

Heparin challenge test in patients undergoing cardiac surgery: dealing with heparin allergy

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A history of heparin hypersensitivity in patients undergoing cardiopulmonary bypass surgery poses the dilemma of which anticoagulant to use. Here, we report the successful use of a heparin challenge test in a 66-year-old female candidate for coronary artery bypass graft surgery with a past medical history of enoxaparin type I hypersensitivity after pulmonary embolism. Challenge and desensitization protocols are effectively used for essential antibiotics in patients with severe infections and/or allergies, or patients with aspirin intolerance requiring revascularization for coronary disease. A successful use of desensitization protocols to unfractionated heparin has been previously described in four patients undergoing cardiac surgery with various schemes. However, our case report indicates that a challenge test may also offer a quick, safe and effective approach in patients with a history of hypersensitivity reactions to heparin with inconclusive diagnostic tests and/

or whenever the use of alternative heparins is tricky. *Blood Coagul Fibrinolysis* 30:000–000 Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

Unfractionated heparin (UFH) is routinely used to prevent thrombosis within the cardiopulmonary bypass (CPB) circuit for its rapid onset of action after intravenous administration, its relative ease of monitoring, and its prompt reversal with protamine sulfate [1,2]. However, heparins may provoke various hypersensitivity reactions thus requiring the use of an alternative anticoagulant in patients undergoing CPB who have been diagnosed with heparin hypersensitivity. Thus, the utmost need for alternatives to UFH calls for changes in the routine practice of open-heart surgery on CPB and a multidisciplinary effort to avoid complications and delaying surgery. Here, we describe the use of a heparin challenge test in a candidate for coronary artery bypass graft surgery with a past medical history of immediate hypersensitivity reaction.

Case report

A 66-year-old female was admitted to the emergency department (ED) with concomitant acute heart failure and non-ST-segment elevation myocardial infarction. On arrival to the ED the patient was shaken, confused and showed tachypnea (32 bpm, SpO₂ 55%, pH 7.17, pCO₂ 75 mmHg, pO₂ 40 mmHg on arterial blood gas analysis), cyanosis, fibrillation with high ventricular rate (135 bpm) and high blood pressure (160/88 mmHg). Chest ultrasound and radiographs were consistent with pulmonary edema, while blood analyses revealed mild anemia (hemoglobin 104 mg/dl, hematocrit 0.36), increased levels of high sensitivity troponin up to 964 ng/ml (normal range 0–16 ng/ml)

and brain natriuretic peptide 354 ng/l (normal range 0–100 ng/l). Kidney function, sodium, potassium and D-dimer levels were all within the normal range.

The patient's past medical history included former smoker, morbid obesity (BMI 42 kg/m²), type 2 diabetes, a pulmonary embolism in 2003, nonvalvular atrial fibrillation treated with oral anticoagulant since 2010, an allergy to ciprofloxacin and an itchy urticarial reaction at the injection site of low-molecular-weight heparin (LMWH, enoxaparin) since 2003. The patient also reported hives on trunk and arms whereupon LMWH treatment was suspended. Warfarin became henceforth the anticoagulant of choice and fondaparinux was used as bridging therapy. The patient's past medical history reported no prior use of UFH.

The patient was admitted to the Department of Medicine for acute heart failure which was successfully treated by ventilatory support with continuous positive airway pressure, intravenous diuretics and nitrate. During hospitalization, apical wall akinesia was detected by transthoracic echocardiogram (ejection fraction 55%) and coronary angiography showed a significant stenosis of the left anterior descendant artery (70%) and the right coronary artery (70%). The coronary angiography was performed through the femoral artery without heparin. The patient was subsequently admitted to the Cardiac Surgery Department for coronary artery bypass graft surgery pending further allergy evaluation given her history of adverse reactions to heparin.

