

# Laboratory heparin resistance in burn injury complicated by venous thrombosis

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## Abstract

Anticoagulation with heparin is required in the management of the burn patient if their clinical course is complicated by venous thrombosis. Heparin therapy is commonly monitored by the activated partial thromboplastin time (APTT) but this assay can be unreliable in patients with acute inflammation because of an increase in plasma factor VIII levels that result in an underestimation of the heparin concentration. We report an example of heparin resistance that occurred in a patient who developed venous thrombosis following extensive second-degree burns. Heparin doses in excess of 60,000 units per day were required to produce a significant elevation in the APTT. The plasma factor VIII level was found to be markedly elevated to 455% and the plasma heparin concentration as determined by the anti-factor Xa assay was disproportionately elevated in relation to the APTT. Physicians treating patients with burn injury complicated by venous thrombosis should be aware of the potential development of factor VIII-related heparin resistance when large amounts of heparin are required to obtain a satisfactory elevation in the APTT. Measurement of the plasma heparin concentration will avoid excessive heparin administration and the serious bleeding which can result. © 1999 Elsevier Science Ltd and ISBI. All rights reserved.

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## 1. Introduction

Patients with burn injury are at increased risk of venous thrombosis with an estimated incidence of 0.4–1.2% [1,2]. Venous thrombosis is usually treated with unfractionated heparin, the dose of which is commonly monitored by the activated partial thromboplastin time (APTT) because of its low cost and rapid turn around time. Some patients require excessive amounts of heparin to prolong the APTT into the therapeutic range. This heparin resistance has been defined as a requirement of more than 35,000 U of heparin in a 24 h period to maintain the APTT in the therapeutic range [3]. Because the APTT assay can be affected by

a number of in vivo factors, this high heparin requirement may be artifactual when compared to results of the anti-factor Xa assay (heparin concentration). In turn, patients requiring anticoagulation can be exposed to excessive amounts of heparin with consequent increased risk for bleeding complications [4–6].

Heparin resistance can be caused by a variety of factors but one important mechanism to recognize clinically is the effect on the APTT assay of elevated plasma factor VIII levels. Elevated factor VIII concentrations shorten the APTT with or without heparin resulting in an underestimate of the plasma heparin concentration [3,7]. Several authors have indicated that heparin therapy can be monitored more effectively in this situation with a heparin assay such as the anti-factor Xa assay rather than with the APTT [3]. In one study, 111 patients with acute deep venous thrombosis, axillary thrombosis or pulmonary embolism who required 35,000 U of heparin or more during the pre-

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Table 1  
Relationship between heparin infusions rate, APTT, and plasma heparin concentration

Hospital day	Heparin infusion <sup>a</sup> rate (U/h)	APTT <sup>b</sup> (s)	Plasma heparin <sup>c</sup> concentration (units/ml)
1	–	23.6	–
2	1200	31.1	–
3	1800	35.6	–
4	1800	37.4	–
5	2500	50.7	–
6	2800	106.1	–
7	2500	76.3	1.1
8	2000	67.9	0.8
9	2000	106.1	–
10	1500	44.9	–
11	LMWH	31.9	0.5

<sup>a</sup> All infusion rates are with unfractionated heparin. LMWH on day 11 denotes low molecular weight heparin (enoxaparin).

<sup>b</sup> The APTT therapeutic range was 48.5–80.8 s, which corresponded to 1.5–2.5 times the mean APTT of the reference range.

<sup>c</sup> The heparin concentration was measured using an anti-factor Xa assay.

vious 24 h were randomized to have their heparin therapy monitored with either the anti-factor Xa assay or the APTT [3]. Although not statistically significant, there were 4 bleeding events in the APTT group compared with one in the anti-factor Xa group whereas there was low frequency of recurrent thrombosis in both groups. The heparin requirement in the latter group was significantly lower than in the APTT group by approx. 10%. The authors concluded that in patients who are heparin resistant by the APTT assay, dosage escalation can be avoided by measuring the heparin concentration rather than using the APTT for therapeutic monitoring.

Burn injury causes several blood coagulation abnormalities including elevated factor VIII [8,9]. One would expect to see heparin resistance in a significant proportion of patients who require treatment with unfractionated heparin because of venous thrombosis. The following is a report of such a case.

## 2. Case report

A 55 year-old male received second degree scald burns over his back, neck, arms, hands and ankles. He received these injuries at an alcohol distillery after inadvertently opening a heated pressurized compartment that contained “mash” from cooking grains. He was treated at a local emergency room and transferred immediately to the University of Kansas Medical Center Burn Unit. He was treated with frequent debridement, dressing changes, and supportive care. On day 7 a split thickness skin autograft obtained from both thighs was performed to close wounds on his back and arms. He was discharged on hospital day 18.

