Management of anticoagulation in patients with subacute heparin-induced thrombocytopenia scheduled for heart transplantation

Sixten Selleng¹, Assad Haneya², Stephan Hirt², Kathleen Selleng¹, Christof Schmid² and Andreas Greinacher¹

¹ Institut für Immunologie und Transfusionsmedizin, Ernst-Moritz-Arndt Universität Greifswald, Germany

² Klinik für Herz-, Thorax- und herznahe Gefäßchirurgie, Klinikum der Universität Regensburg, Regensburg, Germany

S.S. and A.H. contributed equally to this study

Correspondence: Prof. Dr. Andreas Greinacher, Institut für Immunologie und Transfusionsmedizin, Ernst-Moritz-Arndt Universität, D-17475 Greifswald, Sauerbruchstraße, Germany, Tel: +49-3834/865482, Fax: +49-3834/865489. greinach@uni-greifswald.de

Running Head: heart transplantation in patients with subacute HIT

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Abstract:

Anticoagulation management of patients with recent heparin-induced thrombocytopenia (HIT) requiring cardiopulmonary bypass (CPB) surgery is a serious challenge, and especially difficult in patients requiring urgent heart transplantation. As non-heparin anticoagulants during CPB bear a high risk of major bleeding, these patients are at risk to be taken off the transplant list. Short-term use of unfractionated heparin (UFH) for CPB, with restriction of UFH to the surgery itself, is safe and effective in patients with a history of HIT who test negative for anti-platelet factor 4 (PF4)/heparin antibodies. We present evidence that it is safe to expand the concept of UFH-re-exposure to patients with subacute HIT, i.e. patients with recent HIT in whom the platelet count has recovered but in whom anti-PF4/heparin IgG antibodies remain detectable, requiring heart transplantation, if they test negative by a sensitive functional assay using washed platelets. This can be life-saving in patients with end-stage heart failure.
Introduction:

Management of patients with recent heparin-induced thrombocytopenia (HIT) requiring cardiopulmonary bypass (CPB) surgery is a serious challenge for the consulting hematologist. Particularly the choice of adequate anticoagulation management during CPB is problematic. The situation is especially difficult in patients requiring heart transplantation, as the timing of surgery usually cannot be planned in advance, whereas the use of alternative anticoagulants during CPB requires special monitoring and preparation\(^1,2\), and bears a significantly enhanced bleeding risk\(^3\). A major conceptual breakthrough was the recognition that use of unfractionated heparin (UFH) for CPB in patients with a history of HIT is safe and effective, provided that circulating anti-PF4/heparin antibodies are no longer detectable\(^4\). This approach is now a Grade-1 recommendation for patients with a history of HIT requiring CPB\(^2\). However, optimal management of patients with subacute HIT in whom platelet counts have normalized, but in whom anti-PF4/heparin IgG antibodies are still detectable by enzyme-immunoassay (EIA), remains uncertain.

We report evidence that in these patients UFH is an option for anticoagulation during CPB if a sensitive functional assay using washed platelets, e.g. the heparin-induced platelet activation (HIPA) test\(^5\), is negative.

Material and Methods:

Anti-PF4/heparin antibodies were determined by EIA separately for IgG, IgA, and IgM\(^6\); heparin-dependent platelet-activating antibodies were determined by HIPA\(^5\). Heart transplantation was performed according to standard procedure using UFH adjusted by activated clotting time (ACT) and neutralized by protamine after CPB.
Results and Discussion:

Case I: A 55-year-old male patient with severe dilated cardiomyopathy (DCM) and cardiogenic shock was scheduled for high urgency heart transplantation. At day 9 of UFH treatment, HIT developed (platelet count fall from 135x10^9/L to 28x10^9/L; anti-PF4/heparin IgG (optical density [OD]=1.1) and positive HIPA; “4T’s”-score\(^7\)=5). After switch of anticoagulation to argatroban (aPTT 50-60s) platelet counts recovered rapidly. When a donor heart became available one week later, the patient still tested positive for anti-PF4/heparin IgG ([OD]=1.1) but negative in the HIPA, and heart transplantation was performed using standard UFH anticoagulation for CPB. Postoperatively, major bleeding occurred (2100mL in 12 hours) that stopped after surgical revision. Anticoagulation was continued with argatroban. Anti-PF4/heparin IgG declined (OD=0.32 on postoperative day 1), remained negative (<OD 0.4 until postoperative day 13) as did the HIPA, and platelet counts normalized (Figure 1A). Multiorgan failure required prolonged intensive care treatment; however, no thrombotic events occurred, and the patient was discharged 113 days after surgery.

