Treatment of Pulmonary Thromboembolism

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The epidemiology, diagnosis, treatment, and prophylaxis of PE are rapidly advancing. Our array of diagnostic imaging tools has expanded to include echocardiography and spiral chest CT with contrast. We have also gained a keen appreciation for the importance of risk stratification of our patients. The decision to administer thrombolysis or undertake embolectomy may now depend upon the presence of right ventricular dysfunction even if systemic arterial pressure is normal. Finally, the availability of low molecular weight heparins broadens our options for pharmacologic management.

(Key words: pulmonary embolism, thrombophlebitis, low molecular weight heparin, thrombolysis)

Introduction

The clinical spectrum of pulmonary embolism (PE) ranges from small, incidental thrombosis to massive PE associated with sudden death due to cardiogenic shock. Pulmonary arterial obstruction and platelet secretion of vasoactive agents elevate pulmonary vascular resistance. Increased alveolar dead space impairs gas exchange, and stimulation of irritant receptors causes alveolar hyperventilation. Reflex bronchoconstriction augments airway resistance, and lung edema decreases pulmonary compliance (1). Elevation in right ventricular pressure can cause an increase in right ventricular wall tension with consequent right ventricular dilatation, dysfunction, and ischemia.

Mortality

PE continues to have a surprisingly high mortality rate. In our recent experience with the largest registry ever undertaken of 2,454 consecutive hospitalized PE patients (ICOPER: International Cooperative Pulmonary Embolism Registry), the 3 month mortality rate was 17.4% (2). PE itself, not cancer, was the principal cause of death. ICOPER enrolled all PE patients consecutively diagnosed at participating hospitals. In contrast, the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) Registry suggested a benign prognosis if PE is promptly recognized (3). In PIOPED, the overall 3 month mortality rate was about 15%, but only 1 of 10 deaths was ascribed to PE. Cancer, the leading cause of death, accounted for 35% of the mortality. Although these findings might at first glance suggest that mortality from PE itself is rare, patients eligible for PIOPED had to be healthy enough to undergo bilateral pulmonary angiography. Thus, PIOPED patients were probably not as ill as the ordinary PE patient encountered in routine clinical practice and enrolled in ICOPER.

Right Ventricular Dysfunction

Four PE registries (2, 4-6) have demonstrated that right ventricular hypokinesis predicts an adverse clinical outcome. Although fewer than 5% of ICOPER patients presented in cardiogenic shock, right ventricular hypokinesis as assessed by echocardiography occurred in about 40% of patients with normal systemic arterial pressure. Right ventricular hypokinesis was associated with a doubling of the mortality rate at 14 days and with a 1.5 times higher mortality rate at 3 months. In a registry from the Karolinska Hospital, 126 consecutive PE patients underwent echocardiography on the day of initial PE diagnosis (4). The overall one year mortality rate was 15%. However, among those with right ventricular dysfunction, the mortality rate at one year was 3-fold higher than for patients with normal right ventricular function. Similar findings were observed in Kasper’s registry of 317 patients with clinically suspected PE (5). Finally, the much larger Management Strategy And Prognosis of Pulmonary Embolism Registry (MAPPET) enrolled 1,001 patients with PE and right ventricular dysfunction (6). As right heart failure worsened, the mortality rate increased.

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Imaging in the Critically Ill Patient Suspected of PE

Although the presence of DVT can generally be used as a surrogate for PE, a major caveat is that a normal leg imaging test cannot exclude PE if clinical suspicion is moderately high. In a series of 41 PE patients who underwent both pulmonary angiography and bilateral contrast venography of the legs, 12 had negative leg venograms despite positive pulmonary angiograms (7).

Unfortunately, even the high probability lung scan is surprisingly insensitive and in PIOPED, it identified only 41% of patients with PE (8). In the majority of patients with PE, the lung scan is, regrettably, nondiagnostic despite complex revisions of PIOPED diagnostic criteria (9). Ventilation scanning rarely clarifies the interpretation of perfusion lung scans (10). Furthermore, in the presence of high clinical suspicion for PE, the “low probability” lung scan is a potentially lethal reading (11), which is more accurately categorized as “nondiagnostic” (12). The problem is that the term “low probability” can convey a false sense of security to the physician.

