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Chronic thromboembolic pulmonary hypertension; how does it develop and how can it be recognised?

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Abstract

Chronic thromboembolic pulmonary hypertension (CTEPH), which has been recognised in the past in no more than 0.1% patients who had undergone acute pulmonary embolism (APE), is currently being found in as many as 3–8% of these patients.

The pathophysiology of CTEPH is not fully understood, although the relationship with venous thromboembolism has a firm basis. The potential causes of the disease include symptomatic but unrecognised episodes of APE, repetitive episodes of silent pulmonary microemboli and recurrence of symptomatic APE in the course of initial treatment during and after the cessation of secondary antithrombotic prophylaxis. The pathomechanisms postulated are failure to lyse the initial emboli, coagulopathy, thrombosis in situ and peripheral propagation of the residual emboli. The role of arteriopathy in the initial stage of CTEPH is controversial.

CTEPH should be expected in all patients with chronic exertional dyspnoea and exercise intolerance in whom other causes can be excluded. The role of medical history, physical examination, electrocardiography and echocardiography in recognition is under discussion. Early diagnosis, before the development of pulmonary hypertension, is likely to ensure a good prognosis in continuously anticoagulated patients. Most patients, however, are diagnosed late and pulmonary hypertension is already marked. At this stage of CTEPH pulmonary endarterectomy is the treatment of choice for suitable patients with proximal emboli. Diagnosis of CTEPH at the stage of decompensated cor pulmonale considerably worsens the prognosis in solely anticoagulated patients and decreases the benefits of pulmonary endarterectomy. (Folia Cardiol. 2006; 13: 338–342)

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Chronic thromboembolic pulmonary hypertension (CTEPH) is now more generally recognised as a component of chronic venous thromboembolism than previously. The pathophysiology is still debatable and the diagnosis seems to be even more difficult than that of acute pulmonary embolism (APE). At the end of the 20th century it was estimated that CTEPH develops in 0.1–0.5% of patients who have experienced an incident of APE. This means that there are at least 1800 new cases of CTEPH a year in Poland. Recent observations indicate, however, that a higher rate of incidence can be expected. Pengo et al. [3] found that CTEPH developed in 3.8% of patients with APE within a two-year follow-up period. In a study by Remy-Jardin et al. [4] CTEPH was found in as many as 8% of 62 patients after an episode of massive APE. The real incidence of CTEPH may be even greater because it is believed that most of the thromboembolic events which initiate CTEPH are not recognised because they are subsymptomatic or even asymptomatic [5, 6].

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The natural history of CTEPH can start with symptomatic but unrecognised and thus untreated APE events. The symptoms of APE are highly unspecified, both those which occur frequently, such as dyspnoea, chest pain, tachycardia and tachypnoea, and those which occur relatively rarely, such as epistaxis and syncope. The results of anatomopathological studies show that when pulmonary embolism was found to be the cause of death, either alone or as a concomitant disease, antemortem recognition only reached 30% [7, 8]. When APE diagnosis is based solely on clinical symptoms, the percentage of false positive recognition reaches 70% [9]. It seems that the problem of unsatisfactory diagnosis of APE, even when it is fully symptomatic, cannot be solved by the use of advanced diagnostic techniques alone. The continuous awareness that APE occurs relatively often and can be masked by other mostly cardiac diseases is a reason for ordering proper diagnostic tests. Pulmonary embolism should therefore be suspected among patients with atrial fibrillation, chronic cardiac failure, and coronary artery disease. We reported a series of six pulmonary embolism cases in which false diagnosis of myocardial infarction and chronic coronary ischaemic disease was based on symptoms of chest pain and misinterpretation of electrocardiograms. As a consequence, patients were treated continuously with aspirin instead of anticoagulants and this was probably the reason for the development of CTEPH in five of them [10]. Acute chest pain accompanied by electrocardiographic signs of ischaemic injury and/or troponin elevation represent a basis for diagnosing acute coronary syndrome (ACS), although these symptoms may also be found in APE. Of 625 consecutive patients who were admitted to the local catheterisation laboratory for early invasive treatment of ACS, APE was recognised in 7 out of 18 patients in whom coronary angiography had been normal or near normal [11].

It is assumed that some CTEPH cases can develop as a result of recurrent asymptomatic pulmonary microemboli. The frequent occurrence of silent pulmonary embolism in patients with deep venous thrombosis (DVT) was already being reported in the 1980s, although the results were based on a small patient population [12, 13]. These results were confirmed later by the results of a larger multi-centre study involving 622 patients with proximal DVT. In this study silent pulmonary embolism was found in nearly half the patients [14]. In theory, the proper anticoagulation of DVT patients who have concomitant silent pulmonary embolism should prevent persistence of thrombi which could create the substratum for CTEPH development. However, Nielsen et al. who followed scintigraphically 87 patients with symptomatic DVT, 49% of whom had silent pulmonary embolism, could find no resolution of the emboli in 70% of cases after 60 days of observation independent of anti-thrombotic intervention [15]. It can be speculated that chronic pulmonary emboli could be the consequence of previous, possibly multiple, unrecognised untreated and thus unresolved thromboembolic episodes. Obviously, silent pulmonary emboli can be expected even more frequently in patients with asymptomatic DVT. In one anatomopathological study, antemortem silent DVT was found in a majority of autopsies [16]. In a study by Girard et al. [17] 82% of patients with APE had concomittant DVT, which in 75% patients was asymptomatic.

