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Heparin-Induced Thrombocytopenia and Thrombosis: Reversal With Streptokinase A Case Report and Review of Literature

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Heparin-induced thrombocytopenia and thrombosis is associated with a significant incidence of morbidity and mortality. Prompt recognition of this complication and immediate withdrawal of heparin therapy are imperative. This report describes a case of heparin-induced thrombosis and thrombocytopenia with major vascular insufficiency of the extremities. This is the first reported instance of the use of intravenous streptokinase for the treatment of heparin-induced venous thrombosis.

Key words: heparin, thrombocytopenia, thrombosis, streptokinase

INTRODUCTION

Thrombocytopenia following treatment with heparin has been recognized for many years, but heparin-induced thrombosis is less well known. The reported incidence of thrombocytopenia has ranged from 1% to 30% in patients receiving heparin therapy [1–5]. The only study identifying the incidence of thrombocytopenia in normal volunteers, by Schwartz et al. [6], showed that 33% of heparinized normals had decreased platelet counts. Thrombocytopenia occurs more frequently with bovine than with porcine heparin [5,7,8]. Heparin therapy may occasionally be ineffective in the prevention or treatment of thrombosis but paradoxically can cause thrombosis. There has been an increasing interest in the heparin-induced thrombocytopenia and thrombosis syndrome (HITTS). Whether the incidence of HITTS is truly increasing because of the more widespread use of heparin or the increasing frequency is apparent because of increased awareness is not known. HITTS is associated with a very high morbidity and a reported mortality of 18–36% [9–14]. We report a case of heparin-induced thrombocytopenia associated with upper- and lower-extremity venous thrombosis in whom therapy with intravenous streptokinase reversed the near-gangrenous changes and apparently prevented the need for amputation.

CASE REPORT

A 77-year-old Caucasian man with a history of chronic obstructive lung disease presented with a spontaneous right-sided pneumothorax that was treated by chest tube placement. The platelet count initially was 297,000/mm^3. A persistent bronchopleural fistula subsequently developed that required surgical closure. Postoperatively, he was started prophylactically on heparin 5,000 U subcutaneously (SC)q12h. Eight days later, his entire left upper extremity became swollen and tender. There was a deep purple macule over the left antecubital area, where a long brachial central line had been removed. The left upper extremity was discolored; however, the radial and ulnar pulses were easily palpable. A diagnosis of axillary and subclavian venous thrombosis was made and full-dose intravenous heparin begun. At this time, the fibrinogen level was 190 mg/dl, thrombin time 11.3 sec, and fibrinogen split products elevated >40 <80 μg/ml. Antithrombin III and protein C levels were normal at 103% and 108%, respectively. There was no evidence of disseminated intravascular coagulation (DIC) at any

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time. Seventy-two hr later, the left foot became similarly involved, and the left upper extremity was more edematous and discolored. A Doppler study revealed a thrombus in the left ileofemoral vein. The platelet count at this time was 24,000/mm^3. The patient was not on any drugs that could be incriminated for the thrombocytopenia other than heparin. A clinical diagnosis of HITTS was made, and heparin therapy was discontinued. At this time, streptokinase was started with a loading dose of 250,000 U intravenously (IV), followed by a continuous infusion of 100,000 U/hr, which was maintained for 72 hr. The platelet count rose gradually, reaching 140,000/mm^3 4 days later (Fig. 1). Multiple blisters appeared over both the left upper extremity and left lower extremity, and areas of skin necrosis gradually demarcated with well-defined borders. After 36 hr of streptokinase therapy, the patient was placed on coumadin. The near-gangrenous changes in both extremities regressed slowly (Fig. 2).

DISCUSSION

Heparin-induced thrombocytopenia was first observed in man by Fidlar and Jaques [15] in 1948. Thrombocytopenia induced by heparin, although quite common, is not widely recognized. Its incidence in patients receiving heparin has ranged from 1% to 30% [1–5]. Its occurrence is unrelated to the patients' age, sex, blood group, or underlying disease process or to the route or amount of heparin administered [1,9,10,16]. Weismann and Tobin [14] in 1958 first reported the association of arterial thromboemboli and systemic heparin therapy. Natelson et al. [17] in 1969 suggested that thromboembolic events could be caused by heparin-induced thrombocytopenia, later confirmed by Rhodes et al. [9] in 1973.

