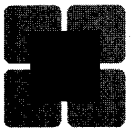

WILLIAM S. WILKE, MD, EDITOR

THROMBOEMBOLIC DISEASE: UNDERDIAGNOSED, UNDERTREATED, DEADLY

Physicians often fail to diagnose and adequately treat thromboembolic disease in nonambulatory hospitalized patients, with tragic consequences. Pulmonary embolism is common: between 21% and 26% of all patients have pathologic evidence of pulmonary embolism at autopsy, and approximately 8% to 9% die of it. Further, the incidence of pulmonary embolism has not changed over the last 30 years. The following brief update attempts to capsulize current concepts in the diagnosis, treatment, and prevention of this problem.

DEEP VENOUS THROMBOSIS

Most patients with deep venous thrombosis have endothelial injury, venous stasis, or hypercoagulability. The risk factors for deep venous thrombosis include increasing age, trauma, immobilization (including stroke), obesity, malignancy, myocardial infarction, congestive heart failure, previous deep venous thrombosis, varicose veins, estrogen use, and parturition. The major complications of deep venous thrombosis are pulmonary embolism and chronic venous insufficiency.

Preventing deep venous thrombosis

Patients over age 40 should receive 5000 U of heparin subcutaneously 2 hours before and every 12 hours after undergoing abdominal or thoracic surgery, as should younger patients with other risk factors. Medical patients confined to bed should also receive 5000 U every 12 hours, or every 8 hours if they are obese. Pneumatic compression stockings may be helpful, especially in patients for whom heparin is contraindicated. Patients undergoing total hip or knee replacement are candidates for low-molecular weight heparin, pneumatic stockings, or warfarin.

Recognizing deep venous thrombosis

The usual clinical signs in the legs are notoriously inaccurate: the most common physical finding is a completely normal examination. A swollen leg, dilated superficial veins, tenderness, a palpable cord, and a positive Homan's sign are suggestive but not diagnostic. A high index of suspicion is the key to diagnosing deep venous thrombosis.

Every patient suspected of having deep venous thrombosis needs a definitive study to confirm or rule it out. Duplex ultrasonography has virtually replaced impedance plethysmography. The study is considered positive if the thrombus is visualized or if the vein is not compressible. Duplex ultrasonography is not nearly as accurate in detecting calf-vein thrombosis as it is in detecting more proximal venous thrombosis, but its sensitivity is improving. It is more than 95% accurate in detecting thrombi in the popliteal vein or in more proximal veins. Approximately 20% of untreated calf thrombi propagate to the popliteal vein, and of those that propagate, 50% cause pulmonary emboli. Venography remains the "gold standard" for diagnosis in equivocal cases.

Treating deep venous thrombosis

Once a diagnosis of deep venous thrombosis is entertained, intravenous heparin therapy should be started immediately and continued until the diagnostic studies are complete. Patients with proximal venous thrombosis should be confined to bed rest for the first 24 hours. Heparin is administered by continuous infusion at approximately 500 U/kg/24 hours after a 5000-U bolus and is adjusted to keep the activated partial thromboplastin time at 50 to 80 seconds.

Warfarin is usually started on the first or second day. Heparin and warfarin should be continued together for a minimum of 4 days, even if the prothrombin time is in the therapeutic range (1.3 to 1.5 times control, or an International Normalized Ratio between 2 and 3 with a target of 2.5). Most

clinicians recommend 3 to 6 months of warfarin therapy after a first episode, 12 months after a second episode, and lifetime warfarin therapy after a third episode.

The major side effect of heparin and warfarin is bleeding. Other side effects of heparin include thrombocytopenia, which is immunologically mediated. This occurs in between 0.3% and 10% of all patients who receive heparin therapy; however, it is clinically significant in only a minority of patients. A smaller percentage of thrombocytopenic patients develop arterial and venous thrombosis while receiving heparin (the "white clot" syndrome). Patients who receive heparin for prolonged periods may develop osteoporosis. Complications related to warfarin other than bleeding include a warfarin embryopathy syndrome; therefore, patients should never receive warfarin during pregnancy. A small number of patients experience warfarin necrosis.

A venous thromboembolic event with no underlying risk factors should prompt a careful search for an underlying neoplasm. Suspicious features include phlegmasia cerulea dolens, migratory superficial thrombophlebitis, thrombophlebitis in unusual sites such as the trunk and arms, highly inflammatory phlebitis, and venous thrombosis that is resistant to anticoagulation therapy.

Although standard anticoagulation therapy is effective in preventing pulmonary embolism in patients with deep venous thrombosis, it probably is not very effective in preventing chronic venous insufficiency. No randomized prospective, controlled trials have definitively shown that thrombolytic therapy prevents chronic venous insufficiency. However, most investigators believe that if a thrombus can be lysed quickly, venous valvular destruction and residual venous obstruction can be prevented.

We believe that patients with iliofemoral deep venous thrombosis who do not have contraindications to thrombolytic therapy should receive it. In patients with phlegmasia cerulea dolens or venous gangrene, thrombolysis is the therapy of choice.