A possible sensitization to latex and chlorhexidine (the antiseptic more frequently used for skin disinfection before subcutaneous injections) was initially excluded via skin prick test (SPT) with purified allergens (Alkallerg, Hørsholm, Denmark; Lofarma, Milan, Italy) and blood analyses for latex-specific IgE antibodies (ImmunoCap, Uppsala, Sweden); immunoCAP, SPT and intradermal test (IDT) with a chlorhexidine gluconate solution for the antiseptic. Next, we assessed a possible allergy to enoxaparin sodium by SPT at a concentration of 10 000 IU aXa/ml and by IDT at increasing concentrations of 100 and 1000 IU aXa/ml (Clexane, Sanofi, Paris, France). Skin tests with enoxaparin yielded negative results both in immediate and delayed (48–72 h) readings, rendering the clinical suspicion of LMWH sensitization unlikely. However, the limited sensitivity of allergy testing – which in our patient was further hampered by the long period elapsed between the putative reaction and the diagnostic assessment – did not allow to definitively exclude a UFH allergy.

The cardiac anaesthesiologists therefore had to ponder whether to use an alternative anticoagulant for CPB – for example bivalirudin, less manageable than heparin – in the face of inconclusive allergy tests. Following a multidisciplinary discussion that included surgeons, anaesthesiologists, blood coagulation expert and allergist, the decision was made to perform a preliminary challenge test with intravenous, UFH, as the optimal strategy to mitigate any potential risk of significant side effects during CPB. UFH (intravenous sodium heparin Epsoclar; Pfizer Italia, Rome, Italy) was administered 5 days before the surgical procedure, under supervision by the ICU, in incremental doses as follows: 100 IU intravenous by continuous infusion during the first hour; 300 IU intravenous during the second hour; and 600 IU intravenous during the third hour. As the patient showed no allergic symptoms, surgery proceeded with heparinized CPB with no complications and an uneventful postoperative course. After surgery, intravenous sodium heparin was smoothly replaced with subcutaneously enoxaparin and later with oral anticoagulants at discharge (apixaban).

Discussion

Thanks to its rapid onset of anticoagulation after intravenous administration, relative ease of monitoring and prompt reversal with Protamine sulfate, UFH is the anticoagulant of choice for cardiac surgery requiring CPB [2].

Although heparins are widely used drugs, hypersensitivity reactions are uncommon. Cell-mediated, cutaneous delayed type IV hypersensitivity reactions (DHRs) are the most common, reported in up to 7.5% of patients receiving heparins, followed by heparin-induced thrombocytopenia (HIT – type II) and type I immediate reactions. Urticarial rash and angioedema are typically associated with IgE-dependent, type I reactions; skin

necrosis due to vasculitis suggests a type III Arthus reaction or HIT, while DHRs are characterized by erythematous, well circumscribed lesions without necrosis at the injection site – though with the possibility of granulomatous inflammation in long-standing use [3].

The history of our patient strongly suggested a type I reaction to enoxaparin, with local skin reactivity and diffuse urticaria. Symptoms disappeared after LMWH withdrawal, and warfarin/fondaparinux was used initially for pulmonary embolism and later for atrial fibrillation. Reports of type I reactions to heparins in the last 2 decades have become exceedingly rare, presumably thanks to improvements in the purification procedures, avoidance of preservatives and additives, a trend towards shorter treatment courses and the anti-inflammatory properties of heparins [4] (Table 1).

In type I hypersensitivity reactions, heparin must be discontinued immediately and the possibility of cross-reactions with alternative heparin formulations thoroughly investigated given the high risk of severe and potentially fatal systemic reactions. Blood analyses to detect specific IgE are currently not available, whilst skin tests (prick and intradermal) may help confirm heparin sensitization and investigate putative cross-reactivity among different formulations. Skin tests should be performed 4–6 weeks after symptom resolution and a variety of different heparins and heparinoid preparations may be used (e.g. including UFH, LMWH, heparinoids and fondaparinux) [5]. However, the sensitivity of most allergy tests with commercial formulations of drugs in the absence of purified haptens – as is the case for heparins – is limited and time-dependent, as it significantly decreases over time. These procedures should be performed by specialists with experience in drug allergy, and with the equipment to manage systemic reactions readily available.