The mechanism of thrombocytopenia in HITTS is believed to be enhanced peripheral destruction of platelets [11,14,18–21]. An immune-mediated mechanism has long been postulated, and many investigators have detected a heparin-dependent platelet-aggregating factor in the blood of patients with this disorder. This platelet-aggregating antibody has been variously shown to be IgM [18,20], IgG–IgA [12], or IgG [9,10,22–24]. In the presence of heparin, this antibody fixes complement to the platelet membrane initiating prostaglandin synthesis with production of endoperoxidases and thromboxane A_2. The incited platelet release reaction liberates serotonin and ADP. The latter, together with the endoperoxidases and thromboxane A_2 induces platelet aggregation. These platelet aggregates combine with fibrin, resulting in the formation of a "white clot" [25,26], which on electron microscopic examination demonstrates predominantly fibrin platelet aggregates with few leukocytes or

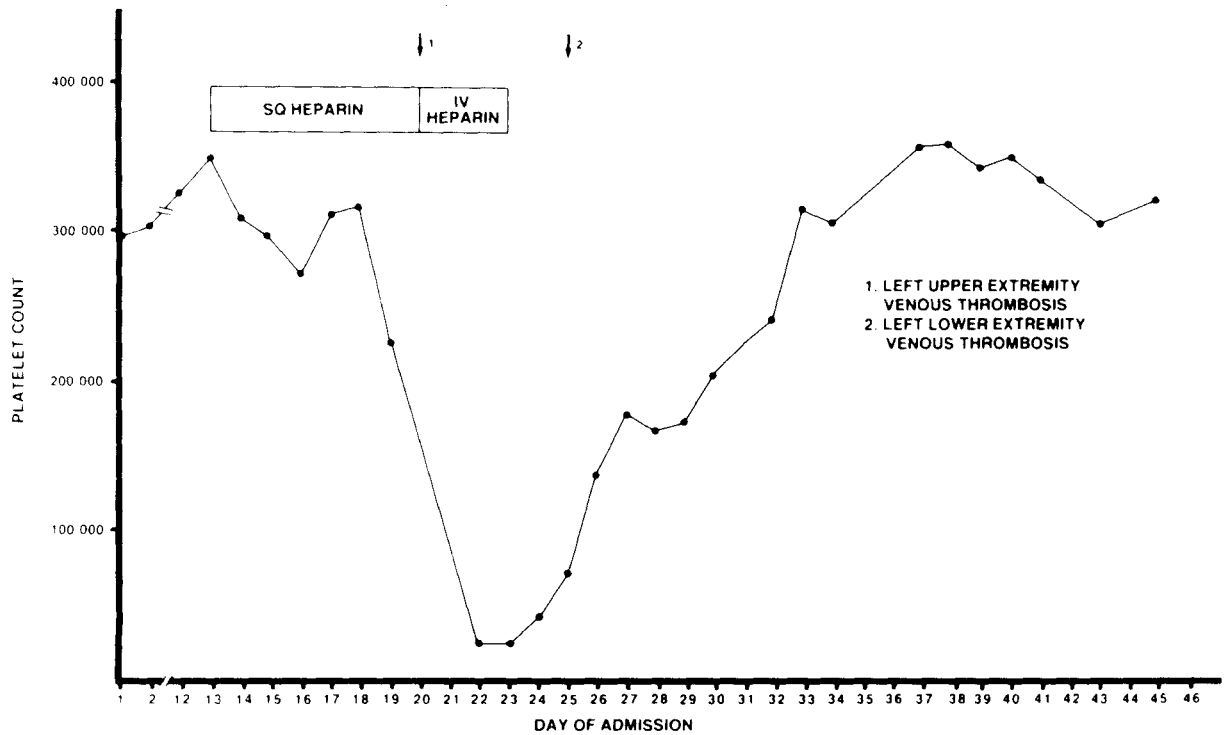

Fig. 1. Serial platelet counts, heparin therapy, and thrombotic complications.

