

## Heparin-Induced Thrombocytopenia and Vascular Surgery

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**Key words.** Argatroban ; coumarin ; heparin ; lepirudin ; thrombocytopenia ; venous limb gangrene.

**Abstract.** Heparin-induced thrombocytopenia (HIT) is of special interest to vascular surgeons as heparin is the predominant anticoagulant used before, during, and after vascular surgery. Further, the prothrombotic nature of this antibody-mediated disorder leads to a high frequency of limb ischemia due to large arterial occlusion by platelet-rich ("white") clots or because of extensive venous thrombosis involving large veins and small venules. This latter syndrome has been associated with coumarin anticoagulation of HIT-associated deep-vein thrombosis (coumarin-induced venous limb gangrene). Non-heparin anticoagulants, such as the direct thrombin inhibitors (lepirudin, argatroban), may be needed for intraoperative management of a patient with suspected acute HIT who requires vascular surgery. The transience of HIT antibodies provides a rationale for intraoperative use of heparin in a patient who has recovered from HIT and in whom HIT antibodies are no longer detectable.

### Unfractionated heparin, vascular surgery, and HIT

Unfractionated heparin (UFH) has a central place in the vascular surgeon's armamentarium, as it permits surgical manipulation of clamped arteries and veins, and is commonly used to prevent or treat perioperative thrombosis. Vascular surgeons therefore are usually familiar with an adverse effect known as heparin-induced thrombocytopenia (HIT). Indeed, vascular surgeons were the first physicians to report a link between heparin treatment and the subsequent occurrence of unusual thrombi (for review : 1). In 1958, Weismann and Tobin (2) reported 10 patients who developed large artery occlusion by platelet-rich thrombi in association with heparin therapy. As these surgeons practiced in the era preceding routine platelet count measurements, the link between thrombosis and heparin-induced *thrombocytopenia* was not made. Subsequently, in the 1970s, a group headed by the vascular surgeon Donald Silver (3) identified thrombocytopenia as a central feature of the HIT syndrome, and also provided preliminary evidence for its immune basis.

### Pathogenesis

HIT is an immune disorder resulting from IgG antibodies that recognize a "self" protein, platelet factor 4 (PF4), when PF4 binds to heparin (for review : 4). Multimolecular complexes of heparin, PF4, and IgG form on platelet surfaces, and occupancy of the platelet IgG Fc receptors by HIT-IgG produces platelet activation. Heparin chains bind PF4 in relation to their length

and degree of sulfation, perhaps explaining why UFH is more likely to cause HIT than low-molecular-weight heparin (LMWH). Platelet activation in HIT is associated with activation of coagulation, as shown by greatly increased markers of in vivo thrombin generation. Once triggered, the prothrombotic risk of HIT remains for at least several days or weeks. Venous thrombosis, such as deep-vein thrombosis (DVT) and pulmonary embolism, occur more often than arterial thrombi (4).

### Syndromes of HIT-associated acute limb ischemia

There are several clinical scenarios whereby a patient with HIT can present to a vascular surgeon (Table 1). Three syndromes involve various presentations of acute limb ischemia (5) (Fig. 1).

#### *Coumarin-induced phlegmasia cerulea dolens and venous limb gangrene*

In 1979, Jonathan Towne, a vascular surgeon in Milwaukee, Wisconsin, and colleagues reported the occurrence of phlegmasia cerulea dolens that progressed to "venous limb gangrene" in two of their seven patients with HIT (1). This represents the first report linking venous limb ischemic necrosis and HIT. However, it remained until the 1997 for an additional pathogenetic link to be made between venous limb gangrene in HIT and use of coumarin (5-8), e.g. warfarin (United Kingdom, North America) or phenprocoumon (continental Europe). The pathogenesis of coumarin-induced venous limb gangrene is the concurrence of uncontrolled

Table 1  
HIT and the vascular surgeon.

Acute limb ischemia (see also Fig. 1)
Acute limb ischemia secondary to HIT : large artery occlusion by "white clots"
Acute limb ischemia secondary to coumarin-induced venous limb gangrene
Acute limb ischemia secondary to microvascular thrombosis in the absence of coumarin
Temporal features of HIT
Typical-onset HIT : the platelet count begins to fall between days 5–10 of heparin therapy (rarely thereafter)
Delayed-onset HIT : the platelet count begins to fall <i>after</i> stopping heparin
Rapid-onset HIT : the platelet count begins to fall within 24 hours of starting (or increasing the dose of) heparin (patients have usually received heparin within the past several weeks)
Complications of HIT
New, progressive, or recurrent limb ischemia
Other arterial thrombosis (e.g., thrombotic stroke, myocardial infarction, mesenteric artery thrombosis, etc.)
Venous thrombosis (e.g., deep-vein thrombosis, pulmonary embolism, cerebral venous thrombosis)
Heparin-induced skin lesions
Acute systemic reaction post-intravenous heparin bolus
Decompensated disseminated intravascular coagulation (DIC)
Intraoperative or early postoperative rapid-onset HIT (due to pre-existing HIT antibodies)
Vascular surgery in patient with previous HIT (HIT antibodies no longer detectable)

thrombin generation (secondary to HIT) interacting with (coumarin-induced) depletion of the vitamin K-dependent natural anticoagulant, protein C. The role of protein C is to downregulate thrombin generation in the microcirculation ; hence, severe protein C depletion increases risk for microvascular thrombosis.