A first-line pragmatic approach in DHRs may be to replace the culprit, that is subcutaneously or intravenously administered heparin. Nonetheless, patch tests and/or intradermal tests should be performed if symptoms do not improve even with the use of a second LMWH, to ascertain any cross-reactivity between different LMWH preparations. The putative role of latex, skin antiseptics and nickel contained in hypodermic needles should always be taken into consideration in delayed hypersensitivity reactions to injected drugs. Finally, heparin must be discontinued if the skin symptoms do not improve, and henceforth replaced with a different anticoagulant [5]. It bears mentioning that, at least theoretically, intravenous administered heparin in sensitized individuals (i.e. with DHR to subcutaneously injected heparins) may reach the skin by way of blood circulation and trigger a generalized eczematous or exanthematic eruption [3]. However, data showed that patients with DHR to heparins tolerate intravenous heparin administration [3]. Significantly, the incidence

Table 1 Type 1 hypersensitivity reactions reported in the literature in the last 2 decades

Case no.	Culprit drug	Test results for the culprit drug	Cross reactivity with other LMWH/UFH/ULMWH	Reference
1	Heparin	Pos (IDT)	Pos (IDT)/-/NT	Berkun Y (2004)
2	Dalteparin	Pos (CT)	NT/Neg (SPT/SST/CT)/NT	Ueda A (2001)
3	Enoxaparin	Pos (IDT/BAT)	Pos (IDT)/Pos (IDT)/NT	Caballero MR (2003)
4	Enoxaparin	Neg (SPT/IDT/BAT)	Pos (IDT/PT)/Pos (BAT)/NT	Caballero MR (2003)
5	Nadroparin	Pos (SPT/IDT)	Pos (SPT/IDT/CT)/Neg (SPT/IDT/PT)/Neg (SPT/IDT/PT)	Bekkenk MW (2005)
6	Dalteparin	Pos (SPT/IDT)	Pos (SPT/IDT)/Neg (SPT/IDT/CT)/Neg (SPT/IDT/CT)	Harr T (2006)
7	Enoxaparin	Pos (IDT)	Pos (CT)/Pos (CT)/Neg (SPT/IDT/CT)	Kavut AB (2012)
8	Enoxaparin	Pos (SPT)	Pos (SPT)/Pos (SPT)/Pos (SPT)	Anders D (2013)
9	Enoxaparin	Pos (IDT/BAT)	Pos (IDT/BAT)/Neg (SPT/IDT/CT)/Neg (SPT/IDT/BAT/CT)	Gonzalez P (2014)
10	Nadroparin	Pos (SPT/IDT/BAT)	Pos/Pos/Pos	Balthazar S (2014)
11	Dalteparin	Pos (SPT)	Pos (IDT)/Neg (SPT/IDT/CT)/Neg (SPT/IDT/BAT/CT)	Cesana P (2016)
12	Dalteparin	Neg (SPT/BAT)	Pos (IDT)/Neg (SPT/IDT)/Neg (SPT/IDT/BAT/CT)	Cesana P (2016)
13	Tinzaparin	Pos (SPT)	NT/NT/Neg (SPT)	Trog LM (2015)
14	UFH	NT	NT	Bottio T (2003)
15	UFH	NT	NT	Fields RM (2002)
16	UFH	NT	NT	Ochroch E (1997)
17	Enoxaparin	NT	NT/NT/pos CT	Leguisamo S (2015)
18	UFH	Pos (DLST)	NT	Katoh S (1993)
19	UFH	NT	NT	Ihara K (2018)
20	Nadroparin	NT	NT	Altıntaş ND (2009)
21	UFH	Pos (SPT, IDT)	Neg (SPT, IDT, CT)/-/NT	Santonsa A (2013)
22	Enoxaparin	Pos (IDT)	Pos (IDT)/Pos (IDT)/NT	Hallai N (2004)
23	UFH	Pos (DLST)	NT	Ohno H (2003)
24	Nadroparin	Pos (SPT)	Pos (SPT, CT)/Neg (PT, SPT, IDT)/NT	Bekkenk MW (2005)
25	Nadroparin	Pos (SPT, IDT)	Pos (SPT, IDT)/Pos (SPT, IDT)/Neg (SPT, IDT, CT)	Buonomo A (2015)
26	Enoxaparin UFH	NT	NT	Tiu A (2004)
27	UFH	Pos (SPT)	NT	Celiskaner Z (2005)
28	UFH, Enox/Nadroparin	Pos (IDT)	-/-/NT	Klos K (2011)
29	Dalteparin	Pos (IDT)	Pos (IDT)/NT/Neg (IDT)	Weber HO (2009)
30	UFH	NT	NT	Dave S (2008)
31	UFH	NT	NT	Parekh K (2005)

