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Heparin-Induced Thrombocytopenia in Cardiac Surgery Patients

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Abstract

Heparin-induced thrombocytopenia (HIT) is a prothrombotic disorder mediated by platelet-activating antibodies that target complexes of platelet factor 4 (PF4) and heparin. Because nearly all patients undergoing cardiopulmonary bypass (CPB) are exposed to heparin and experience a postoperative platelet count fall, it is not surprising that HIT is commonly suspected in this population. However, the incidence of HIT in cardiac surgery patients who receive intraoperative and postoperative unfractionated heparin is much lower than the incidence of suspected HIT, being approximately 1 to 2%. Clinical diagnosis may therefore be particularly challenging because of the need to distinguish the common platelet count fall associated with CPB and surgery from the much less common platelet count fall associated with HIT. A biphasic platelet count pattern is characteristic of HIT in this setting. Laboratory diagnosis is also difficult because of the high frequency of anti-PF4/heparin antibody seropositivity after cardiac surgery in patients without HIT. A unique aspect of management in the cardiac surgery setting is selecting an anticoagulant for intraoperative use in patients with a history of HIT who require cardiac surgery. In this article, we review the epidemiology, clinical diagnosis, and laboratory diagnosis of HIT in cardiac surgery patients and present a conceptual framework for selecting intraoperative anticoagulation in patients with a history of HIT.

Keywords

cardiac surgery; cardiopulmonary bypass; heparin; heparin-induced thrombocytopenia; thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is a feared complication of heparin exposure caused by platelet-activating IgG antibodies that recognize multimolecular complexes of platelet factor 4 (PF4) and heparin.^{1,2} Major clinical manifestations include a fall in platelet

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count and perhaps counterintuitively a profound hypercoagulable state, which may lead to limb- or life-threatening thrombosis. Left untreated, the initial rate of thromboembolism, amputation, and death in patients with acute HIT is 6.1% per day.³ Diagnosis rests on a combination of clinical assessment and laboratory demonstration of anti-PF4/heparin antibodies that activate platelets in a heparin-dependent manner.⁴ Treatment involves discontinuation of heparin and initiation of a nonheparin anticoagulant.⁵

Nearly all patients undergoing cardiac surgery receive intraoperative heparin and experience a fall in platelet count after surgery. It is thus not surprising that the specter of HIT is commonly raised in this population. Several factors conspire to make diagnosis especially challenging after cardiac surgery, including the need to distinguish the common platelet count fall associated with surgery and cardiopulmonary bypass (CPB) from the less common fall associated with HIT, the frequency of digital ischemia, and the high rate of anti-PF4/heparin antibody seropositivity. Management in the cardiac surgery setting also presents unique challenges, particularly decisions about intraoperative anticoagulation in patients with a history of HIT. Herein, we review the epidemiology of HIT after cardiac surgery, discuss special considerations regarding clinical and laboratory diagnosis in this setting, and propose a conceptual framework for selecting intraoperative anticoagulation in patients with a history of HIT who require cardiac surgery.

Epidemiology

HIT occurs in less than 0.1 to 5% of patients exposed to heparin, depending on the patient population, type of heparin, and duration of heparin exposure.⁶ In general, HIT is more prevalent among surgical than medical patients and more common with unfractionated heparin (UFH) than with low-molecular-weight heparin (LMWH).^{7,8} Among certain surgical populations such as orthopedic surgery and trauma patients, the prevalence of HIT has probably declined as UFH has been largely replaced with LMWH in countries where LMWH is available.^{9,10} HIT remains relatively common after cardiovascular surgery, however, possibly because of the continued use of intraoperative UFH.

Prospective and retrospective studies of cardiac surgery patients receiving intraoperative UFH and postoperative UFH thromboprophylaxis suggest an overall incidence of HIT of 1 to 5%.^{8,11–13} Studies differed in how HIT was ascertained and diagnosed, potentially accounting for the variability in incidence estimates.

