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Lethal Thrombosis during Coronary Artery Bypass Graft Surgery

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One of the most common problems in cardiac surgical patients in the immediate postoperative period is a clinically significant coagulopathy. Rarely do patients exhibit accelerated clot formation. We present one such case leading to a fatal outcome.

REPORT OF A CASE

A 76-yr-old, 76 kg man underwent coronary artery bypass grafting because of angina refractory to treatment with oral isosorbide dinitrate and nifedipine. Cardiac catheterization demonstrated multi-vessel disease with preserved ventricular function. Mild hypertension was controlled with hydrochlorthiazide. Four years prior to admission, transurethral prostatic resection had been performed to treat prostatic carcinoma. Since then, the patient took oral diethylstilbesterol 1 mg daily. There were no known metastases; orchiectomy was not performed. The patient denied a history of, or symptoms suggestive of, a bleeding diathesis, or of cerebral, pulmonary, or peripheral embolism. On examination, heart rate was 88 beats/min, and arterial blood pressure 140/90 mmHg. Electrocardiogram (ECG) revealed no evidence of ischemia or infarction. Prothrombin time was 11.6 s (11–13 s normal); activated partial thromboplastin time was 29.8 s (25–40 s normal); packed red cell volume was 38.8%; platelet count was 338,000/mm^3 (normal range 150,000–500,000/mm^3). A serial thrombin test was normal.

Following im morphine and scopolamine, a five-lead ECG and arterial and pulmonary arterial catheters were placed. Anesthesia was induced with sufentanil 3 $\mu g \cdot kg^{-1}$ and lorazepam 2 mg iv. Vecuronium iv facilitated endotracheal intubation. Anesthesia was maintained with additional sufentanil, and low concentrations of halothane in oxygen.

Beef lung heparin, 25000 units, provided anticoagulation; the activated clotting time (ACT) rose from a baseline of 127 s to 577 s. Bypass employed a Bentley-10 oxygenator with clear fluid prime containing 5000 units of beef lung heparin, systemic hypothermia to 26° C rectal, and cold potassium cardioplegia.

The left internal mammary artery (IMA) was grafted to the left anterior descending artery; saphenous vein segments were grafted from aortic root to the first diagonal and right coronary arteries. Total bypass time was 75 min, with aortic cross clamp time of 41 min. Weaning from bypass occurred easily with 1 gm calcium chloride iv. Graft flow was judged very good by palpation. After 300 mg of protamine sulfate iv, infused over 10 min, the ACT measured 127 s. The post-bypass course was characterized by hemodynamic stability and minimal bleeding. No blood products were administered.

One hour after protamine administration, during preparation for patient transport from the operating room table, acute ST segment elevation was noted in ECG leads II and V_5. Mean systemic arterial blood pressure decreased to 50 mmHg and heart rate increased to 120 beats/min. Nitroglycerine (NTG) infusion at 200 μg/min iv and divided doses of nifedipine sublingually (5 mg, then 10 mg) were administered, with no clinical improvement. Dobutamine, 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ iv, was infused to support the circulation. Immediate re-exploration of the chest revealed a dry, bloodless mediastinum. Palpation of the vein grafts suggested that they were occluded. The IMA graft was pulsatile. Heparin, 35000 units iv, was administered, and bypass was re-instituted. A #3 Fogarty catheter passed easily into the native coronary arteries. However, large amounts of fresh thrombus were removed from each vein graft. NTG, 200 μg, was injected into each vein graft. The left anterior descending artery and its anastomosed IMA were probe patent; no thrombus was recovered from those sites.

Weaning from bypass required iv infusions of dobutamine, epinephrine, and amrinone, as well as mechanical support with an intra-aortic balloon pump. Protamine was specifically withheld. Despite maximal support, cardiac index remained well below 2.0 $l \cdot min^{-1} \cdot m^{-2}$. The patient expired shortly after arrival in the intensive care unit from biventricular failure and cardiogenic shock.