Patients with coumarin-induced venous limb gangrene typically have a DVT in the same limb affected by acral (distal) necrosis (Fig. 1). The characteristic clinical triad is : (a) thrombocytopenia ; (b) supratherapeutic international normalized ratio (INR) during coumarin anticoagulation ; and (c) microvascular thrombosis in a limb affected by DVT. The supratherapeutic INR (usually >4.0) is a surrogate marker of severe depletion of protein C. This syndrome differs somewhat from the "classic" form of coumarin-induced skin necrosis, wherein central (rather than acral) tissue sites, such as breast, abdomen, buttocks, thigh, and calf, are affected, and in which patients often have congenital abnormalities of the protein C natural anticoagulant pathway (5-7).

(In contrast, most patients with HIT-associated venous limb gangrene do not have preexisting abnormalities in protein C or antithrombin.)

Fig. 2 illustrates the clinical course of a representative patient with warfarin-induced venous limb gangrene complicating HIT. The patient received warfarin therapy to treat venous thromboembolism associated with HIT. The limb affected by DVT developed acral necrosis when the INR rose to 4.5 (usual therapeutic range, 2.0–3.0). In our hospitals in Hamilton, Canada, coumarin-induced venous limb gangrene was the most common explanation for limb loss in a consecutive series of patients with HIT (7).

#### Acute artery occlusion

For unknown reasons, limb ischemia secondary to acute arterial occlusion is a relatively common thrombotic complication that can affect a patient with HIT (1-4) (Fig. 1). Thus, a patient who develops HIT on any clinical service may present with an acutely ischemic limb, prompting urgent vascular surgery consultation and, potentially, surgical thromboembolectomy of platelet-rich thrombi ("white clot syndrome"). Clinical findings are typical of those seen in any acute large artery occlusion, and can include a cold, pulseless limb that has pain, paresthesia, or weakness. Clues pointing to a possible diagnosis of HIT include concomitant or recent use of heparin, thrombocytopenia, skin lesions at heparin injection sites and venous or arterial thrombi in other vessels.

#### Microvascular thrombosis

Rarely, limb ischemia can occur in the absence of large artery occlusion, and in the absence of coumarin anticoagulation, sometimes with associated DVT in the affected limb(s) (5,8) (Fig. 1). Patients have very low platelet counts, and may have evidence of decompensated disseminated intravascular coagulation (DIC), such as low fibrinogen levels, elevated INR, elevated cross-linked fibrin degradation products (fibrin D-dimers) and red cell fragments or normoblasts (nucleated red cells). The treatment is aggressive anticoagulation with a non-heparin anticoagulant and postponing (if not avoiding) coumarin. Minimal if any benefit from surgery is anticipated in patients with predominant microvascular thrombosis.

#### HIT complicating heparin use by the vascular surgeon

The above scenarios of acute limb ischemia could occur in any clinical setting involving heparin use, and prompt referral to the vascular surgeon. However, vascular surgeons themselves often prescribe heparin for man-