BAT, basophil activation test; CT, challenge test; DLST, drug lymphocyte stimulating test; IDT, intradermal test; LMWH, low-molecular-weight heparin; Neg, negative; NT, not tested; Pos, positive; PT, patch test; SPT, skin prick test; SST, skin scratch test; UFH, unfractionated heparin; ULMWH, ultra-low-molecular-weight heparin.

of DHR with fondaparinux is almost 20 times lower than that of other heparins [5].

Finally, subcutaneous/intravenous provocation/tolerance tests with incremental doses of heparin may be scheduled at a hospital under careful medical supervision to confirm hypersensitivity in selected cases with inconclusive diagnosis, negative skin test and no previous anaphylactic symptoms. The same approach may also apply to the choice of alternative anticoagulants in patients with a well established diagnosis of heparin allergy. In both instances, a 7-day follow-up may be warranted to account for any delayed reactions [6].

Another course of action in case of UFH allergy would be to consider alternative anticoagulant strategies in the management of patients with confirmed hypersensitivity to heparin and high risk of recurrence. However, only bivalirudin has been widely tested in patients undergoing cardiac surgery with CPB, with and without heparin hypersensitivity. Notwithstanding the advantageous pharmacological properties of bivalirudin in such patients [7], its use is challenging owing to the lack of a reversal agent, renal excretion, difficulties in monitoring and interferes with consolidated surgical protocols.

Based on these considerations, and given our patient's irrefutable history of hypersensitivity to enoxaparin but negative skin tests, we opted for a challenge test to

heparin. Incremental doses of UFH (up to a total of 1000 U) were administered without any adverse effect, thus allowing to perform CPB with full-dose heparin a few days later.

Our challenge regimen was very similar to administration schedules used to induce drug tolerance in many conditions, including the use of essential antibiotics in allergic patients with severe infections or aspirin in NSAID-intolerant patients requiring revascularization due to coronary disease [8]. Published protocols on antibiotics desensitization report starting doses ranging from 1/10 000 to 1/100 of the full therapeutic dose, depending on the severity of hypersensitivity reactions. The dose is then steadily increased, if tolerated. When the patient reaches the full therapeutic posology, desensitization is achieved [9–13]. Notably, tolerance is lost over hours or days if the drug is discontinued; likewise with aspirin and any other drug. A desensitization protocol to UFH has been described in the literature in four patients undergoing cardiac surgery, with various schemes that are summarized in Table 2 [14–17]. Particularly, sodium heparin desensitization protocols were more cautious than our challenge test, lasting at least 3 days with a gradual increase of the intravenous heparin dose, and no side effects were reported in any of the described cases. One patient in need of a mitral valve replacement underwent desensitization after developing urticaria from