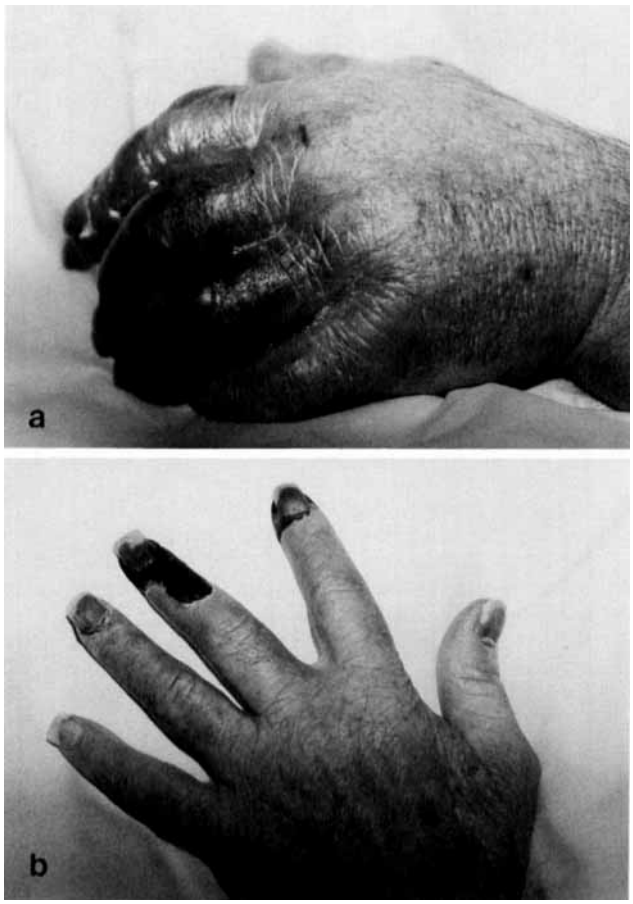

Fig. 2. Left hand during heparin therapy (a) and after streptokinase therapy (b).

erythrocytes. Heparin is also known to have a mild direct platelet-aggregating action [27,28] and may potentiate the action of other platelet-aggregating agents such as ADP and epinephrine [29,30].

A number of laboratory tests have been used to detect the presence of the heparin-dependent platelet-aggregating antibody. These include platelet aggregometry [22–24], [^{3}H]serotonin release from normal platelets in the presence of heparin and the patient's serum [12,16,18], platelet [^{14}C]serotonin release [31], modified technique of platelet factor 3 availability [10], complement fixation [9], complement lysis inhibition assay [20,32], agglutination of heparin-coated sheep erythrocytes [18], platelet-associated IgG assay [5], and enzyme-linked immunosorbent assay (ELISA) [33]. Platelet aggregometry is the most convenient and widely used among these methods. Patient serum (or plasma) is added to normal platelet-rich plasma and heparin, and the mixture is incubated in a platelet aggregometer [22,24]. This test, although specific, is not sensitive (36% sensitivity) [24]. In our patient, platelet aggregation studies were done but were normal. It should be mentioned that platelet-associated IgG is nonspecific and is not diagnostic of heparin-induced thrombocytopenia. Hence, the overall clinical picture should be carefully evaluated before making a definitive diagnosis.

The wide clinical spectrum of complications of HITTS can be divided into thrombotic (more common) and hemorrhagic phenomena. Arterial thrombosis secondary to heparin was first described by Weismann et al. [14] in 1958, and various reports have appeared since [11,12,20, 32,34]. Heparin may also induce extension of preexisting venous thrombi, sometimes resulting in pulmonary embolism [10,11,20,32]. Other manifestations of heparin-induced thrombosis are myocardial infarction [19,20,32], cerebral thrombosis [12,32,35], skin necrosis [11,35], renal artery embolism [12,14], mesenteric ischemia [11,36], spinal artery thrombosis [23], venous graft occlusion [11,24], and bowel infarction [11]. The hemorrhagic complications of HITTS include cerebral hemorrhage [11,20,32], wound hematoma [11,20], gastorintestinal bleeding [1,20,36], adrenal hemorrhage [37], skin bruising [11,22], and consumption coagulopathy [38,39,40]. Patients with HITTS have often required surgical intervention, including thrombectomies [11, 20,32], amputations [11,20,32,35], evacuation of hematomas [11], and excision of necrosed skin [35]. The mortality has been reported to be 18–36% [11–14]. The diagnosis of HITTS is essentially clinical. The typical patient has been on heparin therapy (subcutaneous or intravenous) for 5–10 days. The finding of a low platelet count with recurrent or de novo venous or arterial thromboembolism while the patient is on heparin therapy should alert the physician. Heparin therapy should be discontinued immediately after a clinical diagnosis of HITTS is made. Heparin-dependent antiplatelet antibodies may be present in $\leq$ 72% of patients [9,10,12,20, 24,25,32]. Delay in waiting for the aggregation studies while continuing heparin therapy may result in morbidity or mortality. Once heparin therapy is discontinued, the platelet count rises within 3–6 days [10,22,32]; occasionally, thrombocytosis may be seen.