DISCUSSION

There are several factors that may have contributed to the lethal coronary graft thrombosis in this patient: malignancy in general, prostatic malignancy in particular, estrogen therapy, extra-corporeal circulation, surgical technique, and coronary spasm.

Patients with malignancies, particularly those that are metastatic,[1] commonly exhibit an active clotting process with concomitant fibrinolysis.[2–5] Clotting can be initiated directly by tumor cells *via* plasminogen activation, by thromboplastin generation, and by tumor cell aggregation with platelets and fibrin. The physiologic response to clotting factor consumption is increased production. Depending on the balance between consumption and production, one of three states is obtained:[1,6,7] bleeding (consumption > production); thrombosis (consumption < production); or compensation (consumption = production). Patients with malignancies may have any of those three coagulation states. In particular, prostatic cancer cells are rich in thromboplastin.[6] Not surprisingly, prostatic carcinoma has been linked both with hypercoaguability[8] and excessive bleeding.[8,9] The latter condition is usually associated with widespread metastases.[5] Resection of this patient's primary tumor and the absence of known metastases

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make these factors unlikely to be responsible for a hypercoagulable state that could lead to graft thrombosis.

Patients with prostatic carcinoma who are treated with estrogens display an increased risk of thromboembolic complications,[10,11] including venous thrombosis, pulmonary embolism, and myocardial and cerebral infarctions.[12] The proposed mechanism for this thrombotic tendency (fig. 1) involves estrogen suppression of plasminogen activation[13] and decreased activity of antithrombin III (AT-III).[11,12]

By itself, reversal of anticoagulation for extracorporeal circulation has been found to decrease AT-III levels: 40 patients undergoing open heart surgery displayed depressed AT-III levels measured following reversal of heparin with protamine.[14] This relative AT-III deficiency produces a tendency towards hypercoagulation.

Poor surgical technique is always suspect when an unacceptable anatomic result occurs. In this case, however, all anastomoses were performed by an attending cardiothoracic surgeon with over a decade of active surgical experience using routine techniques for handling and suturing the grafts. While fresh anastomoses might form a likely site for initiation of clotting in a hypercoagulable state, there is no reason to believe that surgical factors alone caused graft occlusion within an hour of termination of cardiopulmonary bypass.

Another possible explanation of these events is the occurrence of coronary spasm, with subsequent low-flow and thrombosis in the vein grafts. Based on the ECG appearance of ST segment elevations, we administered NTG and nifedipine,[15] and the surgeon injected intra-coronary NTG *via* the vein grafts following declotting. Nevertheless, for several reasons, we believe that coronary spasm cannot satisfactorily account for the clotted grafts: ST segment elevation denotes transmural ischemia, and is not pathognomonic of coronary spasm; the ischemia did not respond to appropriate doses of NTG and nifedipine; finally, to implicate coronary spasm as the cause of graft thrombosis in our patient, one must presume not only its simultaneous occurrence in both the right and first diagonal coronary arteries, but also the formation of clot within the few minutes separating hemodynamic deterioration and opening of the chest. Graft clotting associated with coronary spasm has been reported in two patients.[16] However, in that report, the time course was different: one patient had thrombus discovered at autopsy; the other patient's graft was found occluded at a subsequent catheterization. Graft clotting is not typically found in patients who experience post-surgical coronary spasm.[17]

We thus speculate that estrogen therapy and extracorporeal circulation, with its required manipulation of the coagulation system, were the factors predisposing