## Three Ischemic Limb Syndromes in HIT

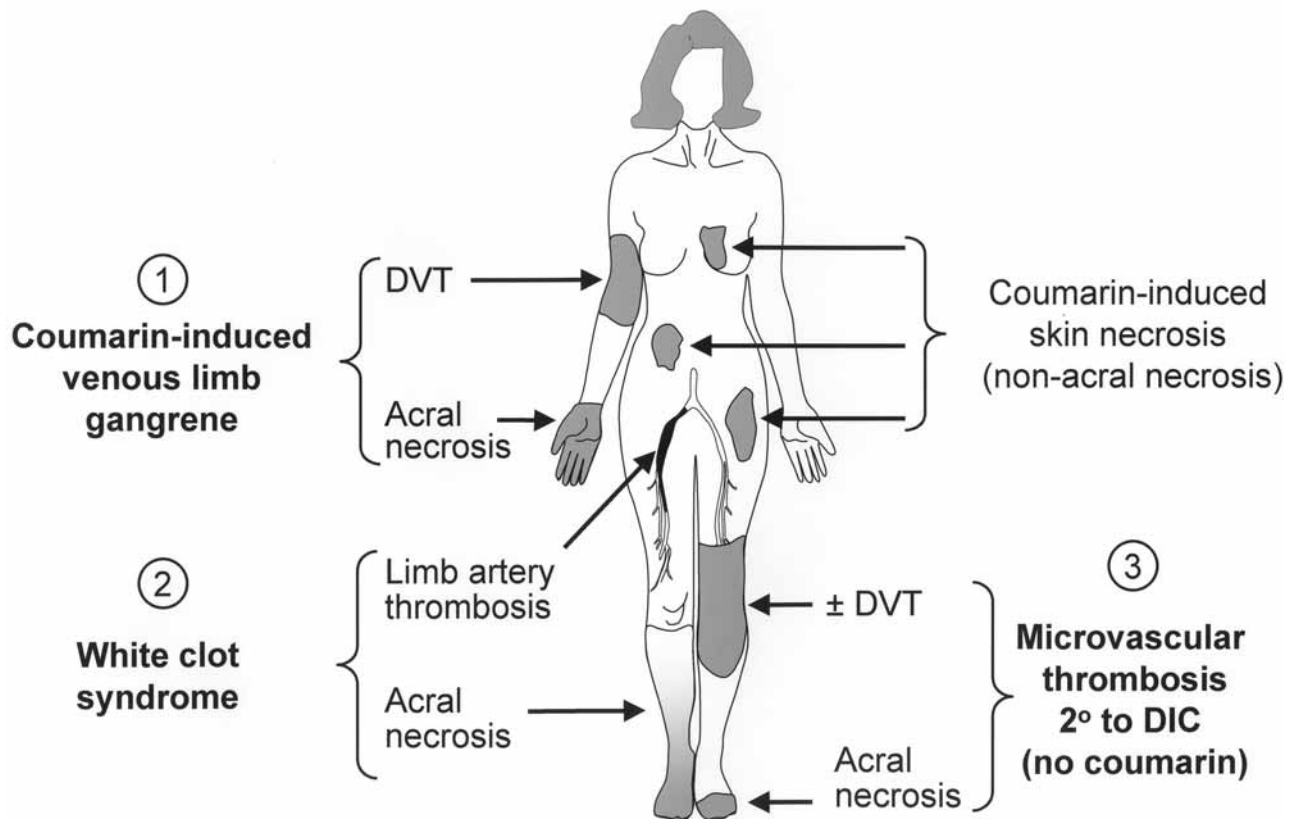


Fig. 1

Three ischemic limb syndromes in HIT. ① *Coumarin-induced venous limb gangrene* is characterized by acral (distal extremity) necrosis in a limb with deep-vein thrombosis (DVT). ② *White clot syndrome* is characterized by large artery occlusion by platelet-rich “white clots.” ③ Rarely, *microvascular thrombosis secondary to disseminated intravascular coagulation* (DIC) can explain acral limb necrosis even in the absence of coumarin therapy; affected limbs may or may not have associated DVT. For comparison, the “classic” form of coumarin-induced skin necrosis is shown, which usually involves non-acral sites, such as breast, abdomen, or thigh. Reprinted, with modifications, with permission (6).

agement of ischemic limbs, often in conjunction with surgical therapy. Thus, the vascular surgical patient can develop any of the complications of HIT, particularly when heparin treatment exceeds 5 days.

### Typical-onset HIT

Typically, the platelet count falls beginning 5 to 10 days after starting an immunizing heparin exposure (9). In the setting of vascular surgery, the immunizing exposure most often is the heparin given during vascular surgery. Thus, if the patient receives subcutaneous, low-dose UFH or LMWH for antithrombotic prophylaxis after vascular surgery, a platelet count fall that begin during this characteristic day 5 to 10 “window” strongly suggests HIT, especially if other plausible causes of thrombocytopenia are not apparent.

Fig. 3 illustrates a patient who developed typical-onset HIT following vascular surgery. The interpretation of the platelet count profile is complicated by (a) perioperative hemodilution, (b) platelet count increase following platelet transfusions, and (c) clearance of the transfused platelets. Nevertheless, between postoperative days 3 to 4, it is apparent that the platelet count is beginning to recover from the postoperative nadir, as expected. However, on postoperative day 5, there is an unexpected decline in the platelet count which was accompanied by formation of strong HIT antibodies.

