinicopathologic syndrome occurs in approximately 2% to 3% of patients, similar to the incidence in other clinical scenarios.
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Heparin-induced thrombocytopenia (HIT) is an immune-mediated response to heparin that curiously causes thrombi. Heparin is used in more than 12 million patients per year,[1] and can cause two forms of thrombocytopenia. HIT type I is a short-lived nonimmune, mild thrombocytopenia usually occurring within the first few hours to days of heparin therapy. HIT type I is a self-limiting clinical diagnosis that does not result in abnormal platelet activation assay results. This review is primarily concerned with immune-mediated thrombocytopenia, or HIT type II, which occurs in at least 1% to 3% of patients receiving unfractionated heparin and in approximately 0.5% to 0.7% of patients receiving low molecular weight heparin. Although thrombocytopenia typically suggests a risk for hemorrhage, patients with HIT are at risk for thrombosis and rarely bleed.

Pathophysiology

To understand the diagnosis of this syndrome, a brief review of the pathophysiology is required. The alpha granules within platelets contain platelet factor 4 (PF4), a cationic 70 amino acid chemokine of the C-X-C subfamily. Platelets secrete PF4 upon activation. Due to its charge and structure, tetramers of PF4 readily bind to negatively charged heparin. Once PF4 is bound to heparin, it undergoes a structural change that occasionally induces an immune response (see Fig. 1).

In some patients, large complexes of antibodies directed against heparin-bound PF4 accumulate on the surface of platelets. At times, these anti-PF4 immunoglobulins will bind to the Fc receptor also present on the platelet surface. This event leads to platelet activation, release of more PF4, and a cycle of events that results in stimulation of more platelets as well as ultimately activation of the coagulation cascade. Therefore, four components are required for the development of this syndrome: (1) heparin, (2) platelets, (3) PF4, and (4) anti-PF4 antibodies.

Clinical Presentation

Absolute or Relative Thrombocytopenia

HIT should be suspected in any patient who develops thrombocytopenia (<150,000 μL) while on heparin therapy. It is important to note that the normal range for platelet counts varies widely (150,000 μL to 450,000 μL), so some patients may have a substantial decrease in their platelet count but remain within in the normal range. Therefore, a >50% decrease in the platelet count should raise a suspicion for this syndrome. HIT should also be suspected in any patient who develops a thrombotic event while on heparin therapy. Importantly, HIT can occur with exposure to any form of hep-

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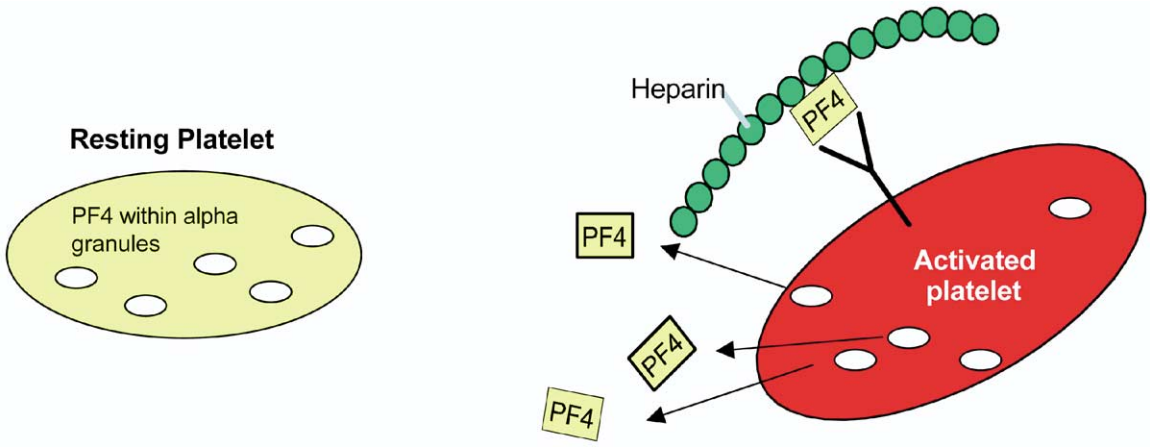