Two groups have examined whether replacement of postoperative UFH with LMWH after cardiac surgery reduces the risk of HIT. Pouplard and colleagues conducted a cohort study of 437 and 1,874 cardiac surgery patients who received postoperative UFH and LMWH, respectively.¹¹ The incidence of HIT was significantly greater in the UFH cohort (2.5 vs. 0.4%, $p < 0.0001$), but baseline differences in the two treatment groups in this nonrandomized study preclude inferences about causation.¹¹ Selleng and coworkers compared UFH and LMWH after cardiac surgery in a prospective cohort study.¹⁴ HIT occurred in 0.9% of patients in the UFH group and 0% in the LMWH group ($p = 0.23$). Interpretation of these results is potentially confounded by indication bias. UFH was administered (in therapeutic doses) only in patients who had an indication for therapeutic

intensity anticoagulation, whereas prophylactic intensity LMWH was given to all other patients.¹⁴

Most epidemiologic data on HIT in cardiac surgery have been collected in patients undergoing coronary artery bypass grafting (CABG) or valve surgery on CPB. There is less information about the risk of HIT with off-pump or other types of cardiac surgery. Several small studies demonstrate a high rate of heparin-dependent platelet-activating antibody formation (7.8–10.6%) after ventricular assist device implantation,^{15–17} though the incidence of clinical HIT in this setting is not well established. The possibility of HIT is frequently raised in patients on extracorporeal membrane oxygenation (ECMO), but data on the incidence of HIT in this group are lacking.¹⁸ In a single center, 22 of 165 (13.3%) patients were classified as having HIT after cardiac transplantation. This figure is probably an overestimate of the true incidence of HIT because not all cases were confirmed with a functional assay.¹⁹

Taken together, published data suggest that the incidence of HIT in adults undergoing CABG or valve surgery on CPB who receive intraoperative UFH and postoperative UFH thromboprophylaxis is on the order of 1 to 2%. More data are needed to determine whether replacement of postoperative UFH with LMWH reduces the risk.

Diagnosis

Although the overall incidence of HIT in cardiac surgery patients is on the order of 1 to 2%,^{8,11,12} suspected HIT in this population is far more common. In contemporary series of consecutive patients referred for HIT laboratory testing because of suspected HIT, 36 to 51% were drawn from the cardiac surgery population.^{20–24}

Heparin use is nearly universal in cardiac surgery patients and nearly all patients experience a platelet count drop following CPB.²⁵ Thus, it is of little surprise that HIT is frequently considered in the context of cardiac surgery. Physicians must therefore rely on a combination of clinical assessment and laboratory testing to differentiate the 1 to 2% of patients with true HIT from the far more numerous patients with thrombocytopenia due to other etiologies.

Clinical Diagnosis

Estimation of the clinical or pretest probability of HIT relies on careful assessment of various clinical features including thrombocytopenia, the timing of the platelet count fall relative to heparin exposure, the presence of thrombosis or other sequelae of HIT, and the likelihood of other causes of thrombocytopenia. As detailed below, each of these features warrants special consideration in cardiac surgery patients.

Timing—In typical-onset HIT, the platelet count fall characteristically begins 5 to 10 days after the immunizing heparin exposure. In cardiac surgery patients, the platelet count fall due to HIT must be differentiated from the fall due to surgery and CPB (after CPB, the platelet count falls by an average of 40%, nadirs 48–72 hours after surgery, and then begins to recover).¹¹ A second fall in the platelet count between postoperative days 5 and 10 is highly

suspicious for HIT. This biphasic pattern is illustrated in the patient example in Fig. 1. In contrast, a platelet count that falls immediately after CBP and remains low without recovery is rarely attributable to HIT and is much more likely to be due to other causes such as infection.²⁶ In a prospective study of 581 cardiac surgery patients, all 3 patients with a biphasic platelet count profile (Fig. 1) and none of 25 patients with early-onset and persistent thrombocytopenia were found to have HIT.¹⁴

In patients with preexisting anti-PF4/heparin antibodies, reexposure to heparin may result in an immediate fall in platelet count or so-called rapid-onset HIT. Such patients have invariably had exposure to heparin within the recent past, usually within the last 30 days.²⁷ It is not uncommon for cardiac surgery patients to have a history of recent heparin exposure (e.g., during preoperative cardiac catheterization). The possibility of rapid-onset HIT must therefore be considered in such patients. However, clinical experience suggests that the UFH administered during cardiac surgery is more likely to be immunizing than preoperative heparin exposure. This explains why early-onset and persistent thrombocytopenia after cardiac surgery is seldom associated with HIT, even among patients with a history of recent heparin exposure.¹⁴