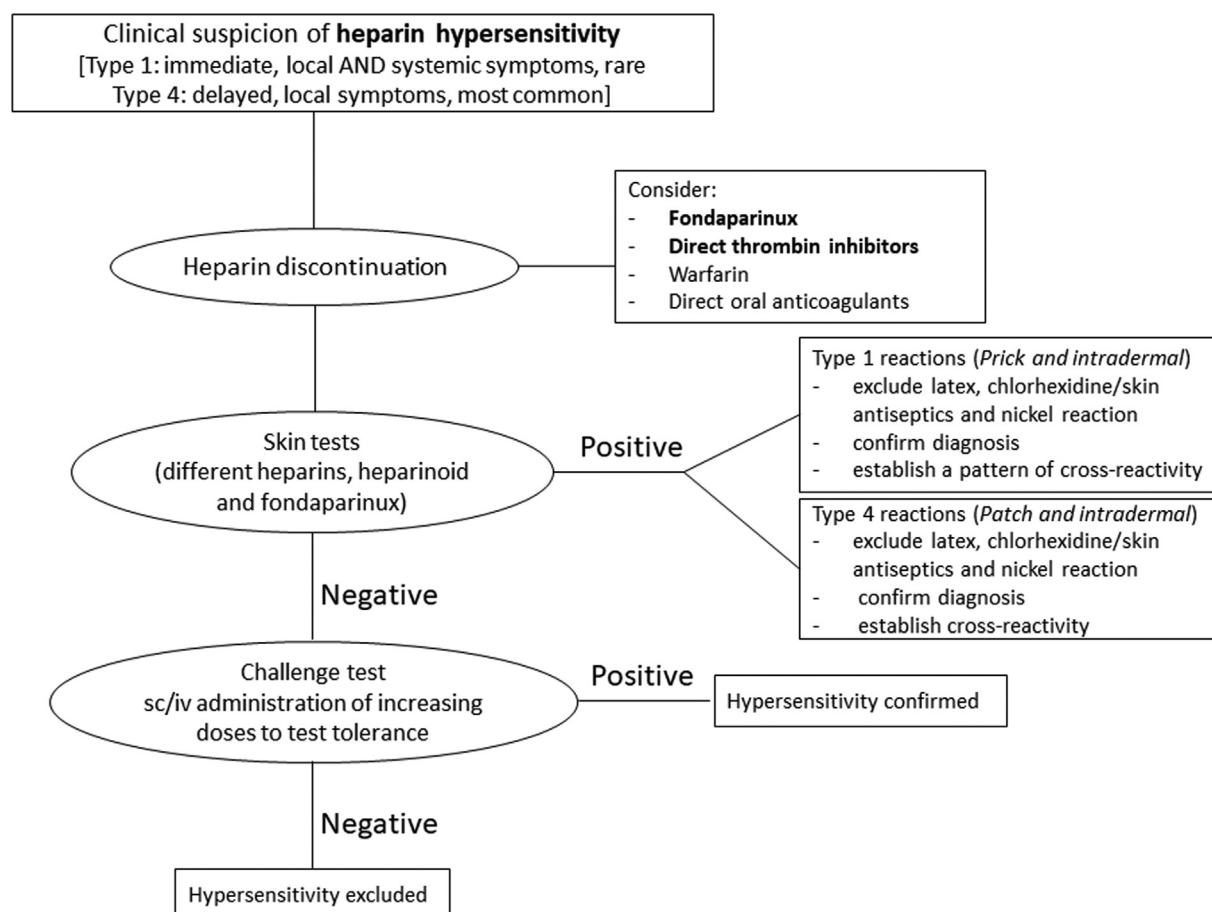
Table 2 Heparin desensitizing protocols described in case reports