Case II: A 55-year old male patient with post-myocardial infarction congestive heart failure (left ventricular ejection fraction 25%) developed HIT at day 7 of UFH therapy (platelet count fall from 259x10^9/L to 97x10^9/L, iliac artery thrombosis; positive anti-PF4/heparin-EIA [HPIA, Diagnostica Stago, France], “4T’s”-score=7). After switching anticoagulation to lepirudin (aPTT 50-60 s) platelet counts recovered. When cardiac function further deteriorated heart transplantation was scheduled. At that time the patient still tested positive for anti-PF4/heparin IgG antibodies by EIA (OD 0.627 OD; cut-off 0.500), but had a negative HIPA test. Three days later a donor heart became available and heart transplantation was performed using standard UFH anticoagulation for CPB with no major bleeding (postoperative chest tube drainage 1200 mL in 48 hours). Lepirudin was restarted about 8 hours after surgery. Anti-PF4/heparin IgG antibodies increased at day 7 following transplantation (OD=1.248), but the
HIPA remained negative (Figure 1B). No thromboembolic complications occurred, and the patient was discharged 35 days after surgery.

**Case III:** A 44-year-old male patient was scheduled for heart transplantation for severe DCM and therapeutic-dose anticoagulation with phenprocoumon was switched to UFH (aPTT 50-60s). One week later, HIT developed (platelet count fall from 330x10^9/L to 78x10^9/L; positive anti-PF4/heparin EIA [HPIA, Diagnostica Stago, France], “4T’s”-score=6). After switch to lepirudin (aPTT 50-60s), platelet counts normalized. Subsequent testing for HIT antibodies within 2 weeks showed a decrease of anti-PF4/heparin IgG levels (from OD 1.099 to 0.526; cut-off 0.500) and a negative HIPA. When a donor heart became available, lepirudin was stopped 4 hours before surgery. Anticoagulation during CPB was performed using standard UFH protocol, with no major bleeding (chest tube drainage 600 mL in the first postoperative 48 hours), lepirudin was restarted (aPTT 50-60s) 6 hours postoperatively (Figure 1C). The further course was complicated by prolonged cardiac shock and intensive care treatment. However, no thrombotic events occurred, and the patient was discharged 91 days after surgery.

Cessation of heparin and use of alternative non-heparin anticoagulation are basic therapeutic principles of HIT. Furthermore, heparin re-exposure in patients with circulating platelet-activating anti-PF4/heparin antibodies should be avoided, as this can cause "rapid-onset" HIT, complicated by thromboembolic events or anaphylactoid reactions. However, HIT antibodies unusually become undetectable within three months following an episode of HIT. Further, in patients with previous HIT in whom antibodies are no longer detectable, it takes at least five days for antibodies to recur following heparin re-exposure. These observations, together with the significantly enhanced bleeding risk if alternative anticoagulants are used during CPB, has led to the strategy of short-term use of UFH for CPB surgery when the patient tests negative for HIT antibodies, with restriction of heparin to the surgery itself.
Recently Schroder et al.\textsuperscript{14} reported a retrospective case series of patients with a positive PF4/heparin EIA re-exposed to heparin for heart transplantation without an increase of adverse events as compared to antibody negative patients. However, in the view of numerous reports showing acute onset HIT in patients with biologically-relevant circulating antibodies\textsuperscript{15} this strategy may bear a substantial risk in the individual patient. Most hematologists would be very reluctant to recommend heparin re-exposure if anti-PF4/heparin IgG antibodies are still present.