Six days later, the patient returned when he developed swelling of both lower extremities. Duplex color doppler studies showed thrombosis and noncompressi-

bility of the lesser saphenous and popliteal vein on the right, and short segmental thrombosis within the posterior tibial and peroneal veins distal to the popliteal system on the left. The patient was treated with a 5000 U bolus of unfractionated heparin followed by a constant heparin infusion of 1000 U/h. The heparin dose was increased progressively over the next 5 days because of the inability to elevate the APTT to within the therapeutic range of 1.5–2.5 times the mean of the reference range. An infusion rate of 1500–2800 U/h corresponding to over 60,000 U of heparin in 24 h was required to achieve a therapeutic APTT. Blood samples for anti-factor Xa assays were collected to evaluate the mechanism of heparin resistance. The relationship between heparin dose, APTT, and heparin level are shown in Table 1. Additional laboratory tests gave the following results: factor VIII, 455% (reference range, 50–150%), antithrombin III, 76% (reference range, 80–120%), erythrocyte sedimentation rate, 100 mm (reference range, 0–20 mm), and fibrinogen, 523 mg/dl (reference range, 200–400 mg/dl). Warfarin was initiated on day 7. On day 10, unfractionated heparin was discontinued and low molecular weight heparin (enoxaparin) was administered intravenously at a dose of 1 mg/kg twice daily to maintain a therapeutic range of 0.35–0.70 units/ml plasma as measured by the anti-factor Xa assay. Enoxaparin was continued until the international normalized ratio rose into the therapeutic range of 2.0–3.0. The patient was discharged on day 12 in good condition. He had experienced complete resolution of his lower extremity swelling.

## 3. Discussion

This case report demonstrates that heparin resistance can occur in burn patients who develop venous

thrombosis. The mechanism in this case was believed to be a 3-fold elevation in plasma factor VIII concentration which blunted the dose-response relationship between heparin concentration and the APTT and resulted in an underestimation of the heparin concentration [3,7]. This was confirmed by an excessively high heparin concentration of 1.1 unit/ml at a time when the APTT was within the therapeutic range. The relative insensitivity of the APTT to heparin resulted in the use of heparin doses in excess of 60,000 U per 24 h.

The cause of elevated factor VIII levels in burn injury is unclear. Factor VIII is synthesized by endothelial cells and released constitutively into plasma. It is possible that burn injury damages endothelial cells which results in the release of large amounts of factor VIII into the circulation. Burn injury also produces a marked inflammatory response with the release of cytokines that could promote factor VIII release [10]. In this case an increase in erythrocyte sedimentation rate and plasma fibrinogen were evidence for a marked acute phase response. The precise mechanisms that result in an elevated factor VIII concentration merit further investigation.

Other causes of heparin resistance have been demonstrated. Antithrombin III deficiency can cause a blunted APTT response to heparin therapy because of reduced formation of the heparin-antithrombin complex [11–13]. However, in one study, only 1% of cases of heparin resistance were attributed to antithrombin III deficiency indicating that this is an uncommon cause of heparin resistance [3]. High doses of intravenous nitroglycerin also shorten the APTT disproportionately by apparently producing a dysfunctional antithrombin molecule manifested as a low ratio of functional to antigenic antithrombin [14].

Heparin also binds to specific plasma proteins [15], endothelial cells [16,17], and monocytes [18], all of which have been implicated as causes of heparin resistance. On the other hand, the heparin binding proteins platelet factor 4 and histidine rich glycoprotein do not appear to be important causes of heparin resistance in most patients with venous thrombosis [15]. The possible role of these factors in the burn patient is unknown.

Physicians should perform additional laboratory studies when the amount of heparin required to attain a therapeutic level of the APTT exceeds 35,000 U in 24 h. Factor VIII-associated heparin resistance can be identified by demonstrating an elevated factor VIII level together with a disparity between the APTT and heparin concentration as measured by an anti-factor Xa assay. This can result in either a subtherapeutic value for the APTT with an adequate heparin concentration or adequate APTT value with an excessively high heparin level. If the APTT underestimates the

true heparin level, then therapy should be monitored with the anti-factor Xa assay. The therapeutic range most commonly reported in the literature for the anti-factor Xa assay is 0.35–0.70 units heparin/ml plasma [3,19] but this range varies depending on the test kit used by the clinical laboratory.

Plasma antithrombin levels should also be measured to evaluate for the rare case of heterozygous antithrombin deficiency. If significantly deficient, antithrombin replacement therapy should be considered to obtain a sufficiently high heparin-antithrombin concentration in plasma for adequate clinical anticoagulation with heparin [11–13].

In summary, burn patients are susceptible to heparin resistance because of elevations in factor VIII that accompany the physiological response to burn injury. Physicians treating patients with burn injury complicated by thrombosis should be aware of this phenomenon and avoid excess heparin doses and potentially serious bleeding.

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