### Delayed-onset HIT

Rarely, the immunizing heparin exposure leads to generation of HIT antibodies that do not appear to require continuing exposure to pharmacologic heparin to be

## Venous Limb Gangrene after Cardiac Surgery

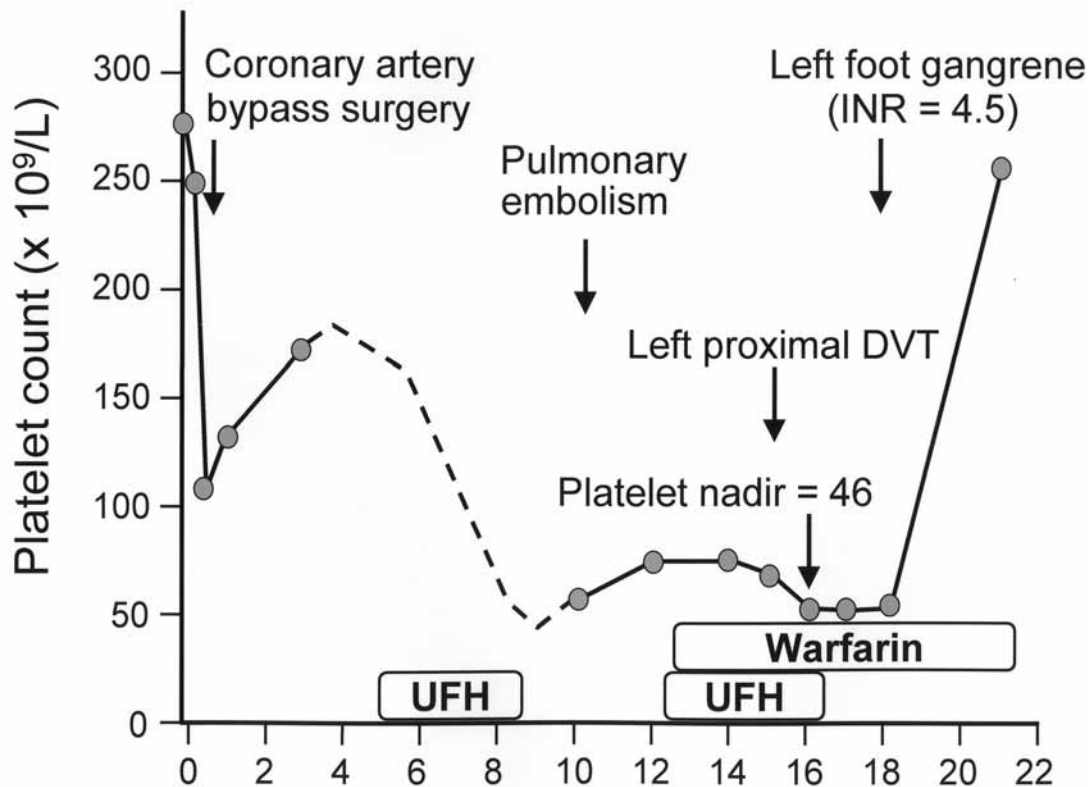


Fig. 2

Venous limb gangrene after cardiac surgery. A 54-year-old male developed HIT complicated by pulmonary embolism and deep-vein thrombosis (DVT) during antithrombotic prophylaxis with unfractionated heparin (UFH). The patient was treated with warfarin, a coumarin anticoagulant. Despite rapid platelet count recovery, he developed acral foot necrosis in the limb affected by DVT, which coincided with the time the international normalized ratio (INR) reached 4.5 (usual therapeutic range, 2.0–3.0).

pathogenic (8,10). Thus, the onset of thrombocytopenia and thrombosis beginning several days after heparin has been stopped can indicate severe HIT. If heparin is given to such a patient, the platelet count will decline further. Typically, these patients have higher titers of HIT antibodies than patients with more typical presentations of HIT (10).

### Rapid-onset HIT

This refers to a patient who is recognized as having HIT only after use of heparin that leads to an abrupt decline in the platelet count, i.e., within 24 hours of starting (or increasing the dose of) heparin (9). The platelet count fall results from heparin being given (or dose increased) to a patient who already has circulating HIT antibodies that resulted from an exposure within the past several days or weeks (generally, within the previous 100 days).

### Thrombotic complications of HIT

HIT can be complicated by virtually any type of arterial or venous thrombosis (4,8). However, there is a predilection to involvement of vessels with chronic disease (e.g., atherosclerosis) (11), acute injury (e.g., recent use of intravascular catheters) (8), or immobility. Thus, a patient who has undergone vascular reconstructive surgery, and who develops HIT one week later faces the risk of acute arterial or venous thrombosis involving the same (or adjacent) vessels involved in the surgery (12).

Such a patient could also develop other arterial thrombotic events, such as acute thrombotic stroke, myocardial infarction, or mesenteric artery thrombosis. Venous thrombotic events are also quite common, particularly DVT and pulmonary embolism. Less common venous thrombotic syndromes that are well-described in the context of HIT include cerebral venous thrombosis

and adrenal hemorrhagic infarction (associated with adrenal vein thrombosis) (4,8).