Spiral chest CT scanning with contrast is a new diagnostic approach best suited for identifying PE in the proximal pulmonary vascular tree (13). Another promising new technology is gadolinium-enhanced magnetic resonance pulmonary angiography (14), which can display the anatomy of the pulmonary arteries as well as provide an assessment of right ventricular wall motion.

Transthoracic echocardiography is particularly useful in critically ill patients with suspected PE (15) and can help identify conditions which mimic PE such as myocardial infarction, dissection of the aorta, or pericardial tamponade. The thrombus itself is rarely visualized. Signs of right ventricular pressure overload include: right ventricular dilatation, right ventricular hypokinesis, pulmonary arterial hypertension as assessed by Doppler, interventricular septal flattening and displacement into the left ventricle, and impaired left ventricular relaxation with a “D-shaped” left ventricle in cross section. Detection of right ventricular hypertrophy suggests that the process is chronic, subacute, or acute superimposed upon chronic. The McConnell Sign appears to be specific for acute PE and is a pattern of regional right ventricular dysfunction in which right ventricular apical wall motion remains normal despite hypokinesis of the right ventricular free wall. A “hinge point” is observed at the border of the mid apical free wall and the apex (Figs. 1, 2) (16). Those patients with a pulmonary artery systolic pressure that exceeds 50 mm Hg at presentation (estimated by echocardiography Doppler) are most likely to have persistent right ventricular dysfunction, with little improvement after the initial 6 weeks of treatment (17).

Contrast pulmonary angiography remains the gold standard. It can generally be performed safely (18) and may resolve the dilemma of high clinical suspicion despite nondiagnostic lung scanning, normal venous ultrasonography, and normal echocardiography. It is especially worthwhile to undertake angiography in the presence of high clinical suspicion, nondiagnostic lung scanning, and a normal venous ultrasound of the legs.

Therapy

Heparin accelerates the action of antithrombin III, prevents additional thrombus from forming, and permits endogenous fibrinolysis to dissolve some of the PE clot. Heparin promotes endothelialization of thrombus and decreases the likelihood of its embolization from the venous wall. Patients suspected of PE should be expeditiously and intensively anticoagulated with heparin even while the diagnostic work-up is under way. A bolus (average 7,500 Units) followed by a continuous infusion of unfractionated heparin (average 1,250 Units/hour) usually achieves rapidly a therapeutic activated partial thromboplastin time (PTT) between 60 to 80 seconds. Heparin nomograms facilitate proper dosing (19). Heparin without oral anticoagulation is used throughout pregnancy to manage PE (20). Heparin is also employed in Trousseau’s Syndrome for both acute...
Figure 2. Segmental right ventricular free wall excursion (mean±SEM) by centerline analysis as a function of right ventricular free wall segment. Centerline excursion in patients with acute pulmonary embolism (PE) was near normal at the apex (hatched area) but abnormal at the mid-free wall and base (p<0.02 vs normal). Centerline excursion in patients with primary pulmonary hypertension was reduced compared with normal subjects in all segments (p<0.03). Reprinted with permission from: McConnell MV, Solomon SD, Rayan ME, Come PC, Goldhaber SZ, Lee RT. Regional right ventricular dysfunction detected by echocardiography in acute pulmonary embolism. Am J Cardiol 78: 469-473, 1996.

and chronic therapy, because oral anticoagulation usually fails to prevent recurrent thrombosis (21). Recently, inpatient administration of low molecular weight heparin has been shown to be as safe and effective as unfractionated heparin to treat hemodynamically stable PE (22, 23).

Inferior vena caval (IVC) filters appear to offer no advantage compared with anticoagulation alone in patients with free-floating proximal DVT (24). Filters do not halt the thrombotic process and may cause massive leg edema due to caval thrombosis. In a randomized controlled trial of 400 DVT patients, IVC filters plus anticoagulation did not reduce mortality compared with anticoagulation alone (25). However, an IVC filter is indicated for PE patients who present with active hemorrhage or recurrent PE despite intensive and prolonged anticoagulation.

Warfarin can be safely started immediately after obtaining a therapeutic PTT or heparin level. Loading warfarin does not shorten the usual 5 days needed to achieve adequate oral anticoagulation. An initial average dose of 5 mg usually suffices (26, 27), except for small, debilitated, or elderly patients in whom a 2 mg dose is prudent, or large, young, otherwise healthy patients in whom a 7.5 mg dose is reasonable. Although the target International Normalized Ratio (INR) is usually considered 2.0–3.0, it should generally be maintained close to the upper part of this range.

