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Increased Heparin Requirement with Hypereosinophilic Syndrome

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Hypereosinophilic syndrome is characterized by idiopathic eosinophilia of the blood and bone marrow with diffuse organ infiltration with eosinophils. Cardiovascular involvement is characterized by cardiomyopathy often with subendocardial fibrosis and mural thrombosis.[1,2] We report a case of mitral and tricuspid valve replacement complicated by hypercoagulability requiring more than twice the routine heparin dose for cardiopulmonary bypass.

REPORT OF A CASE

A 26-year-old man with hypereosinophilic syndrome and increasing heart failure underwent a mitral and tricuspid valve replacement with Bjork-Shiley prosthetic valves. Postoperatively, anticoagulation was maintained with coumadin, 5 mg daily, prolonging the pro thrombin time (PT) to 16.5 s (control 11.7 s). Three months later, he developed increasing cardiac failure and a left visual field defect, secondary to a cerebral embolus seeding from a prosthetic heart valve. Fluoroscopy revealed only 15° (normal 60°) movement of the tricuspid valve and obstructing clot. The patient subsequently lost femoral pulses and emboli to the femoral bifurcation was suspected. In an attempt to achieve adequate anticoagulation, coumadin administration was terminated and heparin, 16,000 units, was given subcutaneously every eight hours prolonging the partial thromboplastin time (PTT) to 60.8 s (control 30.4 s). Femoral pulses returned and normal tricuspid valve motion was seen at subsequent fluoroscopy.

One month later he was again admitted to the hospital with intractable heart failure from an immobile tricuspid valve. Heparin, 2500 units every hour, resulting in a PTT of 59.7 s (control of 31.2 s) failed to prevent emboli. An extensive evaluation of factors predisposing the

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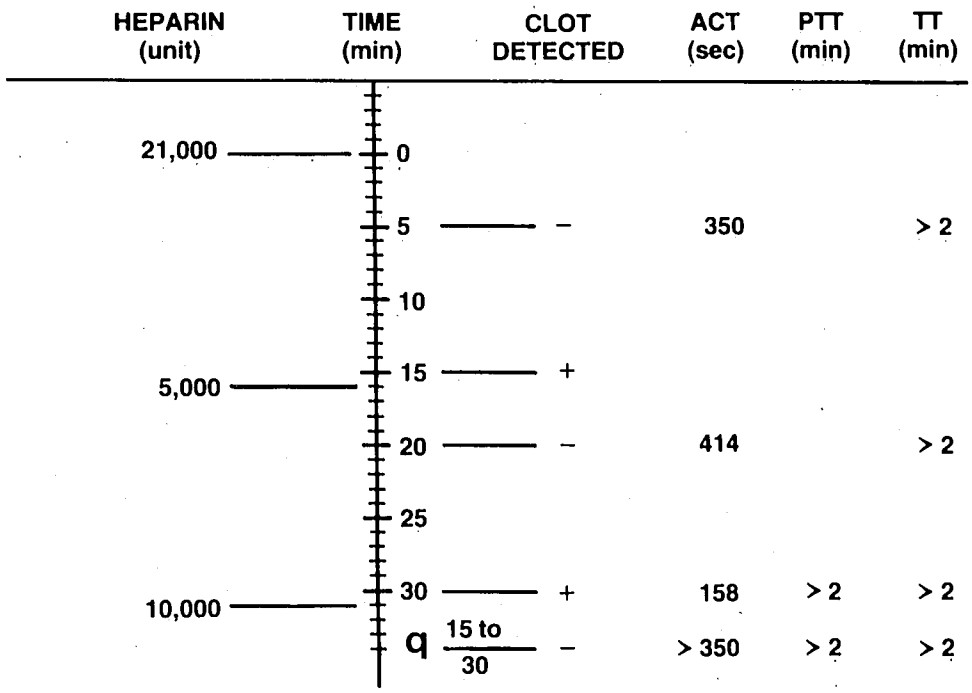

FIG. 1. Correlation between heparin administration, the presence of a clot and coagulation variables. (−) = no clot present; (+) = clot visibly present; $\frac{q\ 15\ to}{30}$ = every 15 to 30 minutes; ACT = activated clotting time; PTT = partial thromboplastin time; TT = thrombin time.

patient to systemic embolization was done. However, the values for antithrombin III, platelet factor 4, beta gamma globulin, plasminogens, and plasmins were normal. Medical therapy of 0.25 mg digoxin, po, qd, 40 mg furosemide, po, qd, and continuation of the therapy for hypereosinophilia of 40 mg prednisone, po, qod, and 2500 mg hydroxyurea, po, qd, did not relieve the symptoms. Surgical intervention was recommended to replace the valves with potentially less thrombogenic porcine xenografts.

The heparin was discontinued eight hours prior to surgery. Immediately prior to surgery, laboratory values included Hgb 8 g/dl, Hct 23 per cent, WBC 35,900 cells/mm^3 with 87 per cent eosinophilia, platelets 45,000 cells/mm^3, pro thrombin time 12.0 s (control 12.2 s), partial thromboplastin time of 47.9 s (control 28–35 s), and thrombin time (TT) of 28.3 s (control 28–35 s). Anesthesia was induced with the intravenous administration of 20 mg diazepam, 12 mg morphine, and 75 mg thiopental and maintained with an additional 20 mg morphine and nitrous oxide. Prior to the institution of cardiopulmonary bypass, the activated clotting time (ACT) was 110 s.