*Miscellaneous complications of HIT*

A minority of patients who develop HIT during subcutaneous injections of UFH or LMWH develop skin lesions at the heparin injection sites (8). Known as *heparin-induced skin lesions*, these can range from erythematous plaques to skin necrosis. There is evidence

that patients who develop heparin-induced skin lesions are at especially high risk of developing concomitant arterial thrombosis (8). In some patients, the platelet count fall indicating HIT can be modest, or may even begin a few days after the heparin has been stopped on account of the skin lesions.

Another unusual syndrome linked to HIT is known as “acute systemic reactions” (8) These follow intravenous bolus injection of heparin to a patient who has circulating HIT antibodies, beginning about 5 to 30 minutes

## Thrombocytopenia after Vascular Surgery

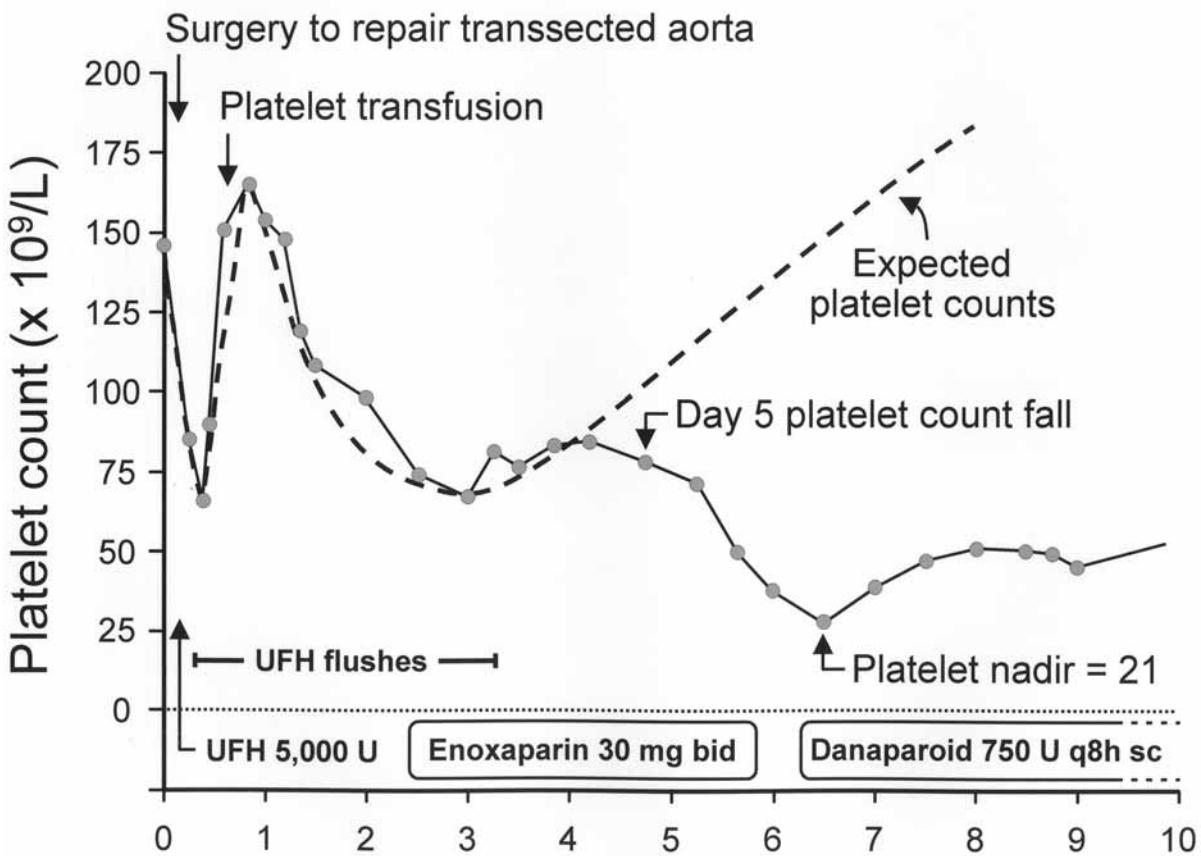


Fig. 3

Thrombocytopenia after vascular surgery. A 53-year-old female who underwent emergency vascular surgery for transected aorta following a motor vehicle accident developed typical-onset HIT. The platelet count fluctuations during the first four postoperative days were related to perioperative hemodilution (day 0), platelet transfusion followed by clearance of the transfused platelets (days 0–2), and the initial phase of postoperative platelet count recovery (days 3–4). Subsequently, on day 5, the patient developed typical-onset HIT while receiving the low-molecular-weight heparin, enoxaparin; the platelet count nadir of 21 × 10<sup>9</sup>/L was reached on day 6. The patient tested strongly positive for HIT antibodies (platelet serotonin release, 99%; normal range <10% release; PF4-dependent enzyme-immunoassay, 0.921 absorbance units; normal, <0.450 units). Although this patient was treated with low-dose danaparoid, it is now recommended to give therapeutic-dose danaparoid to patients with “isolated HIT,” i.e., HIT recognized because of thrombocytopenia alone.