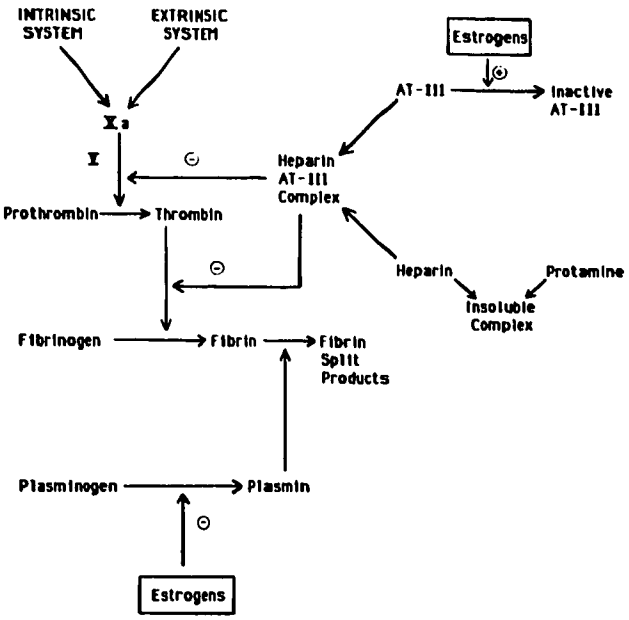

FIG. 1. The final common pathway of the coagulation cascade showing the two sites at which estrogen act to promote thrombosis. Estrogens inhibit conversion of plasminogen to plasmin, thereby inhibiting the breakdown of fibrin to fibrin split products. Estrogens also partially inactivate AT-III. Heparin activates AT-III and thus counteracts the AT-III inhibitory effect of estrogens. By forming a complex with heparin, protamine antagonizes the salutory action of heparin.

this patient to his lethal thrombotic event. We presume diethylstilbesterol decreased AT-III activity in this patient to a subclinical extent, allowing a normal ACT elevation following heparin administration. Extracorporeal circulation then further reduced AT-III levels. Reversal of heparin with protamine uncovered this AT-III activity deficiency leading to thrombus formation at the sites of recent vascular mechanical disturbance: the saphenous vein grafts. We presume that, during the hour-long post-bypass course, thrombus was slowly forming undetected, until total graft occlusion resulted in transmural ischemia and hemodynamic deterioration.

This unfortunate clinical result raises three crucial questions regarding the perioperative management of patients receiving estrogen therapy. First, can one predict which patients have a hypercoagulable state? Second, how long does a hypercoagulable state persist once estrogen therapy is discontinued? And third, is there a therapeutic intervention which can reliably counteract an estrogen-induced thrombogenic tendency?

With respect to the first question, one can measure AT-III plasma levels,[18] plasma functional AT-III activity,[18] or factor Xa inhibitory activity.[19,20] One investigation demonstrated 100% sensitivity and 90% specificity of plasma functional AT-III for predicting thrombo-

sis in eight of 48 post-surgical patients.[18] Studies linking Xa inhibitory activity with thrombosis in patients are lacking. No currently available test has been shown to possess a high predictive value for a hypercoagulable state. The second question, the duration of the hypercoagulable state, has no direct answer in the literature. While the Xa inhibitory activity returns to normal 2–5 weeks after discontinuation of estrogen therapy,‡ whether this corresponds with decreased risk of thrombus formation is not known.

The last question seeks a means by which estrogen-induced thrombogenesis may be overcome immediately. Low-dose heparin effectively treats the estrogen-induced decline in AT-III activity in rabbits[20] and in humans.[19,21,22] When faced with the need for extracorporeal circulation in a patient on estrogen therapy, one reasonable but untested approach might be to reverse anticoagulation only partially using protamine at the conclusion of cardiopulmonary bypass, and to utilize low-dose heparin postoperatively if surgical considerations allow. Outcome data for this therapeutic plan do not yet exist.

We present a case of lethal graft thrombosis during coronary artery bypass grafting in a patient with a history of estrogen therapy for prostatic cancer. We speculate that this complication was related to a hypercoagulable state that arose from estrogen therapy. Such an alteration in coagulation factor dynamics would not be predicted by routine laboratory tests. We believe that estrogen therapy should be discontinued several weeks prior to manipulation of the coagulation system for extracorporeal circulation.

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