Figure 1 Pathophysiology of HIT. The pharmacologic agent heparin can bind to platelet factor 4 (PF4), a protein secreted from platelets on activation. Once bound to heparin, PF4 undergoes a conformational change that in some patients induces an antibody-mediated immune response. Large complexes of immunoglobulin, heparin and PF4 can accumulate on the platelet surface and stimulate the platelet by the Fc portion of the antibody interacting with the platelet's FcγRII receptor. Once activated, the platelet sheds highly procoagulant microparticles that contribute to the activation of the coagulation cascade. In addition, the activated platelets secrete more PF4 to propagate the process. (Color version of figure is available online at http://www3.us.elsevierhealth.com/semtcvs/.)

arin, through various routes of administration, and in multiple clinical scenarios.[2] Although HIT is more common in patients receiving intravenous heparin, HIT may even occur in patients receiving heparin flushes, hemodialysis, and heparin-coated catheters.[3]

Timing Is Everything

Frequently patients with this syndrome have multiple potential causes for thrombocytopenia; therefore it is important to exclude other explanations including medications or infections. Large retrospective studies of HIT have suggested that the timing of the onset of thrombocytopenia relative to the initial heparin exposure is useful to help establish, or exclude, this diagnosis. Type II HIT usually begins between 4 and 14 days after the start of heparin treatment in patients who have not received heparin in the last few months.[4] This is consistent with the time period for most immune responses, approximately one week after exposure to an antigen.

Occasionally, HIT can occur in as few as 12 hours after the intiation of heparin therapy in patients who have been recently exposured to heparin.[4] This "rapid-onset" HIT is due to preexisting anti-PF4 antibodies that developed during the prior heparin exposure (see above). It bears mentioning that several groups have described patients who appeared to develop thrombocytopenia weeks after discontinuation of heparin (so called "delayed-onset" HIT).[5,6] However, it is unclear whether these patients truly had HIT that began weeks after heparin therapy, or whether they merely had the syndrome diagnosed after a long period of time.

A Hypercoagulable Disease

Since platelets are consumed in HIT as they become activated, the clinical presentation of this syndrome is thrombocytopenia. However, it is unusual for the thrombocytopenia to actually cause bleeding. Instead, HIT is a highly prothrombotic disease (Table 1). It is estimated that new thromboses (HITT) occur in as many as 50% of patients with HIT.[7] For patients with thrombosis, up to 21% of patients will undergo limb amputation, and up to 30% will die.[8,9] Consequently, the costs associated with the complications of HIT are substantial.

It should be realized that the incidence of HIT-related clinical events is greatest immediately after diagnosis.[10] More importantly, clinical studies report that cessation of heparin alone frequently fails to prevent thromboses or the development of new thrombotic events.[7,11,12] In HITT, both venous and arterial thromboses are common and may occur just after the thrombocytopenia.

HIT in Cardiovascular Disease

HIT more commonly occurs in the venous than arterial system (ratio of 3 to 4:1). However, cardiovascular patients in whom there often exists a nidus for thrombus formation, the venous to arterial ratio of complications occur at a ratio of 0.3 to 0.7:1. The presence of in-dwelling catheters also influences this balance as the arterial thrombosis most frequently happens in the geographical context of a punctured artery.[13]

Because of its reliable and rapid reversibility, unfractionated heparin is usually preferred for many cardiovascular procedures. Preexisting damaged vessels provoke the heparin-PF4 antibody development (up to 70%) as manifested by the elevated level of detectable antibodies in this patient pop-

Table 1 Incidence of Sequelae of Untreated HIT

New thromboses	10–52%
Amputation	~20%
Death	~30%
Bleeding	Rare