Obesity and Thromboembolic Disease

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Pulmonary embolism (PE) is the third most frequent cardiovascular disorder after coronary heart disease and stroke,\textsuperscript{1} but the diagnosis is often overlooked. An important clue for establishing a suspicion of PE is the presence of risk factors. PE and deep venous thrombosis (DVT) are manifestations of the same disease and are often considered together as venous thromboembolism (VTE), that is, PE or DVT. Among patients in whom the diagnosis of DVT was made, 96% had one or more risk factors and 76% had two or more.\textsuperscript{2} Obesity has been thought to be a risk factor for venous PE and DVT for many years, but strong data in support of this were established only recently in women\textsuperscript{3,4} and in men and women.\textsuperscript{5}

**INCIDENCE OF PULMONARY EMBOLISM**

In the years during which antithrombotic prophylaxis has been used extensively, PE was shown at autopsy in 24% of patients who died in acute-care hospitals, 22% who died in chronic-care hospitals, and 5% who died as outpatients.\textsuperscript{6} Remarkably, even in patients who had large or fatal PE at autopsy, most cases (78%) were unsuspected or undiagnosed ante mortem, and this was true of university hospitals and tertiary care centers in addition to community hospitals.\textsuperscript{7} In a study of unselected patients at autopsy that used postmortem pulmonary arteriography in addition to gross dissection and microscopic examination, in all 34 cases of PE, PE was found in muscular pulmonary artery branches (0.1–1 mm in diameter).\textsuperscript{8} Only 8 cases (24%) had PE in elastic arteries (>1 mm in diameter). Microscopic examination showed PE in pulmonary arterioles (0.03–0.1 mm in diameter) in 13 (38%) of those who had grossly visible PE.\textsuperscript{8}

Throughout the United States, from 1979 through 2001, the number of patients discharged from short-stay nonfederal hospitals with PE was 2,741,000, the number with DVT was 6,475,000, and the number with VTE (defined as PE or DVT) was 8,575,000.\textsuperscript{9} During this 23-year period, the average population-based incidence of PE in hospitalized patients was 47 per 100,000 population, the incidence of DVT was 112 per 100,000 population, and the incidence of VTE was 148 per 100,000 population.\textsuperscript{7} Among patients 20 years of age or older, an average of 0.4% of hospitalized patients were diagnosed with PE.\textsuperscript{10} The incidence of PE in hospitalized patients did not change over 21 years.\textsuperscript{10} The incidence of PE in hospitalized patients was nearly the same in men and women,\textsuperscript{11} and it was the same in whites and blacks.\textsuperscript{12} VTE, however, is less frequent in Asian-Pacific Islanders,\textsuperscript{13} Alaskan Natives, and Americans Indians.\textsuperscript{14}

**DEEP VENOUS THROMBOSIS**

Among patients at autopsy who had full-limb dissection in years before the general use of

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antithrombotic prophylaxis, 43% had DVT. The incidence of DVT in hospitalized patients increased from 0.8% in 1979 to 1.3% in 1999. This may represent an increasing availability and use of venous ultrasound during much of that period. Early diagnosis and treatment of DVT may have prevented a parallel increase in the incidence of PE in hospitalized patients.

The number of patients who died from PE in 1998 based on death certificates was 24,947. This equates to nine deaths attributable to PE per 100,000 population.

Among all patients with PE throughout the United States, irrespective of treatment or severity of PE, the estimated case fatality rate (death attributable to PE per 100 patients with PE) in 1998 was 7.7%. The case fatality rate in short-stay hospitals in metropolitan Worcester in 1985 through 1986, 12%, was somewhat higher than calculated during those years. The estimated case fatality rate from PE increased exponentially with age.

Various clinical investigations, such as the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED), showed lower case fatality rates, but most fatalities from PE occur within the first 2.5 hours after the diagnosis is made. Obviously excluding such patients from clinical investigations. Also, most investigations excluded severely ill patients, such as those in shock.