Thrombocytopenia—Percentage fall in platelet count is measured from the peak platelet count after heparin exposure to the nadir platelet count. The platelet count characteristically declines by 50% in HIT, although approximately 10% of patients experience a more modest fall of 30 to 50%.²⁸

The nadir platelet count need not fall below the conventional laboratory threshold for thrombocytopenia of $150 \times 10^9/L$. This point is particularly important to bear in mind in the evaluation of surgical (including cardiac surgery) patients for HIT. Following cardiac surgery, the platelet count typically surpasses the preoperative baseline on postoperative days 5 to 7, peaks at approximately day 14, and remains elevated above baseline for several weeks before returning to preoperative levels.¹¹ A patient who develops HIT during the period of postoperative thrombocytosis may experience a significant decline (50%) in platelet count that does not fall below $150 \times 10^9/L$.²⁹

Thrombosis and Other Manifestations—Thromboembolism occurs in 30 to 50% of patients with HIT and may be venous or arterial.^{30–32} Although lower extremity deep vein thrombosis and pulmonary embolism are the most common thrombotic manifestations of HIT, there is a predominance of arterial thromboembolism, most commonly involving the extremities, in cardiac surgery patients.³³

Digital ischemia is a frequent finding among cardiac surgery patients and may be taken as a sign of HIT. Although HIT may cause small vessel thromboembolism and digital ischemia, other etiologies such as hypotension, vasopressors, and underlying peripheral arterial disease are probably more common in this setting.⁶

Other Causes of Thrombocytopenia—A deliberate assessment of the likelihood of other causes of thrombocytopenia should be undertaken in all patients with suspected HIT. As noted previously, after CPB the platelet count falls by a mean of 40% over the ensuing 48

to 72 hours. A lesser fall is expected after off-pump surgery.²⁵ In one study, intra-aortic balloon pump use resulted in a mean fall in the platelet count of 63% over 4 days. The platelet count recovered rapidly once the balloon pump was removed.³⁴ ECMO is associated with thrombocytopenia, though data on the degree of platelet count fall are lacking.¹⁸ Thrombocytopenia due to drugs other than heparin must also be considered. Particular to cardiac patients, thrombocytopenia due to use of the glycoprotein IIb/IIIa antagonists occurs in 0.2 to 2% of patients and may appear within hours of infusion.³⁵ An immune response to protamine sulfate, a reversal agent for UFH used during cardiac surgery, has been recently described.^{36–38} Although 25 to 30% of patients have detectable antiprotamine antibodies 4 to 6 weeks after surgery, the clinical relevance of these antibodies including their contribution to thrombocytopenia is questionable.³⁹

Scoring Systems—Scoring systems have been developed to assist clinicians in incorporating the aforementioned laboratory and clinical characteristics into an estimate of the probability of HIT. The most extensively studied scoring system is the 4Ts score (Table 1).^{20,40} Patients are evaluated across four domains (*Thrombocytopenia, Timing, Thrombosis, and other causes*) and are assigned a score of 0, 1, or 2 points for each domain, yielding a maximum summative score of 8. A 4Ts score of 0 to 3 points, 4 to 5 points, and 6 to 8 points is said to correspond to a low, intermediate, and high probability of HIT, respectively. In a systematic review and meta-analysis of 13 studies, the negative predictive value of a low probability 4Ts score was 99.8% (95% confidence interval [CI]: 97.0–100.0%). The positive predictive value of an intermediate and high probability 4Ts score was 14% (9–22%) and 64% (40–82%), respectively. Although all 13 studies included in the meta-analysis enrolled cardiac surgery patients, the studies did not provide patient-level data necessary for defining operating characteristics of the 4Ts score specific to the cardiac surgery population. A sensitivity analysis showed that the negative predictive value of a low probability 4Ts score remained high irrespective of whether a study included a large (>36%) or a small (<18%) proportion of cardiac surgery patients, suggesting that a low probability 4Ts score may be a robust means of ruling out HIT in cardiac surgery patients.⁴¹ The 4Ts score is limited by modest interobserver agreement.⁴² In one real-world study, raw interobserver agreement ranged between 48 and 65%.⁴³ Although the interobserver agreement of the 4Ts score specific to cardiac surgery patients has not been reported, one could speculate that there is potential for subjective interpretation and inter-rater variability in this setting. Despite these concerns, we believe that the 4Ts score is a useful tool for estimating the clinical probability of HIT after cardiac surgery, provided that special considerations unique to this setting are borne in mind. The 4Ts score and special considerations for cardiac surgery patients are shown in Table 1.