The most important step in the management of HITTS is prompt withdrawal of heparin therapy. Patients with established thrombi are at increased risk of further thrombosis and embolism and are unfortunately left without effective anticoagulation when heparin therapy is discontinued. Various drugs have been tried in this situation. Warfarin has been used by various investigators [1,5,9,11,41], but its long latent period of action is an obvious disadvantage. Dextran therapy has been recommended [11,15,42], as have antiplatelet drugs, such as aspirin and dipyridamole [9,11,20,42]. The use of low-molecular-weight heparin has been under study, and various workers [43–45] have reported success, even in patients with thrombosis. It has been suggested,

however, that laboratory testing for cross-reactivity be performed before this drug is administered. Platelet transfusions are probably contraindicated [10,19,35], in view of immune destruction of platelets and the risk of further propagation of the "thrombus."

Streptokinase was identified as a secretory product of Lancefield group C β-hemolytic streptococci. Sherry [46] in 1954 showed that streptokinase acted on plasminogen to produce plasmin. Its clinical usefulness was first demonstrated by Johnson and McCarthy [47] in 1959. Streptokinase forms an equimolar complex with plasminogen. This activator complex is capable of converting plasminogen to plasmin, resulting in fibrinogen dissolution and digestion of clotting factors V, VIII, prothrombin, and fibrin. The increased levels of plasmin in the circulating blood results in high concentrations of fibrin and fibrin degradation products [47–51].

The effectiveness of systemic thrombolytic therapy in the dissolution of a thrombus is well established. However, its use in the patient with venous thrombosis associated with heparin has not been described. Intra-arterial streptokinase (or urokinase) has been shown to be effective in the dissolution of arterial thrombi [53,54] associated with HITTS. Pulmonary embolism resulting from this syndrome has been treated with streptokinase [44,55]. Although thrombosis of the extremities (both arterial and venous) is not an uncommon finding in HITTS, the use of intravenous streptokinase for this has so far not been described. It should be noted that Leroy et al. [45] used fibrinolytic treatment (urokinase) in conjunction with low-molecular-weight heparin for acute ischemia of the lower limbs.

Intravenous streptokinase therapy used in our patient resulted in the reversal of the near-gangrenous changes in both the upper and lower extremities resulting from venous thrombosis secondary to heparin therapy. The present case demonstrates the effectiveness of systemic thrombolytic therapy in this situation. Further studies may be needed to substantiate its continued value in patients with heparin-induced thrombocytopenia and thrombosis.

SUMMARY

Thrombocytopenia and thrombosis are not rare complications of heparin therapy. Declining platelet counts, increasing heparin requirements to maintain therapeutic levels of anticoagulation, and the occurrence of unexplained recurrent arterial or venous thromboembolism, myocardial infarction, or pulmonary embolism should alert one to the diagnosis of HITTS. Heparin should be withdrawn promptly, rather than increased. Platelet aggregation studies should be obtained, and an alternate form of anticoagulation started. The present case demonstrates the effectiveness of intravenous streptokinase for venous thrombosis in HITTS. The potential complications of heparin therapy are unpredictable, insidious in onset, and often life-threatening. It is therefore essential to observe the patient closely and monitor the platelet count whenever heparin is to be given for more than a few days.