We now provide prospective data indicating that short-term use of UFH is feasible in patients with subacute HIT in whom anti-PF4/heparin IgG antibodies are still detectable by EIA, but who show a negative washed platelet activation assay. Washed platelet activating assays have a higher specificity for biologically active HIT antibodies and provide among all other HIT tests the best specificity for clinical HIT\textsuperscript{16}. Therefore, a negative functional assay suggests that residual biologically-active antibodies are unlikely to be present\textsuperscript{17,18}. This strategy is feasible in countries in which functional HIT tests are available by a network of trained laboratories, providing the assays in a turnaround time and quality allowing to base clinical decisions on the test result (potential alternative approaches are given in Table 1).

In two of the patients no functional assay was performed at the time when acute HIT was diagnosed. However, the residually detectable anti-PF4/heparin IgG antibodies, together with the clinical presentation (Figure 1), were very suggestive of recent HIT when anticoagulant management during heart transplantation had to be decided. None of the three patients developed platelet-activating antibodies, and there was no evidence for HIT-related thrombotic events after re-exposure to UFH. As compared to non-HIT patients (illustrated as grey shaded area in the figure), however, platelet count recovery after heart transplantation seemed to be somewhat delayed. This might indicate that the persistent antibodies, although not causing thrombosis, may still impair platelet count recovery.
These three patients indicate that the concept of short-term use of UFH during CPB in patients with previous HIT might be expanded to patients with subacute HIT in whom anti-PF4/heparin IgG antibodies are still detectable by EIA, but who test negative by a sensitive platelet activation assay. This strategy increases the feasibility of heart transplantation in patients with end-stage heart failure.

**Authorship:**

Contribution: A. Greinacher designed the study. A. Haneya, S. Selleng, S. Hirt and C. Schmid collected and analyzed data. S. Selleng, K. Selleng and A. Greinacher wrote the manuscript. All authors revised the manuscript.

Conflict-of-interest disclosure: All authors declare no competing financial interests.
Reference List:


Figure legend:

Figure 1: Three patients scheduled for heart transplantation with end-stage heart failure complicated by subacute heparin-induced thrombocytopenia (HIT) are shown. In all three patients, heart transplantation was successfully performed using short-term unfractionated heparin (UFH) during transplantation despite a positive anti-PF4/heparin IgG by enzyme-immunoassay (EIA). Results of the EIA test are represented by black vertical bars, the results of the heparin-induced platelet-activating (HIPA) test are given as text, platelet count courses are represented by lines. The grey shaded area represents ± standard deviation of mean platelet counts of 10 consecutive non-HIT patients after heart transplantation. The clinical course and laboratory test results obtained from another hospital in patients II and III are given at the left hand side of the figure. Criteria to diagnose HIT in patient I were: the platelet fall >50% after 9 days of heparin treatment, the positive anti-PF4/heparin IgG, the positive HIPA, and the rapid increase of platelet count after switching from heparin to argatroban. Criteria to diagnose HIT in patient II were: the platelet fall >50% after 7 days of heparin treatment, complicated by iliac artery embolism, the positive anti-PF4/heparin IgGAM by a commercial EIA, and the rapid increase of platelet count after switching from heparin to lepirudin. Criteria to diagnose HIT in patient III were: the platelet fall >50% after 7 days of heparin treatment, the positive anti-PF4/heparin IgGAM by a commercial EIA, and the rapid increase of platelet count after switching from heparin to lepirudin. (CPB-cardiopulmonary bypass, IABP-intraaortic balloon pump, OD-optical density).

Table 1: Washed platelet assays for excluding clinically relevant HIT antibodies such as the serotonin release test (requiring radioactivity\textsuperscript{16}) or the heparin-induced platelet activation (HIPA) test (does not require radioactivity\textsuperscript{16}) are not commercially available and require specialized laboratories. Access to functional assays varies between medical systems. In some countries a network of trained laboratories offers the HIPA test with a ≤ 48h turnaround time, while in other...
countries it is a major problem to get samples tested within reasonable time for clinical decision processes. In these settings, there is increasing evidence that some maneuvers may help to use the PF4/heparin enzyme immunoassay (EIA) alone for deciding on the strategy of anticoagulation during cardiac surgery or heart transplantation. These maneuvers are not optimal, but given the consequences of taking a patient off the heart transplant list they might be acceptable.