Other clinical scoring systems for HIT remain to be validated.^{23,44,45} One such scoring system, developed by Lillo-Le Louët and colleagues, was designed specifically for assessment of HIT after CPB.⁴⁴ The model was derived from 84 patients with suspected HIT following CPB. Independent risk factors for HIT in the derivation cohort included a biphasic platelet count profile, an interval of 5 days from CPB to suspected HIT, and a CPB duration of 118 minutes. These variables were used to build a model, which correctly

classified 34 of 35 HIT-positive patients and 28 of 49 HIT-negative patients in the derivation cohort. The Lillo-Le Louët model has not been validated in an independent cohort.

Laboratory Diagnosis

In view of the challenges of clinical diagnosis, physicians must rely heavily on HIT laboratory testing to assist with diagnosis. Laboratory assays for HIT fall into two categories, immunological and functional. Immunoassays detect circulating anti-PF4/heparin antibodies, irrespective of whether they are able to activate platelets and cause HIT. Functional assays such as the serotonin release assay and heparin-induced platelet activation assay detect only those antibodies that have the capacity to activate platelets in a heparin-dependent manner. Immunoassays are more widely available and highly sensitive, but are associated with limited specificity.^{46,47} Functional assays are highly specific for HIT, but are complex to perform, require specialized reagents and methods, and are thus offered by only a small number of specialized reference laboratories, often with turnaround times of several days. As such, functional assays may be useful for diagnostic confirmation, but results are generally not available to inform initial management decisions.

The seroprevalence of anti-PF4/heparin antibodies among cardiac surgery patients is striking. Preoperative antibodies are present in 5 to 22%.⁴⁸ Within 1 week after CPB, 22 to 52% of patients have circulating anti-PF4/heparin antibodies.^{49–52} Given that the incidence of HIT in this setting is only 1 to 2% (see section on Epidemiology), the implication of these data is that false-positive immunoassay results will outnumber true positives by at least 10:1. Using an IgG-specific detection system and/or increasing the diagnostic threshold may improve specificity,^{53,54} but the potential for overdiagnosis remains enormous.⁵⁵ The risks associated with a false diagnosis of HIT are significant and include exposure to costly parenteral nonheparin anticoagulants and their attendant risk of major bleeding (~1% per day).⁴ Therefore, immunoassay testing must be coupled with careful clinical assessment and a positive immunoassay test should be confirmed with a functional assay.

Several studies have investigated whether anti-PF4/heparin antibodies in cardiac surgery patients without HIT are associated with adverse outcomes. In a systematic review of five studies, preoperative antibodies were not associated with postoperative thromboembolism or mortality.⁴⁸ Data regarding the clinical relevance of anti-PF4/heparin antibodies detected after surgery are mixed. Several studies suggest a higher incidence of myocardial infarction, stroke, venous thromboembolism, and death in antibody-positive patients,^{51,56,57} while others do not.^{49,50,52,58} In general, an immunoassay should only be ordered in a cardiac surgery patient with suspected HIT (i.e., should not be used for “screening” unselected patients) because the clinical relevance of anti-PF4/heparin antibodies in patients without HIT is not established and because the high rate of seropositivity could lead to misdiagnosis and inappropriate management.

Management

The clinical and immunological response to suspension of heparin in a patient with acute HIT follows a predictable pattern. Platelet count recovery occurs within 10 days of heparin cessation in 90% of patients, though it may take weeks in a minority of individuals.