After an initial PE, six months of anticoagulation prevents far more recurrences than 6 weeks (28). Indefinite anticoagulation is controversial among patients with recurrent PE because the likelihood of major bleeding increases as the duration of anticoagulation increases (29). Whether patients with Factor V Leiden and an initial PE should receive prolonged courses of anticoagulation remains sharply debated (30). However, it is certain that patients with idiopathic PE should receive more than 3 months of anticoagulation (31).

**Thrombolysis**

Although there is consensus that thrombolysis can be lifesaving in patients with massive PE, controversy persists regarding its use in PE patients with stable systemic arterial pres-
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In the new millennium, our ability to risk stratify PE patients has become more sophisticated. Specifically, we now search for signs of right ventricular dysfunction to detect patients with impending hemodynamic instability. Thrombolysis may: 1) function as a "medical embolectomy", with lysis of massive pulmonary arterial thrombus, thereby preventing the downhill spiral of right heart failure; 2) prevent the continued release of serotonin and other neuropeptides which might otherwise lead to worsening pulmonary hypertension; 3) dissolve much of the source of the thrombus in the pelvic or deep leg veins, thereby decreasing the likelihood of recurrent PE.

Of the three available thrombolytic regimens for PE, rt-PA 100 mg as a continuous infusion over 2 hours appears to be the most effective and safe, based upon clinical trial reports. Importantly, the time window for PE thrombolysis is quite wide: 14 days. In addition, cost can be controlled by omitting unnecessary blood tests for clinical management such as fibrinogen, fibrin (ogen) split products, and thrombin time.

A randomized controlled trial (32) and multivariate analysis of a large German registry (33) suggest that among patients with right ventricular dysfunction, thrombolysis may lower the rate of recurrent PE compared with heparin alone. However, the risk of major hemorrhage rises with increasing age and body mass index (34). If aggressive intervention is warranted in the setting of failed or contraindicated thrombolysis, transvenous catheter (35) or open surgical embolectomy (36) should be considered. With increasing frequency, catheter thrombectomy is being integrated into our therapeutic armamentarium (37).

After thrombolysis for PE, right ventricular regional function and global function normalize in most patients who present with right ventricular hypokinesis (38). Thrombolysis increases the depressed fractional area change, especially in the mid-right ventricular free wall (Fig. 3).

Low Molecular Weight Heparins

Low molecular weight heparins have superior bioavailability, require less frequent injections, and have lower rates of heparin induced thrombocytopenia than unfractionated heparin.
(39). In Europe and in the Western Hemisphere, they are rapidly replacing unfractionated heparin for therapy of most patients with deep venous thrombosis. The low molecular weight heparins permit outpatient treatment or abbreviated hospitalization, without any increase in recurrent venous thromboembolism or bleeding. They do not ordinarily require laboratory monitoring and are simply administered as subcutaneous injections once or twice daily based upon weight. This weight-based dosing must be modified and generally halved in patients with renal insufficiency or massive obesity. Under these circumstances, a plasma anti-factor Xa level is useful when obtained at the midpoint between injections, with a target range of 0.5 to 1.0 Units/ml.

Low molecular weight heparin has been compared with unfractionated heparin in one large French trial of PE patients (40) and in several other trials of deep venous thrombosis patients, some of whom had PE (25, 41, 42). In each study, the low molecular weight heparin group had at least as good an outcome as the group receiving conventional unfractionated heparin with a continuous intravenous infusion.

Conclusions

The epidemiology, diagnosis, treatment, and prophylaxis of PE are rapidly advancing. Our array of diagnostic imaging tools has expanded to include echocardiography, and spiral chest CT with contrast. We have also gained a keen appreciation for the importance of risk stratification of our patients. The decision to administer thrombolysis or undertake embolectomy may now depend upon the presence of right ventricular dysfunction even if systemic arterial pressure is maintained. Finally, the availability of low molecular weight heparins broadens our options for pharmacologic management.

References

30) Ridker PM. Long-term, low-dose warfarin among venous thrombosis