## Acute Intraoperative White Clot Syndrome

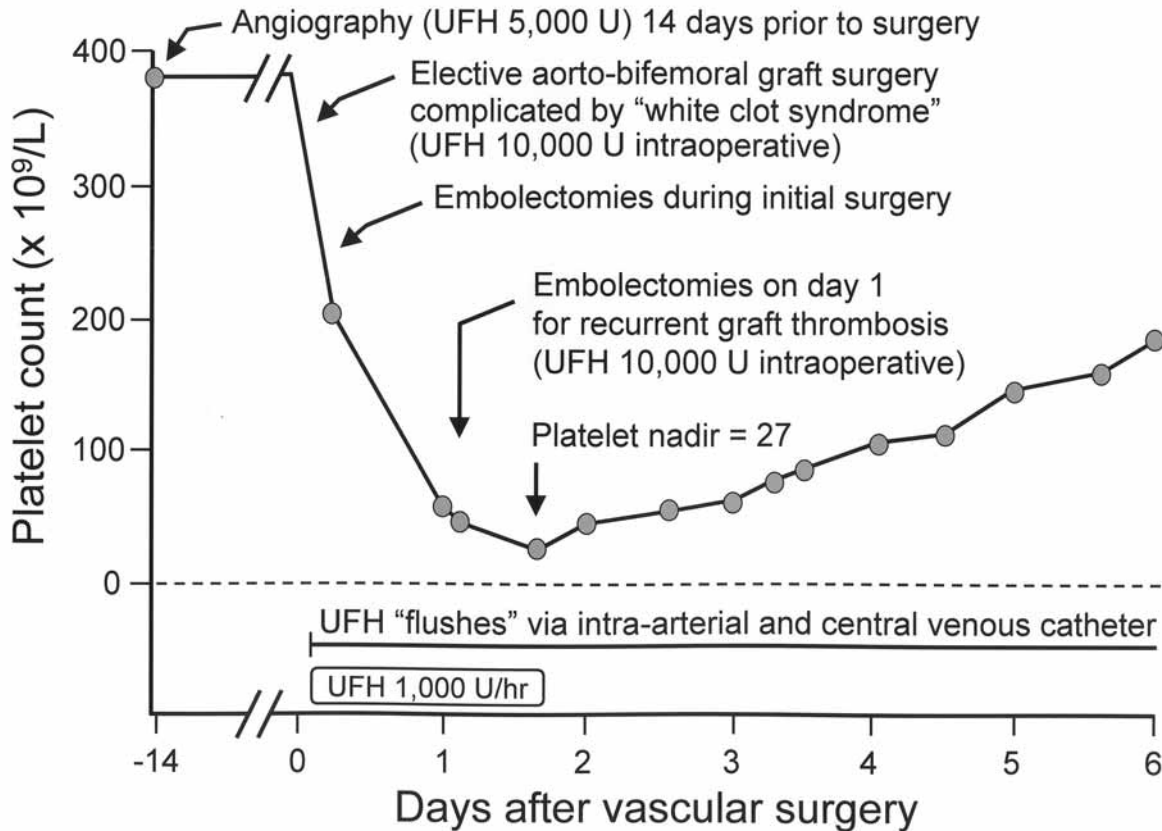


Fig. 4

Acute intraoperative HIT. A 48-year-old female received 5,000 U UFH during diagnostic angiography 14 days prior to elective aorto-bifemoral surgery. This is believed to have explained the unexpected occurrence of acute intraoperative HIT complicated by "white clot syndrome" during elective vascular surgery, with the platelet count nadir of  $27 \times 10^9/L$  being reached between postoperative days 1 and 2. Recurrent graft thrombosis and death occurred on postoperative day 9 (not shown). Reprinted with permission (13).

post-injection. The symptoms and signs can range from inflammatory (e.g., fever, chills, flushing) to cardiovascular (tachycardia, chest pain or tightness, cardiac arrest) to respiratory (tachypnea, dyspnea, respiratory arrest) to gastrointestinal (diarrhea) to neurologic (transient global amnesia, pounding headache). Abrupt declines in the platelet count invariably accompany such acute systemic reactions.

Although most patients have elevated cross-linked fibrin degradation products (fibrin D-dimer), a minority with very severe HIT show laboratory evidence of decompensated DIC, including elevated INR, reduced fibrinogen, red cell fragments or even circulating nucleated red cells in the peripheral blood film. As discussed earlier, these patients may be at higher risk of developing limb ischemia due to microvascular thrombosis.

