From acute pulmonary embolism to chronic thromboembolic pulmonary hypertension

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Chronic thromboembolic pulmonary hypertension (CTEPH), a disease associated with considerable morbidity and mortality, is the consequence of unresolved thromboembolic occlusion in pulmonary vasculature. CTEPH was considered a rare disease occurring in 0.1-0.5% of patients with pulmonary emboli who survive. Recently, a much higher incidence was reported and some risk factors such as a previous pulmonary embolism (PE), an idiopathic form of PE and the severity of perfusion defect at the time of diagnosis have been identified. Exertional dyspnea is the main symptom at the beginning of the disease while later on patients may suffer from syncope related to low cardiac output or hemoptysis as a consequence of high pulmonary artery pressure. In suspected patients, a confirmation of pulmonary arterial hypertension should be ascertained at transthoracic echocardiography. Then the obstructive nature of the disease may be revealed by ventilation-perfusion lung scan but is better described at pulmonary angiography. Computed tomography scan may be useful to rule out confounding disorders. To prevent recurrences, long-term oral anticoagulants to maintain an INR between 2.5 and 3.5 (target 3.0) are indicated. Treatment of severe CTEPH is essentially surgical (thromboendarterectomy). This procedure may be difficult when distal branches of pulmonary vascular tree are involved. In selected cases, alternative therapies may be the arterial pulmonary vessel angioplasty and lung transplantation.

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Pulmonary embolism (PE) is a common life-threatening disease early after its occurrence with a late high mortality rate linked to underlying comorbidities, especially cancer and cardiopulmonary diseases. Morbidity after PE comprises a high recurrence rate in patients with permanent risk factors or idiopathic disease or, less frequently, in conditions linked to unresolved PE that lead to pulmonary hypertension and is thus termed chronic thromboembolic pulmonary hypertension (CTEPH).

Epidemiology and risk factors

On the basis of patients with PE who survive and the annual rate of patients with CTEPH in the United States, the estimated incidence of this condition was thought to be 0.1-0.5%[1,2]. The incidence appears to be much higher in Japan where some genetic factors might be involved[3,4]. No data are available on its incidence in patients after a first episode of PE and risk factors for the development of the disease were unknown. We have recently reported data on long-term follow-up of 223 patients after a first episode of PE and of 82 patients with one or more previous episodes[5]. Seven of 223 patients (5 in NYHA class II and 2 in NYHA class III) developed CTEPH within the first 2 years (cumulative incidence 3.8%, 95% confidence interval 1.1-6.5). None of the remaining patients developed CTEPH after 2 years. CTEPH was more frequent in patients with a previous PE occurring in 11 of 82 patients. In fact, at multivariate analysis, one or more previous PE was the strongest risk factor for developing CTEPH (odds ratio 19.0, 95% confidence interval 4.5-79.8). Other significant risk factors were an idiopathic form of PE, the severity of perfusion defect at the time of diagnosis and a younger age. Recently, a case-control study comparing patients with CTEPH and patients with acute PE showed that splenectomy, ventriculo-atrial shunt for the treatment of hydrocephalus and chronic inflammatory disorders were associated with an increased risk of CTEPH[6].

Pathophysiology

What is the fate of thrombi in the pulmonary vasculature after an episode of PE?

According to some authors, thrombi in the pulmonary vessels are lysed early in the majority of cases[7]. In fact, perfusion lung scan showed that large part of perfusion recovery was complete within the first month[8]. However, in the THESEE study in which perfusion lung scan was performed in 157 patients 8 days and 3 months after acute PE, a residual obstruction after 3 months was found in 66% of patients and 10% had no resolution at all[9]. If reperfusion is not complete, CTEPH may occur[10], a disease associated with considerable morbidity and mortality[11-13]. Alternatively, it has been hypothesized that *in situ* thrombosis and pulmonary arteriopathy are common causes of vascular occlusion leading to CTEPH and that PE is unlikely to be a common cause of this disease[14]. A consistent amount of both *in situ* formed or embolized persistent thrombi may contribute to switch on the disease while its progression is independent of vascular occlusion or new thromboembolic events but probably associated with vascular remodeling and the development of a hypertensive vascular arteriopathy common to other types of pulmonary hypertension[15,16]. In any case, the reason why only some patients develop CTEPH is still unknown. Apparently, no alterations of the coagulation or fibrinolytic systems or of the pulmonary endothelium are present. However, a high rate of antiphospholipid antibodies has been reported in these patients[17,18].

Clinical presentation

Exertional dyspnea is the main symptom in patients with CTEPH. Usually it is mild at the beginning of the disease, physical examination is negative and patients are not seen by any physician for a long time unless other signs or symptoms occur. Late during the disease, in fact, patients may suffer from syncope related to low cardiac output or hemoptysis as a consequence of high pulmonary artery pressure. In some cases, the past medical history is not relevant or patients mention a trauma at the lower limbs or a diagnosis of "pneumonia". Two women in our series referred mild dyspnea during a previous pregnancy. In many cases CTEPH develops after an episode of PE. A high pulmonary arterial pressure at the time of PE indicates the occurrence of a previous unrecognized episode of PE. Therefore, follow-up of patients after PE is mandatory to ascertain whether no or poor resolution at lung scan is present. Usually this evaluation takes place 6 to 12 months after the acute episode when discontinuation of anticoagulation is considered. At that time, an evaluation of pulmonary artery pressure by means of echocardiography as well as screening for thrombophilia is usually performed. If anticoagulation withdrawal is possible but residual obstruction at lung scan or pulmonary hypertension is present, then several unanswered question arise: is it worth continuing oral anticoagulant treatment? What prophylaxis in situations at risk? Further investigations? In symptomatic patients, oral anticoagulant treatment should be continued indefinitely to avoid recurrences and the patients should be studied by right side catheterization and pulmonary angiography. In patients without symptoms other causes of perfusion lung scan abnormalities and other causes of pulmonary hypertension should be ruled out. Usually in these patients a thoracic spiral computed tomography (CT) scan is performed (Table I).