Cae no.	Skin tests	Intervention	Desensitization protocol	Side effects	Reference
1	Negative (SPT)	Mitral valve replacement	Day 1: 50 IU sc UFH; after 40 m 250 IU sc UFH; after 40 m 500 IU sc UFH Day 2: 500 IU sc UFH; after 40 m 1500 IU sc UFH; after 40 m 3000 IU sc UFH Day 3: 500 IU iv UFH; after 40 m 1500 IU iv UFH; after 40 m 3000 IU iv UFH Day 4: 5000 IU iv UFH together with antihistamine drugs (4 mg clorpheniramine maleate) for 3 days	No	[16]
2	Positive (IDT)	CPB	Day 1: 100 IU iv UFH in 1 l normal saline in 24 h Day 2: 1000 IU iv UFH in 1 l normal saline in 24 h Day 3: 5000 IU iv UFH in 1 l normal saline in 24 h Day 4: 5000 IU sc UFH twice daily till surgery	No	[17]
3	Negative (SPT and IDT)	Cardiac transplantation	Day 1: 0.5 IU/h iv UFH in 12 h, then 1.5 IU/h iv UFH in 12 h Day 2: 4.5 IU/h iv UFH in 12 h then 13.6 IU/h iv UFH in 12 h Day 3: 40.8 IU/h iv UFH in 12 h then 122.5 IU/h iv UFH in 12 h Day 4: 367.4 IU/h iv UFH in 12 h, then 1008.0 IU/h iv in 12 h	No	[14]
4	Not performed	Pulmonary valve replacement	Premedication with acetaminophen and diphenhydramine Day 1: 10 IU iv UFH in 1 l saline in 24 h (at 42 ml/h) Day 2: 100 IU iv UFH in 1 l saline in 24 h Day 3: 1000 IU iv UFH in 1 l saline in 24 h Day 4: 5000 IU iv UFH in 1 l saline in 24 h Day 5: 500 IU/h iv UFH for 24 h Day 6: 100 IU/h iv UFH 3 h before initiating surgery	No	[15]

CPB, cardiopulmonary bypass; IDT, intradermal tests; iv, intravenous; sc, subcutaneous; SPT, skin prick test; UFH, unfractionated heparin.

subcutaneously calcium heparin or intravenous sodium heparin, with negative skin tests [16]. The sodium heparin desensitization protocol consisted of subcutaneously and intravenous UFH administration (from 50 IU

subcutaneously to 5000 IU intravenous) combined with antihistamines [16]. The second patient required CPB but he developed generalized severe pruritic, well circumscribed erythematous skin rashes at the injection site

Fig. 1

Clinical algorithm for patients with suspicion of heparin sensitivity.

of intravenous heparin with clinical evidence of bronchospasm, and subsequent positive IDT tests [17]. For the desensitization protocol, sodium heparin was diluted in 1 l of normal saline and administered intravenously over 24 h (100–5000 IU). The third case was a cardiac transplant candidate for nonischemic cardiomyopathy and his chart revealed a past pruritic, urticaria-like rash localized on his back after administration of intravenous UFH for atrial fibrillation [14]. He was then exposed to enoxaparin without any apparent adverse effects. The heparin desensitization protocol lasted 4 days and required gradually increasing intravenous infusion velocity every 12 h [14]. The final case described was a pulmonary valve replacement with a history of generalized hives and itching immediately after surgical intervention attributed to heparin infusion [15]. The desensitization protocol was adapted from the previous case [14] and premedication with acetaminophen and diphenhydramine, and starting from 10 IU diluted in 1 l saline over 24 h instead of 100 IU given the occurrence of generalized itching, shortness of breath, diarrhea and chest tightness within 10 min from the first infusion.

In conclusion, hypersensitivity reactions to heparins can be managed with different diagnostic and therapeutic approaches (Fig. 1) to allow patients to safely undergo cardiac surgery with adequate anticoagulation. Among the different strategies, a challenge test may represent a quick, safe and effective tool in patients awaiting cardiac surgery with a history of hypersensitivity reactions to heparin and inconclusive allergy tests.

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Conflicts of interest

There are no conflicts of interest.

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