HEMOSTASIS AND OBESITY

Various abnormalities of hemostasis have been described in obesity, mainly concerning fibrinolysis, and increased plasminogen activator inhibitor-1 (PAI-1) in particular, but other abnormalities of coagulation have been reported as well. Circulating microparticles have also been observed in obesity. These would suggest that obesity would be a risk factor for VTE. Microparticles are fragments shed from the plasma membrane after challenge of cells by a variety of stimuli (procoagulant, proinflammatory, or apoptogenic). Some of them bear active tissue factor, and all of them expose procoagulant aminophospholipids, phosphatidylserine, and phosphatidylethanolamine, which confer a procoagulant phenotype. Mean levels of microparticles, expressed as nanomolar phosphatidylserine equivalents (nMPSeq), were compared in obese patients (mean body mass index [BMI] = 42.2 kg/m²) and controls (mean BMI = 20.9 kg/m²). Obese patients showed higher levels of microparticles (10.6 versus 3.2 nMPSeq). The increased levels of circulating microparticles reflect cell activation and could account for an increased risk for thrombotic complications in obesity.

Evidence in recent years has shed light on the fibrinolytic and hemostatic abnormalities in obese patients. BMI correlates with plasma levels of PAI-1. Specific PAI-1 mRNA expression in human adipocytes from subcutaneous and visceral origins indicates that fat cells are a source of circulating PAI-1. PAI-1 acts as an inhibitor of tissue- and urokinase-derived plasminogen activators, thereby interfering with the conversion of plasminogen to plasmin and decreasing fibrinolytic activity. This mechanism of PAI-1–mediated inhibition of fibrinolysis is illustrated by in vitro experiments in which blockade of PAI-1 action through the addition of anti–PAI-1 monoclonal antibodies resulted in an increased rate of fibrinolysis with reduction of thrombus growth. Inflammatory cytokines produced by adipose cells, namely, tumor necrosis factor-α and interleukin-1, have been reported by some but not all to participate in the increased production of PAI-1 in obese individuals through humoral or paracrine mechanisms. The regulation of the synthesis and release of PAI-1 from adipocytes still remains to be clarified.

Additional mechanisms contributing to prothrombosis in obesity include increased platelet aggregability mediated through increases of von Willebrand factor and hypercoagulability attributable to higher levels of plasma fibrinogen, factor VII, and factor VIII. In the European offspring study by the European Atherosclerosis Research Study (EARS), fibrinogen, factor VIIc, and PAI-1 were positively correlated with BMI. Conversely, adjusted odds of large weight gain, defined as greater than the 90th percentile in middle-aged adults, have been associated with higher fibrinogen levels, and adjusted odds ratios for large weight gain were linked with higher levels of factor VIII and von Willebrand factor. Marked weight reduction through bariatric surgery for morbid obesity leads to significant decreases of fibrinogen, factor VII, and PAI-1, although factor VIII or von Willebrand factor remained unchanged.

Since 1927, obesity has been suggested to be a risk factor for fatal PE. Investigations that reported an increased risk for VTE attributable to obesity have been criticized because they failed to control for hospital confinement or other risk factors. High proportions of patients with VTE have been found to be obese, but the importance of the association is diminished because of the high proportion of obesity in the general population. Some investigations showed an increased risk ratio for DVT or PE in women, but data in men were less compelling. The Nurses’ Health Study showed that the age-adjusted risk ratio for PE in women with
a BMI of 29.0 kg/m² or greater was 3.2 compared with the leanest category of less than 21.0 kg/m². The Framingham Heart Study showed that Metropolitan relative weight was significantly and independently associated with PE among women but not among men. The “Study of Men Born in 1913” showed that Metropolitan relative weight was significantly and independently associated with PE among women but not among men. The “Study of Men Born in 1913” showed that men in the highest decile of waist circumference (≥100 cm) had an adjusted relative risk for VTE of 3.92 compared with men with a waist circumference less than 100 cm, however. Among 1272 outpatients (men and women), the odds ratio for DVT, comparing obese (BMI >30 kg/m²) with nonobese patients, was 2.39. Others showed a similar odds ratio for DVT of 2.26 compared with nonobese patients. Conversely, the Olmsted County, Minnesota case-control study found no evidence that current BMI was an independent risk factor for VTE in men or women. Others did not show obesity to be a risk factor for VTE in men.