PULMONARY EMBOLISM

Ninety percent of patients who suffer a pulmonary embolism have deep venous thrombosis in the legs as a source. Symptoms related to pulmonary embolism are nondescript and may be associated with other disease entities. Symptoms of pulmonary embolisms are dyspnea, pleural pain, apprehension, cough, hemoptysis, sweating, and syncope. Signs associated with pulmonary embolism are rales, increased second pulmonic heart sound, phlebitis, third and fourth heart sounds, sweating, cyanosis, increased respirations, increased pulse, and fever. Any constellation of symptoms or signs may be present. A high index of suspicion is necessary for accurate diagnosis. Chest roentgenography, electrocardiography, and arterial blood gas measurements are useful in ruling out other causes; however, these may show any number of nonspecific abnormalities or may be completely normal, even in the presence of a pulmonary embolism.

The ventilation-perfusion lung scan is indicated in patients who are suspected of having a pulmonary embolism. In the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) trial, a high-probability lung scan had a specificity of 97%, but a sensitivity of only 42%.

Unfortunately, most patients have indeterminate or "nondiagnostic" scans. Duplex ultrasonography of the legs can clarify the issue. If the results of ultrasonography are positive, treatment should be started. Treatment can be withheld if the ventilation-perfusion scan is nondiagnostic and ultrasonography gives negative results, but serial duplex studies should be performed.

Pulmonary arteriography remains the gold standard. It should be performed if there has been a high-probability lung scan but if a contraindication to anticoagulation exists, or if there has been a nondiagnostic scan with a high clinical suspicion for pulmonary embolism, before insertion of an inferior vena cava filter, before pulmonary embolectomy, and perhaps before initiating thrombolytic therapy.

Echocardiography can tell to what degree a pulmonary embolus impairs right ventricular function. Echocardiographic abnormalities associated with acute pulmonary embolism may reverse after thrombolytic therapy. These include a dilated right ventricle, a hypokinetic free wall of the right ventricle, tricuspid regurgitation with increased flow velocity across the tricuspid valve, and elevation in pulmonary arterial systolic pressure.

Therapy of pulmonary embolism

Thrombolytic therapy is currently recommended for any patient with a massive pulmonary embolus, a significant obstruction of two or more segmental arteries or one lobar artery, or a pulmonary embolus of any size causing cardiac hemodynamic compromise. Trials have shown that thrombolytic therapy de-

creases pulmonary artery pressures quickly and improves the results of the lung scan and arteriogram at 12 and 24 hours. However, thrombolytic agents produced no overall decrease in mortality compared with heparin therapy.

Thrombolytic therapy should not be used in patients with active internal bleeding or a recent stroke (within 2 months). It also should not be used in anyone who has an intracranial neoplasm or abscess. The major complication associated with thrombolytic therapy is bleeding; this can be minimized by selecting the patient carefully and avoiding invasive procedures. Vessels that cannot be directly compressed should not be invaded.

The inferior vena cava can be interrupted with a filter to prevent recurrence of a massive pulmonary embolism or chronic recurrent small emboli. Other indications for this procedure are a contraindication to anticoagulation in a patient with deep vein thrombosis or pulmonary embolism, major complications with anticoagulation, and recurrent pulmonary embolism despite adequate anticoagulation.

JEFFREY W. OLIN, DO
Department of Vascular Medicine
The Cleveland Clinic Foundation

SUGGESTED READING

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MEDICAL TREATMENT OF PITUITARY TUMORS

Medical therapy produces better results than surgery in patients with prolactin-secreting adenomas, which account for about half of all pituitary adenomas. Dopamine agonists such as bromocriptine (Parlodel) and pergolide (Permax) effectively reduce prolactin secretion and reduce the size of these tumors, but these drugs are not very effective in treating acromegaly, where they lower elevated growth hormone and insulin-like growth factor-1 levels only 10% of the time. A relatively new agent, octreotide (Sandostatin), is about 90% successful in treating acromegaly, and it also may be used to treat the quite rare pituitary tumors that secrete thyroid-stimulating hormone.

HYPERPROLACTINEMIA AND PROLACTINOMAS

Prolactin is unusual in that it is controlled primarily by an inhibiting factor, dopamine. Drugs that deplete dopamine stores or that directly stimulate prolactin secretion can elevate serum prolactin levels. Some of the more commonly used drugs that can do this include metoclopramide, methyldopa, oral contraceptives, and the phenothiazines. Prolactin levels are elevated in pregnancy, chronic renal failure, and primary hypothyroidism. Trauma and tumors that affect the hypothalamus or stalk also may raise prolactin levels. For the same reason (injury or traction on the stalk), primary empty sella syndrome is sometimes associated with hyperprolactinemia.

In women, hyperprolactinemia produces galactorrhea, changes in periods, and infertility. Men may experience infertility or impotence, or they may present later in the course of the disease, when a mass effect from the growing tumor produces changes in visual fields or severe headaches. Symptoms in women tend to be proportional to circulating levels of prolactin.

Because prolactin-inhibiting factor may be obstructed by structural lesions, there may be a high prolactin level in patients who have tumors that don't actually make prolactin. These are called pseudoprolactinomas.

Diagnosis of prolactinomas

Once a high serum prolactin level is found and nontumor causes are ruled out, magnetic resonance imaging and endocrine studies should be performed as clinically indicated to rule out deficiencies of adrenocorticotropic hormone or thyroid-stimulating hormone. The prolactin level is usually proportional to the size of the tumor.

Thus, the finding of a large tumor with a prolactin level of only 60 implies the presence of a pseudoprolactinoma. In most cases, prolactin-stimulating drugs, hypothyroidism, or an empty sella result in prolactin levels between 30 and 90 ng/mL. Pregnant women can have prolactin levels between 100 and 200 ng/mL, and in kidney failure the prolactin levels