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REFERENCES

1. Bell WR, Tomasulo PA, Alving BM, Duffy TP: Thrombocytopenia occuring during the administration of heparin. A prospective study in 52 patients. Ann Intern Med 85:155–160, 1976.
2. Cines DN, Kaywin P, Bina M, Tomaski A, Schreiber AD: Heparin-associated thrombocytopenia. N Engl J Med 303:788–795, 1980.
3. Nelson JC, Lerner RG, Goldstein R, Cagin NA: Heparin-induced thrombocytopenia. Arch Intern Med 138:548–552, 1978.
4. Malcolm ID, Wigmore TA, Steinbrecher UP: Heparin-associated thrombocytopenia: Low frequency in 104 patients treated with heparin of intestinal mucosal origin. Can Med Assoc J 120:1086–1088, 1979.
5. King DJ, Kelton JG: Heparin-associated thrombocytopenia. Ann Intern Med 100:535–540, 1984.
6. Schwartz KA, Royer G, Kaufman DB, Penner JA: Complications of heparin administration in normal individuals. Am J Hematol 19:355–363, 1985.
7. Bell WR, Royall RM: Heparin-associated thrombocytopenia: A comparison of three heparin preparations. N Engl J Med 303:902–907, 1980.
8. Powers PJ, Carter C, Kelton J, Hirsh J: Heparin associated thrombocytopenia: A randomized trial comparing beef lung and pork intestinal mucosal heparin. Blood 58:720A, 1981 (abst).
9. Rhodes GR, Dixon RH, Silver D: Heparin induced thrombocytopenia with thrombotic and hemorrhagic manifestations. Surg Gynecol Obstet 136:409–416, 1973.
10. Babcock RB, Dumper CW, Scharfman WB: Heparin-induced immune thrombocytopenia. N Engl J Med 295:237–241, 1976.
11. Silver D, Kapsch DN, Tsoi EKM: Heparin-induced thrombocytopenia, thrombosis and hemorrhage. Ann Surg 198:301–305, 1983.
12. Cimo PL, Moake JL, Weinger RS, Ben-Menachem Y, Khalil KG: Heparin-induced thrombocytopenia: Association with a platelet aggregating factor and arterial thrombosis. Am J Hematol 6:125–133, 1979.
13. Hussey CV, Bernhard VM, McLean MR, Fabian JE: Heparin induced platelet aggregation: In vitro confirmation of thrombotic complications associated with heparin therapy. Ann Cli Lab Sc 9:487–493, 1979.
14. Weismann RE, Tobin RW: Arterial embolism occuring during systemic heparin therapy. Arch Surg 76:219–227, 1958.
15. Fidlar E, Jaques LB: The effect of commercial heparin on the platelet count. J Lab Clin Med 33:1410–1423, 1948.
16. Fratantoni JC, Pollet R, Gralnick HR: Heparin-induced thrombocytopenia: Confirmation of diagnosis with in vitro methods. Blood 45:395–401, 1975.
17. Natelson EA, Lynch EC, Alfrey CP Jr, Gross JB: Heparin-induced thrombocytopenia. An unexpected response to treatment of consumption coagulopathy. Ann Intern Med 71:1121–1125, 1969.
18. Wahl TO, Lipschitz DA, Stechschulte DJ: Thrombocytopenia associated with antiheparin antibody. JAMA 240:2560–2562, 1978.
19. Ansell J, Deykin D: Heparin-induced thrombocytopenia and recurrent thromboembolism. Am J Hematol 8:325–332, 1980.
20. Rhodes GR, Dixon RH, Silver D: Heparin induced thrombocytopenia:

Eight cases with thrombotic–hemorrhagic complications. Ann Surg 186:752–758, 1977.
21. Hrushesky WJ: Subcutaneous heparin-induced thrombocytopenia. Arch Intern Med 138:1489–1491, 1978.
22. Chong DH, Grace CS, Rozenberg MC: Heparin-induced thrombocytopenia: Effect of heparin platelet antibody on platelets. Br J Haematol 40:531–540, 1981.
23. Chong BH, Pitney WR, Castaldi PA: Heparin-induced thrombocytopenia: Association of thrombotic complications with heparin-dependent IgG antibody that induces thromboxane synthesis and platelet aggregation. Lancet 2:1246–1249, 1982.
24. Kelton JG, Sheridan D, Brian H, Powers PJ, Turpie AG, Carter CJ: Clinical usefulness of testing for a heparin-dependent platelet-aggregating factor in patients with suspected heparin-associated thrombocytopenia. J Lab Clin Med 103:606–612, 1984.
25. Towne JB, Bernhard VM, Hussey C, Garancis JC: White clot syndrome: Peripheral vascular complications of heparin therapy. Arch Surg 114:372–377, 1979.
26. Chang JC: White clot syndrome associated with heparin-induced thrombocytopenia: A review of 23 cases. Heart Lung 16:403–407, 1987.
27. Carreras LO: Thrombosis and thrombocytopenia induced by heparin. Scand J Hematol 25(suppl):64–80, 1980.
28. Eika C: Inhibition of thrombin induced aggregation of human platelets by heparin. Scand J Hematol 8:216–222, 1971.
29. Salzman EW, Rosenberg RD, Smith MH, Lindon JN, Faureau L: Effect of heparin and heparin fractions on platelet aggregation. J Clin Invest 65:64–73, 1980.
30. Eika C: On the mechanism of platelet aggregation induced by heparin, protamine and polybrene. Scand J Hematol 9:248–257, 1972.
31. Sheridan D, Carter C, Kelton JG: A diagnostic test for heparin-induced thrombocytopenia. Blood 67:27–30, 1986.
32. Kapsch DN, Adelstein EH, Rhodes GR, Silver D: Heparin-induced thrombocytopenia, thrombosis and hemorrhage. Surgery 86:148–155, 1979.
33. Howe SE, Lynch DM: An enzyme-linked immunosorbent assay for the evaluation of thrombocytopenia induced by heparin. J Lab Clin Med 105:554–559, 1985.
34. Gervin AS: Complications of heparin therapy. Surg Gynecol Obstet 140:789–796, 1975.
35. White PW, Sadd JR, Nensel RE: Thrombotic complications of heparin therapy including six cases of heparin-induced skin necrosis. Ann Surg 190:595–608, 1975.
36. Lindsey SM, Maddison FE, Towne JB: Heparin-induced thromboembolism: Angiographic features. Radiology 131:771–774, 1979.
37. Cheng TC: Thrombocytopenia associated with minidose heparin therapy. Postgrad Med J 70:73–78, 1981.
38. Klein HG, Bell WR: Disseminated intravascular coagulation during heparin therapy. Ann Intern Med 80:477–481, 1981.
39. VanAken WG: Thrombocytopenia (and consumption coagulopathy) induced by heparin. A case report. Scand J Hematol 25:(suppl 25):85–90, 1980.
40. Zalcberg JR, McGrath K, Dauer R, Wiley JS: Heparin-induced thrombocytopenia with associated disseminated intravascular coagulation. Br J Haematol 54:655–660, 1983.
41. Baird RA, Convery FR: Arterial thromboembolism in patients receiving systemic heparin therapy. J Bone Joint Surg 59A:1061–1064, 1977.
42. Herring WB, Shelburne PF: Heparin-induced thrombosis. N C Med J 45:159–162, 1984.
43. Roussi JM, Houbouyan LL, Goguel AF: Use of low-molecular-weight heparin in heparin-induced thrombocytopenia with thrombotic complications. Lancet 1:1183, 1984.
44. Benhamou AC, Gruel Y, Barsotti J, Castellani L, Marchand M, Guerois C, Leclerc MH, Delahousse B, Griguer P, Leroy J: The white clot syndrome or heparin associated thrombocytopenia and thrombosis. Int Angiol 4:303–310, 1985.
45. Leroy J, Leclerc MH, Delahousse B, Guerois C, Foloppe P, Gruel Y, Toulemonde F: Treatment of heparin-associated thrombocytopenia and thrombosis with low molecular weight-heparin (CY 216). Semin Thromb Hemost 11:326–329, 1985.
46. Sherry S: The fibrinolytic activity of streptokinase activated human plasmin. J Clin Invest 33:1054–1063, 1954.
47. Johnson AJ, McCarthy WR: The lysis of artificially induced intravascular clots in man by intravenous infusion of streptokinase. J Clin Invest 38:1627–1643, 1959.
48. Sherry S, Gustafson E: The current and future use of thrombolytic therapy. Annu Rev Pharmacol Toxicol 25:413–431, 1985.
49. Marder VJ, Sherry S: Thrombolytic therapy: Current status (first of two parts). N Engl J Med 318:1512–1520, 1988.
50. Marder VJ, Sherry S: Thrombolytic therapy: Current status (second of two parts). N Engl J Med 318:1585–1595, 1988.
51. Sharma GVRK, Cella G, Parisi AF, Sasahara AA: Drug therapy—thrombolytic therapy. N Engl J Med 306:1268–1276, 1982.
52. Volgesang GB, Bell WR: Treatment of pulmonary embolism and deep venous thrombosis with thrombolytic therapy. Clin Ch Med 5:487–494, 1984.
53. Fiessinger JN, Aiach M, Roncato M, Debure C, Gaux JC: Critical ischemia during heparin-induced thrombocytopenia. Treatment by intra-arterial streptokinase. Thromb Res 33(2):235–238, 1984.
54. Krueger SK, Andres E, Weinand E: Thrombolysis in heparin-induced thrombocytopenia and thrombosis. Ann Intern Med 103:159, 1985.
55. Cohen JI, Cooper MR, Greenberg CS: Streptokinase therapy of pulmonary emboli with heparin-associated thrombocytopenia. Arch Intern Med 145:1725–1726, 1985.