Analysis of the database of the National Hospital Discharge Survey showed compelling evidence that obesity is a risk factor for VTE. Among patients hospitalized in short-term hospitals throughout the United States, in whom obesity was coded among the discharge diagnoses but not defined, 91,000 (0.8%) of 12,015,000 had PE. Among hospitalized patients who were not diagnosed with obesity, PE was diagnosed in 2,366,000 (0.3%) of 691,000,000. DVT was diagnosed in 243,000 (2.0%) of 12,015,000 patients diagnosed with obesity and in 5,524,000 (0.8%) of 691,000,000 who were not diagnosed with obesity.

The relative risk for PE, comparing obese patients with nonobese patients, was 2.18, and for DVT, it was 2.50. The relative risks for PE and DVT depended on age. Obesity had the greatest impact on patients younger than 40 years of age, in whom the relative risk for PE in obese patients was 5.19 and the relative risk for DVT was 5.20. The higher relative risk for obesity in younger patients may have reflected the fact that younger patients uncommonly have multiple confounding associated risk factors, which would make the risk for obesity inapparent.

Obese female patients had a greater relative risk for DVT than obese male patients: 2.75 versus 2.02. The incidence of PE and DVT in hospitalized obese female patients was higher than in obese male patients. In female patients younger than 40 years of age, the relative risk for DVT comparing obese with nonobese patients was 6.10. In male patients younger than 40 years of age, the relative risk for DVT was 3.71.

The proportion of hospitalized patients diagnosed with obesity was within a narrow range (1.4%–2.4%) over the 21-year period of observation from 1979 through 1999, indicating consistency in the diagnostic process. Previous investigators used several indices of obesity, including BMI greater than 35 kg/m² and BMI of 30 to 35 kg/m², BMI of 29 kg/m² or greater, weight greater than 20% of median recommended weight for height, and (for men) waist circumference of 100 cm or greater. It is likely that all patients diagnosed with obesity in the National Hospital Discharge Survey database were in fact obese, irrespective of the criteria used. Some obese patients may not have had a listed discharge diagnosis of obesity, however, and they would have been included in the nonobese group. This would have tended to reduce the relative risk for obesity in VTE.

A synergistic effect of oral contraceptives with obesity has been shown. The odds ratio of DVT in obese women (BMI ≥30 kg/m²) who were users of oral contraceptives ranged from 5.2 to 7.8 compared with that in with obese women who did not use oral contraceptives, and among women with a BMI of 35 kg/m² or greater, the odds ratio was 3.1 compared with similar obese nonusers of oral contraceptives.

Obesity is also a risk factor for recurrent VTE. Among 1107 patients followed for an average of 46 months after a first unprovoked VTE and withdrawal of anticoagulant therapy, 168 had recurrent VTE. Mean BMI was higher in those with recurrent PE than in those without recurrence (28.5 versus 26.9). Four years after discontinuation of anticoagulation therapy, the probability of recurrent PE was 9.3% among patients with a normal weight (BMI <25 kg/m²), 16.7% among overweight patients (BMI of 25–29 kg/m²), and 17.5% among obese patients (BMI ≥30 kg/m²). The hazard ratio of recurrence was 1.3% among overweight patients and 1.6% among obese patients.
Enoxaparin was shown to be effective for thromboprophylaxis in morbidly obese patients after bariatric surgery. With various dosing regimens among 544 patients, PE occurred in 0.7% and none of the patients developed DVT. All cases of PE occurred after the cessation of enoxaparin, 7 days to 1 month after surgery.

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REFERENCES