Functional assays and immunoassays become negative at a median of 50 and 85 days, respectively.²⁷ On the basis of this stereotyped sequence of events, HIT may be conceptually divided into phases (Table 2).⁵⁹ *Acute HIT* persists until platelet count recovery and is a period of markedly increased thrombotic risk. The period from platelet count recovery until the functional assay becomes negative is termed *subacute HIT A*. Subacute HIT B is the phase after the functional assay becomes negative, but before the immunoassay becomes negative. Finally, once anti-PF4/heparin antibodies are no longer detectable by immunoassay, the patient is said to have *remote HIT*. This conceptual framework is useful because it reflects the multiple phases in which HIT is encountered and the different management questions with which clinicians are confronted in clinical practice, particularly in the cardiac surgery setting.⁵⁹

The management of acute HIT after cardiac surgery is similar to the management of acute HIT in other settings and will not be reviewed here. The reader is referred to recent clinical practice guidelines and review articles for more information.^{59–62} Herein, we focus on an aspect of management unique to the cardiac surgery setting: selection of intra-operative anticoagulation in patients with a history of HIT.

Intraoperative Anticoagulation for Cardiac Surgery

Selection of the intraoperative anticoagulant for cardiac surgery depends primarily on the phase of HIT (Table 2). UFH is the preferred choice in patients without a history of HIT because of its measurability, reversibility, low cost, and familiarity to surgeons and perfusionists. However, it is unsafe to expose patients with acute HIT or subacute HIT A to heparin because of the risk of HIT recurrence or exacerbation. In these patients, cardiac surgery should be postponed if possible until the functional assay becomes negative (i.e., subacute HIT B) and ideally until anti-PF4/heparin antibodies are no longer present (i.e., remote HIT). If surgery cannot be delayed, a nonheparin anticoagulant such as bivalirudin should be used. Bivalirudin protocols for both on-pump and off-pump surgery have been published.^{63–66} Alternatively, the patient may be treated with preoperative plasma exchange to remove platelet-activating antibodies and enable intraoperative UFH. This approach appears to be safe, but data are limited.^{67,68}

In patients with subacute HIT B or remote HIT, UFH is the intraoperative anticoagulant of choice (Table 2). The safety of administering intraoperative UFH in patients with remote HIT was first established in a series of 10 patients undergoing cardiac surgery. None developed HIT or recrudescence of HIT antibodies.⁶⁹ There is mounting evidence that intraoperative UFH is also safe in patients with subacute HIT B. In three patients with subacute HIT B who required urgent cardiac transplantation, treatment with intraoperative UFH did not result in clinical recurrence.⁷⁰ Similar findings were reported in a recently published series of 10 patients.⁷¹

In patients with subacute HIT B, it is advisable to delay surgery until anti-PF4/heparin antibodies are no longer detectable. In patients with subacute HIT B in whom surgery cannot be delayed and in patients with remote HIT, intraoperative UFH is recommended over a nonheparin anticoagulant (Table 2). When a cardiac surgery patient with a history of HIT is

reexposed to heparin, exposure should be strictly limited to the intraoperative setting. If pre- or postoperative anticoagulation is indicated, a nonheparin anticoagulant should be used.

Conclusion

Even as the incidence of HIT falls in other clinical settings due to replacement of UFH by LMWH,⁷² HIT remains a threat in cardiac surgery patients, perhaps in part because of the continued preference for intraoperative UFH. HIT affects 1 to 2% of patients who undergo CPB followed by postoperative UFH thromboprophylaxis. More data are needed to determine whether LMWH thromboprophylaxis is associated with a reduction in the incidence of HIT.

The number of cardiac surgery patients in whom HIT is suspected far exceeds those in whom the disease is ultimately confirmed. Several factors contribute to the high rate of suspicion and the potential for overdiagnosis of HIT in this population including the ubiquity of heparin exposure and thrombocytopenia, the frequent presence of digital ischemia, and the striking proportion of anti-PF4/heparin seropositivity among patients without HIT. Careful clinical assessment with special consideration of the features characteristic of HIT after cardiac surgery (Table 1) is therefore paramount to determine which patients are appropriate for HIT laboratory testing. Of equal importance, positive immunoassay results should be confirmed with a more specific functional assay to minimize the short- and long-term harms of misdiagnosis.⁷³

In patients with a history of HIT who require cardiac surgery, laboratory testing may be used to define the phase of the disease and guide decisions about intraoperative anticoagulation (Table 2). UFH is recommended in those with remote HIT and subacute HIT B. In patients with acute HIT or subacute HIT A, a nonheparin anticoagulant (e.g., bivalirudin) or preoperative plasma exchange should be used if surgery cannot be delayed.