### Acute intraoperative or early postoperative HIT

A very rare presentation of HIT is the unexpected occurrence of intraoperative or early postoperative "white clot syndrome" with rapid-onset HIT complicating elective vascular surgery (13). An explanation for such an unusual event could be the unexpected presence of high levels of HIT antibodies in the patient's blood at the time of vascular surgery, perhaps resulting from recent exposure to heparin, particularly 10 days to 3 weeks earlier. This time frame is relevant because HIT antibodies tend to reach their peak levels about two weeks after an immunizing exposure to heparin. Since vascular surgery itself leads to abrupt declines in the platelet count (due to hemodilution and platelet consumption), it can be difficult to diagnose perioperative rapid-onset HIT based

upon the platelet count fall alone, unless the decrease is much more dramatic than expected. Also, patients can develop acute graft occlusion for reasons other than HIT.

Fig. 4 illustrates a patient suspected as having acute intraoperative and early postoperative HIT (13). In this case, the presumed immunizing heparin exposure occurred fourteen days prior to surgery, when the patient received 5,000 units of UFH during diagnostic angiography. A pertinent aspect of this case was the ongoing administration of heparin "flushes" even after intravenous therapeutic-dose UFH had been stopped because of suspected HIT. This may have contributed to recurrent graft thrombosis and death on postoperative day nine (not shown on Fig. 4).

### Vascular surgery in a patient with previous HIT

A remarkable feature of HIT antibodies is their transient nature. Kelton and I have shown that HIT antibodies typically decline to undetectable levels at a median of 50 to 80 days, depending upon the type of assay performed to detect their presence (9). Further, once HIT antibodies are no longer detectable, a brief heparin re-exposure is safe, because it takes at least 5 days for HIT antibodies to be regenerated (if they are regenerated at all). Accordingly, it is appropriate medical practice to anticoagulate a patient with a previous history of HIT with UFH to permit cardiac or vascular surgery provided that HIT antibodies are no longer detectable using one or more sensitive assays. It may also be safe to use heparin in a patient who has only a weakly positive enzyme-immunoassay result, but a negative "functional" assay (e.g., washed platelet activation assay).

### Alternative anticoagulants during vascular surgery

The vascular surgeon faced with a patient with limb-threatening ischemia due to large artery occlusion by platelet-rich white clots has the dilemma of how to perform potentially limb-salvaging thrombectomy in a setting in which UFH is at least relatively, if not absolutely, contraindicated. For this situation, several alternative anticoagulants are available that can provide acceptable intraoperative anticoagulation. However, minimal experience has been reported for use during vascular surgery, and so the surgeon has to judge the risk-benefit ratio of any planned operative procedure.

#### *Recombinant hirudin (lepirudin, desirudin)*

Lepirudin and desirudin are hirudin derivatives, i.e., their structure closely resembles the potent thrombin inhibitor manufactured in nature by the medicinal leech. Both agents are prepared using recombinant biotechnology. Lepirudin is approved for the treatment of throm-

bosis complicating HIT in Europe, the United States, Canada, and Australia (in contrast, desirudin is marketed only in Europe for prevention of DVT post-orthopedic surgery). Off-label use for intraoperative anticoagulation during vascular surgery (primarily using lepirudin) has been reported (12, 14-17). The drug can be administered as an intravenous bolus over a minute, although this rarely is complicated by acute anaphylaxis, especially if patients have been exposed within the past few weeks (17). The half-life is approximately 80 minutes, although this increases considerably in a patient with renal insufficiency. Thus, dosing must be dramatically reduced in a patient with suboptimal renal function (17). Lepirudin is usually monitored using the activated partial thromboplastin time (APTT), with the usual target range being about 1.5 to 2.5-times the patient baseline (or, alternatively, 1.5-2.5-times the mean of laboratory normal range). There is no antidote.

Table 2 lists regimens for use of recombinant hirudin during and following vascular surgery. There is much greater experience using lepirudin than desirudin in the setting of HIT.

Table 2  
Protocol for r-hirudin\* anticoagulation  
during vascular surgery.

Intraoperative bolus\*\* : 0.2-0.4 mg/kg i.v. (immediately before vascular clamping) followed by 0.1-0.15 mg/kg/h\*\*\* (target APTT, 1.5-2.5X baseline) ;

Intraoperative "flush" solution consisting of 0.1 mg/mL lepirudin (maximum, 250 mL administered during surgery) ;

Postoperative anticoagulation, ranging from 0.10 mg/kg/h (target APTT 1.5-2.0X baseline APTT) or 15 mg given twice daily by subcutaneous injection in patients at relatively low risk for postoperative reocclusion (e.g., surgery involving aorta, iliac, femoral, or carotid arteries) to 0.15 mg/kg/h (target APTT 1.5-2.5X baseline) for patients at relatively high-risk of postoperative reocclusion (e.g., popliteal bypass).\*\*\*

The protocol described summarizes published literature (12,14-17) and represent "off-label" use of r-hirudin.