Diagnosis

CTEPH is usually suspected in patients with unexplained exertional dyspnea. At first visit, ECG data (suggestive of right ventricular dysfunction such as a negative T wave in the precordial leads V_1-V_4) or chest X-ray (right descending pulmonary artery diameter > 20 mm or an avascular area with pleuritic change) may reinforce the hypothesis[19]. A confirmation of pulmonary arterial hypertension then comes from transthoracic echocardiography. Finally the obstructive nature of the disease is shown by ventilation-perfusion lung scan identifying one or more mismatched defects. However, the perfusion lung scan often underestimates pulmonary vascular obstruction which is better described at angiography[20]. Pulmonary angiography is considered the "gold standard" for the evaluation of CTEPH[11,21] and CT scan cannot substitute pulmonary angiography in the diagnosis of CTEPH[11]. In fact, a normal CT scan does not exclude the diagnosis of CTEPH. However, CT scan may be useful to evaluate the status of pulmonary parenchyma and to rule out confounding disorders determining unilateral obstruction such as pulmonary artery sarcoma, vasculitis, cancer or mediastinal fibrosis.

Treatment

To prevent recurrences, long-term oral anticoagulants to maintain an international normalized ratio between 2.5 and 3.5 (target 3.0) are indicated in patients with CTEPH. According to NYHA class, oxygen may

Table I. Evaluation of patients after 6-12 months from acute pulmonary embolism (PE).

Re-evaluation of causes of PE, consider new symptoms and physical examination
Transthoracic echocardiography with SPAP measurement
Perfusion lung scan
Compression ultrasound of the lower limbs
Thrombophilia screening
D-dimer determination (to decide for possible OAT discontinuation)

OAT = oral anticoagulant treatment; SPAP = systolic pulmonary artery hypertension.

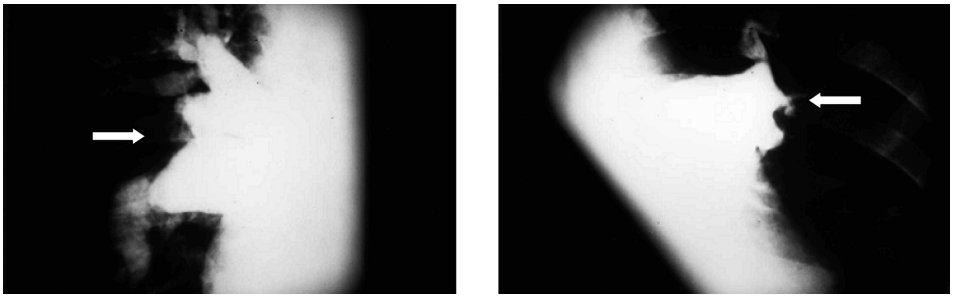

Figure 1. *Proximal amputation of the right and left main branches of the pulmonary artery* (arrows).

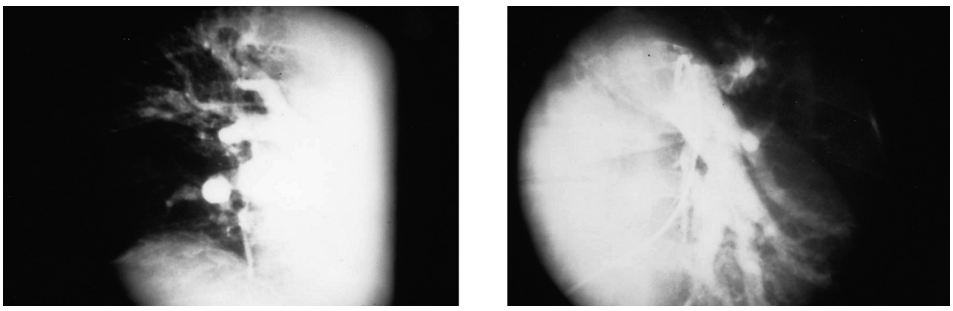

Figure 2. *Distal occlusions of the pulmonary artery branches.*

be administered. The use of diuretics, digoxin or vasodilators is not recommended unless strictly necessary. Treatment of severe CTEPH is essentially surgical (thromboendarterectomy-TEA). For extreme situations the ultimate treatment is lung transplantation. When pulmonary vessel obstruction is proximal, as shown in figure 1, surgical TEA is possible but it may be difficult when distal branches of the pulmonary vascular tree are involved (Fig. 2).

In selected cases, an alternative therapy may be angioplasty of the arterial pulmonary vessels. In a series of 18 patients with CTEPH, Feinstein et al.[22] performed a mean of 2.6 procedures and 6 dilations. Follow-up was 36 months during which a significant improvement of starting NYHA class was observed. Eleven patients showed reperfusion edema.

CTEPH is a complication of venous thromboembolism that is caused by incomplete resolution of pulmonary emboli. Untreated patients with CTEPH eventually progress to right heart failure and death. Treatment is essentially surgical.

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