For more than a decade, experts have predicted the demise of HIT. While its incidence has, indeed, fallen in other clinical settings due to declining use of UFH, it remains a real problem in the cardiac surgery setting, where UFH, for the foreseeable future, will continue to be the intraoperative anticoagulant of choice. We would therefore do well to continue to investigate HIT in the cardiac surgery setting with a focus on developing strategies for prevention and improved clinical and laboratory diagnostic tools.

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Fig. 1.

Example of biphasic platelet count pattern typical of HIT after cardiopulmonary bypass surgery. A 77-year-old woman underwent elective aortic valve replacement on cardiopulmonary bypass (CPB) on postoperative day 0. She received unfractionated heparin during surgery and prophylactic intensity enoxaparin beginning on postoperative day 2. Her preoperative platelet count was $294 \times 10^9/\text{L}$. As expected, her platelet count fell after CPB to a nadir of $97 \times 10^9/\text{L}$ on postoperative day 3 and then began to recover. Beginning on postoperative day 9 (9 days after initial heparin exposure), she experienced a second platelet count fall. Two days later, she became hypoxic and was diagnosed with pulmonary embolism. An anti-PF4/heparin enzyme-linked immunoassay was markedly positive at 2.80 optical density units and a serotonin-release assay was positive. This case illustrates the characteristic biphasic platelet count pattern that is typical of HIT after surgery with CPB.

Table 1

The 4Ts score and special considerations in application of the 4Ts score to cardiac surgery patients

4Ts	2 points	1 point	0 point	Cardiac surgery considerations
Timing of platelet count fall	Clear onset between days 5–14 or platelet fall 1 day (prior heparin exposure within 30 d)	Consistent with days 5–14 fall, but not clear (missing platelet counts) or onset after day 14 or fall 1 d (prior heparin exposure 30–100 d ago)	Platelet count fall 4 d without recent exposure	A biphasic platelet count pattern is typical of HIT after CPB surgery Early-onset and persistent thrombocytopenia after CBP is rarely HIT
Thrombocytopenia	Platelet count fall >50% and platelet count nadir $20 \times 10^9/L$	Platelet count fall 30–50% or platelet nadir $10–19 \times 10^9/L$	Platelet count fall <30% or platelet nadir $<10 \times 10^9/L$	Percent fall in platelet count is calculated from peak platelet count following heparin exposure to nadir platelet count The nadir platelet count need not fall below $150 \times 10^9/L$, particularly in surgical patients who have postoperative thrombocytosis
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis at heparin injection sites; anaphylactoid reaction after IV heparin bolus	Progressive or recurrent thrombosis; nonnecrotizing (erythematous) skin lesions; suspected thrombosis (not confirmed)	None	Digital ischemia due to hypotension, vasopressors, and/or underlying peripheral arterial disease may mimic HIT-associated small vessel thromboembolism
Other causes of thrombocytopenia	None apparent	Possible	Definite	Common alternative causes in cardiac patients include CPB, IABP, ECMO, infection, and other medications that can cause thrombocytopenia (e.g., glycoprotein IIb/IIIa antagonists)

Abbreviations: CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; IABP, intraaortic balloon pump.

Note: A total score of 0–3, 4–5, and 6–8 points is said to correspond to a low, intermediate, and high probability of HIT, respectively.

Table 2

The multiple phases of HIT and suggestions for intraoperative anticoagulation in patients with a history of HIT

Phase	Platelet count	Functional assay	Immunoassay	Suggestion
Acute	Decreased	+	+	1. Delay surgery 2. If surgery cannot be delayed, use an alternative anticoagulant (e.g., bivalirudin) or treat with preoperative plasma exchange until functional assay becomes negative
Subacute A	Recovered	+	+	
Subacute B	Recovered	–	+	1. Delay surgery 2. If surgery cannot be delayed, use heparin
Remote	Recovered	–	–	1. Use heparin