\* Recombinant hirudin (r-hirudin) includes lepirudin (available in Europe, North America, Australia, and elsewhere) and desirudin (Europe). Only lepirudin is approved for treatment of thrombosis complicating HIT.

\*\* An intraoperative bolus of r-hirudin may not be required if the patient is already anticoagulated with r-hirudin at the time of vascular surgery.

\*\*\* In case of renal insufficiency, dosing must be decreased by up to 90%. As anesthesia results in decreased renal perfusion, the dose of lepirudin should be reduced by approximately 30% (with APTT adjustments) during surgery and in the early postoperative period even in a patient stably anticoagulated prior to surgery. The APTT should be monitored frequently during and following surgery.

### Argatroban

Argatroban is a direct thrombin inhibitor derived from arginine that binds reversibly to the active site pocket of thrombin. Its half-life is about 40–50 minutes, and it undergoes hepatobiliary excretion. Argatroban is non-immunogenic, and has not been associated with anaphylaxis or other allergic reactions. It is also monitored using the APTT (target, 1.5–3.0X baseline) in most clinical situations, although intraoperative use of the activated clotting time (ACT) during vascular surgery has been reported (18,19). Ohteki and colleagues (18) reported use of argatroban for intraoperative anticoagulation in 16 patients undergoing peripheral vascular surgery. In 8 patients, bolus administration of argatroban (0.05 or 0.10 mg/kg given to 4 patients each before arterial clamping) led to increases in ACT from baseline (88 s) to 132 and 150 s, respectively (peak at 15 min), although the ACT had returned to near-baseline at 30 min. post-bolus (to 96 and 98 s, respectively). Subsequently, these investigators treated 8 additional patients with the following protocol: 0.10 mg/kg bolus, followed by 2 µg/kg/min infusion (0.12 mg/kg/h). This resulted in an intraoperative mean ACT at 30 min of about 150 s, which the investigators judged acceptable for surgery. The authors suggested this protocol could be useful for patients in whom arterial clamping for more than 30 min was anticipated. Alternatively, in a single case report, Tokuda and coworkers (19) reported administering argatroban by constant infusion alone (2.7 µg/kg/min), beginning 30 minutes prior to arterial clamping.

### Danaparoid

This “heparinoid” with predominant anti-factor Xa, rather than anti-thrombin, activity continues to be available in Europe and Canada (it has been withdrawn from the US market) (20). It is an effective anticoagulant for managing HIT-associated thrombosis, but its long half-life (anti-factor Xa activity, 25 h) and inability to inhibit clot-bound thrombin makes it less than ideal for vascular surgery indications. The usual regimen is to administer 2,250 anti-factor Xa units by intravenous injection to achieve rapid anticoagulation (adjusted to 1,500 and 3,000 units for patients <60 and >75 kg, respectively). Intraoperative “flushing” can be achieved using danaparoid solution prepared as 750 U in 250 mL normal saline (maximum, 50 mL if the intraoperative bolus has been given). Postoperatively, patients can be anticoagulated using either low-dose (e.g., 750 U twice or thrice daily by subcutaneous injection) or therapeutic-dose protocols (e.g., 200 U/h by intravenous infusion or 2,250 U twice daily by subcutaneous injection).

### Preoperative and postoperative anticoagulation

A patient with HIT-associated thrombosis who requires intraoperative anticoagulation with a non-heparin anticoagulant may very well be receiving anticoagulation during the immediate pre- and postoperative period. Thus, there may be no need for a full intraoperative bolus of anticoagulant, if the patient already has therapeutic drug levels when starting vascular surgery. In addition, there is the dilemma of whether to continue the anticoagulant immediately postoperatively, or whether to suspend infusion until postoperative hemostasis appears secure, and then resume anticoagulation until resolution of HIT and associated thrombosis. However, the high prothrombotic tendency of acute HIT suggests that continuing anticoagulation even during the immediate postoperative period is appropriate in most situations.

Another important issue that is beyond the scope of this article is the importance of avoiding coumarin in the setting of acute HIT, and postponing its initiation in low, maintenance doses only after there has been substantial resolution of thrombocytopenia. This topic is discussed elsewhere (4,7,8).

### Conclusion

The vascular surgeon often plays an important diagnostic or therapeutic role in patients with HIT, particularly in the setting of acute limb ischemia. The availability of non-heparin anticoagulants with rapid onset of action means that surgical intervention is feasible even when UFH is contraindicated because of HIT.

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