*Requirements for relying on a functional assay:
- use either platelets of 2 known sensitive donors or a panel of 4 donors. Do not pool donor platelets but test the patient serum with each donor platelets separately
- use a known negative and a know weak positive control serum which must give the expected results
- use low heparin concentrations (0.2 IU/mL) and high heparin concentrations (100 IU/mL) to show that the high heparin concentrations inhibit the reaction
- use the monoclonal antibody IV.3 to show that platelet activation is Fc-RIIa dependent
- use apyrase in the washing buffer during platelet activation to exclude desensitization of platelets by adenosindiphosphate
- heat inactivate patients serum 56°C, 30 min and add hirudin 5 IU/mL (final concentration) to exclude complement and thrombin dependent platelet activation

†Grades of recommendation were applied according to the systematic of the American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines 2008² (OD - optical density, Ig - immunoglobulin).
Figure 1
Table 1: Strategies to base the decision process of perisurgery anticoagulation in patients with a recent history of heparin-induced thrombocytopenia awaiting heart transplantation

<table>
<thead>
<tr>
<th>EIA result</th>
<th>Functional assay result*</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>negative</td>
<td>negative</td>
<td>Use heparin\textsuperscript{12}. \textit{Grade of recommendation 1B}\textsuperscript{†2}.</td>
</tr>
<tr>
<td>positive</td>
<td>positive</td>
<td>Postpone surgery and retest by functional assay every 3 days. If functional assay becomes negative use heparin during surgery and alternative anticoagulants post surgery. \textit{Grade of recommendation 1B}\textsuperscript{†2}.</td>
</tr>
<tr>
<td>positive</td>
<td>positive</td>
<td>In high urgency situation use alternative anticoagulants bivalirudin (\textit{Grade of recommendation 1C}\textsuperscript{†2})&gt;lepirudin (2C\textsuperscript{†2}) &gt; heparin+epoprostenol (2C\textsuperscript{†2})=heparin +tirofiban (2C\textsuperscript{†2}) if the transplant team is trained to handle the alternative anticoagulants during and post surgery.</td>
</tr>
<tr>
<td>positive</td>
<td>negative</td>
<td>In high urgency situation use heparin. \textit{Grade of recommendation 2C}\textsuperscript{†2}.</td>
</tr>
<tr>
<td>positive</td>
<td>not available within acceptable time</td>
<td>Repeat EIA with conjugate specific for IgG. If negative use heparin during surgery and alternative anticoagulants post surgery as IgM and IgA antibodies are very unlikely to cause clinical HIT\textsuperscript{19}. \textit{Grade of recommendation 2C}\textsuperscript{†2}.</td>
</tr>
<tr>
<td>positive</td>
<td>not available within acceptable time</td>
<td>Repeat EIA and add to a second well 100 IU/mL heparin. If there is not a &gt;50% decrease in OD in the presence of high heparin, the antibody is not PF4/heparin complex specific and heparin can be used during surgery\textsuperscript{20}. \textit{Grade of recommendation 2C}\textsuperscript{†2}.</td>
</tr>
<tr>
<td>positive</td>
<td>not available within acceptable time</td>
<td>PF4/heparin EIA IgG positive and inhibited by high heparin: Perform the EIA in duplicate. If both tests give an OD &lt; 1.0 use heparin\textsuperscript{14}. \textit{Grade of recommendation 2C}\textsuperscript{†2}. In this case it is a feasible backup safety measure to have epoprostenol or tirofiban at hand during surgery which could be given in case clotting starts to manifest during surgery due to HIT antibodies. Both substances will to immediately block platelet activation or aggregation, respectively. \textit{Grade of recommendation 2C}\textsuperscript{†2}.</td>
</tr>
</tbody>
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