Heparin, 3 mg/kg (21,000 units), was injected into the heart. Subsequent values of ACT, PTT, and TT, and presence or absence of gross clot are shown in fig. 1. Fifteen minutes after the initial dose of heparin, the surgeon noted a clot on the tip of the superior vena cava cannula when preparing for cardiopulmonary bypass. Additional heparin was then given 16 min after the first dose. Bypass was instituted 21 min after the first heparin dose and the patient cooled to 30°C. However, the pump technician reported poor venous return and observed small clots in the overflow line 30 min following the first heparin dose. More heparin was then injected into the pump at 31 min and ACT, TT, and PTT were measured every 15–30 min during the 2 and 21 min total bypass time; all variables demonstrated adequate anticoagulation.

Immediately prior to termination of cardiopulmonary bypass, the ACT was 261 s, PTT 68 s, TT greater than 2 min, and platelet count of 50,000 cells/mm^3. After successful weaning from bypass, protamine was titrated and a total dose of 300 mg resulted in ACT 110 s, PT 19.2 s, PTT 54 s, and TT of 48 s.

On disassembly of the cardiopulmonary bypass machine heavy clotting on the Tricot® lining of the oxygenator was found. The patient, however, was alert 8 h after surgery and demonstrated no renal, pulmonary, or central nervous system compromise.

DISCUSSION

Hypereosinophilic syndrome encompasses multiple disorders that present excessive eosinophils in the blood and diffusely infiltrating organs. Depending upon the major system involvement, it has been designated as pulmonary infiltration with eosinophilia, Loeffler's endocarditis parietalis fibroplastica, endomyocardial fibrosis with eosinophilia, eosinophilic leukemia, eosonophilic gastritis, eosinophilic cystitis, and disseminated eosinophilic collagen disease. There is a male predominance with an age range of 7–65 years.[2] The etiology is unknown and average duration of illness is 18 months with death attributed to progressive cardiac failure in the majority of cases.[3-5]

The major morbidity and mortality results from cardiac involvement. Symptoms reported are dyspnea (55 per cent), congestive heart failure (53 per cent), mitral regurgitation (47 per cent), cardiomegally (36 per cent), and T wave inversion (36 per cent).[6] Histiologic exam of the myocardium reveals eosinophilic infiltration with patchy fibrosis with mural thrombosis formation in the left ventricle in more advanced cases.[1]

A 5 per cent incidence of systemic embolization is reported clinically, though organ emboli are often found at autopsy.[6] Our cases had multiple episodes of embolization despite anticoagulation and thrombocytopenia. The thrombocytopenia of our patient is unique and is

attributed to hydroxyurea, a recent addition to the therapeutic regimen for hypereosonophilia. Hydroxyurea causes hemopoietic depression involving leukopenia, megablastic anemia and thrombocytopenia and blocks DNA synthesis through action on ribonucleoside diphosphace reductase.[7]

The etiology of the embolization and a laboratory test to predict the thrombotic tendency of the hypereosinophilic patient is unknown. Therefore, extreme difficulty was anticipated in achieving adequate anticoagulation during cardiopulmonary bypass. However, in our case, the absence of clot seemed to correlate with a therapeutically prolonged ACT. When our patient's ACT was near the normal value (less than 160 s), thrombosis was evident despite heparin administration and prolonged PTT and TT.

The ACT is a nonspecific test that detects deficiencies of any procoagulant other than factor VII[8] which correlates with the concentration and the semilogarithmic disappearance of heparin in the blood.[9,10] An ACT value of less than 300 s indicates insufficient heparin during a surgical procedure; more than 600 s indicates overheparinization.[10]

We recommend the ACT be carefully monitored in patients with hypereosinophilic syndrome. In our particular case, the ACT seemed to reflect the degree of anticoagulation though this cannot be explained theoretically. In view of the clinical embolization that may occur with hypereosinophilic syndrome, the need for additional heparin may be necessary and dose titrated by ACT monitoring.

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Prevention of Rigidity during Fentanyl–Oxygen Induction of Anesthesia

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Induction and maintenance of anesthesia with high-dose fentanyl and oxygen has been shown to cause minimal changes in cardiovascular dynamics in patients with mitral valvular disease[1] and in those undergoing surgery for myocardial revascularization.[2] Stanley and Webster[1] found that 10 μg/kg did not significantly change any cardiovascular variable studied and that 20 μg/kg produced a significant decrease in heart rate and mean arterial pressure without affecting stroke volume, cardiac output, central venous pressure, or peripheral vascular resistance. One of the frequently reported disadvantages of fentanyl is the development of chest and abdominal wall rigidity. In a series of 359 patients, 285 (79.4 per cent) developed this complication[3] following an infusion of 8.8 μg/kg administered over a period of 1 min, resulting in slight to total inability to inflate the chest. More recently, Comstock *et al.*[4] using 200 μg/min fentanyl reported a high incidence of rigidity associated with hypercarbia and Kentor *et al.*[5] using 50 μg/kg infused over 60 s reported 100 per cent occurrence of rigidity. Stanley,[1] infusing 50–200 μg/kg fentanyl reported no incidence of rigidity. Lunn *et al.*[2] using 300 μg/min fen-

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