CTEPH can develop as a final outcome of embolic recurrence in the course of symptomatic and recognised episodes of APE. These may be expected mostly during the first two weeks after the initial episode and can be considerably limited by appropriate therapy [18, 19] The recurrence can also occur during proper secondary thromboembolic prophylaxis and their number sharply increases, up to 4–5%, after anticoagulation has been stopped. Subsequently, the level of recurrence decreases to reach a steady 0.5% in the 9th month [20]. This raises the problem of termination of the anticoagulation and in this context the individual risk of recurrence and bleeding should be taken into account. The mode of anticoagulation during secondary thromboembolic prophylaxis also exerts a significant impact on embolic recurrence. In a study comparing the results of conventional anticoagulation (INR 2–3) with subtherapeutic (INR 1.5–2) it was shown that the risk of recurrence was diminished by 90% and 64% respectively without significant differences in the bleeding [21]. The impact of recurrence on CTEPH development, however, has not been established. In common with others, we have found that, at least in anticoagulated APE patients, recurrence did not increase pulmonary hypertension [22–24]. Instead CTEPH may develop after episodes of recurrent pulmonary embolism in non-anticoagulated patients [1, 25].

CTEPH can also develop in patients with APE and with pulmonary hypertension at the time of diagnosis. In some pulmonary hypertension does not return to normal despite adequate therapy and the choice of therapy administered during APE does not seem to influence the outcome. The results of randomised trials have shown that thrombolysis resolves pulmonary emboli more rapidly that

anticoagulation during the first 24 hours, although this effect has been lost by the 7th day of therapy [26]. These results were confirmed by observations made over the course of a year which were unable to show that fibrolysis administered during the acute stage of pulmonary embolism was any more successful at preventing patients from developing CTEPH than anticoagulation [22, 24]. Indeed, this depends largely on baseline pulmonary artery pressure. Pulmonary hypertension is found in approximately 70––80% of patients with APE, despite the fact that mean pulmonary artery pressure hardly ever exceeds 40 mm Hg, even in patients with massive APE [27]. It can reach much higher values in patients with concomitant cardiopulmonary disease or if it results from previously unrecognised, recurrent pulmonary embolism episodes [28]. Ribeiro et al. [22], who performed serial echocardiographic studies during a one-year follow up of patients after an APE episode, found that pulmonary hypertension decreased only during the first 6 weeks of routine treatment and that patients with a baseline pulmonary artery pressure > 50 mm Hg have the potential to develop CTEPH. The results of our own study indicate, however, that during anticoagulation extended to one year pulmonary hypertension decreases or even returns to normal after the six-week period in some patients. This may suggest that prolonged secondary thromboembolic prophylaxis after an episode of APE can be more effective in preventing patients with APE from developing CTEPH [24].

Therefore despite the mysterious nature of CTEPH as emphasised by numerous investigators, behind many cases lie unrecognised symptomatic or inappropriately treated APE episodes and insufficient secondary antithrombotic prophylaxis. This implies that CTEPH can, potentially, be more efficiently prevented in future, provided that APE diagnosis and therapy are improved. It would also be helpful to determine why CTEPH is activated only in some patients after APE. Even if the connection between CTEPH and venous thromboembolism has reliable a basis, its aetiopathogenesis has not been fully established. It is not known whether "residual" emboli after an APE episode and silent pulmonary embolism accompanied DVT can activate CTEPH; their nature remains barely understood. It is possible to speculate that they represent the "exhaustion" of endogenous fibrinolysis following the repeated occurrence of emboli, yet fibrinolysis defects are rarely found [29]. The results of studies on coagulation are not uniform and in one recent report a significantly higher concentration of antiphospholipid antibodies was found in CTEPH than in patients with idiopathic pulmonary arterial hypertension. As a result, silent thrombotic changes could propagate distally and initiate CTEPH [30]. The significance of "in situ thrombosis", however, is not obvious. There is also a hypothesis that both in CTEPH and in idiopathic pulmonary arterial hypertension the primary lesions are arteriopathic in nature and that thrombosis is merely a secondary process [31].

The diagnosis of an early stage of CTEPH in patients without an obvious history of APE is extremely difficult. The symptoms may be slight or patients may be asymptomatic, although pulmonary pressure is constantly increasing. At first it is contained within the normal range at rest. However, it can rise during effort. Measurement of pulmonary pressure during an exercise test may well be helpful in recognising the early stages of the disease. In the natural history of CTEPH this period is termed the "honeymoon period", which usually passes into the symptomatic period with increased fatigue and dyspnoea on exertion. These symptoms are, however, highly non-specific. Thus the increased awareness of the relatively high incidence of CTEPH should lead to the disease being taken into account, especially in patients in which the reason for chronic dyspnoea on exertion is not clear. We found CTEPH in as many as 28 out of 90 (31%) consecutive patients who were admitted with this symptom, although the high percentage of CTEPH patients was obviously specific to our specialised department [32]. Early diagnosis of CTEPH may be of vital value. It is believed that patients with mild and moderate pulmonary hypertension can benefit from proper anticoagulation alone. In our own material of newly diagnosed CTEPH patients who had not yet been operated on, all those with pulmonary arterial systolic pressure < 55 mm Hg survived the three-year study. Pulmonary hypertension decreased and exercise tolerance improved [33].

At a more advanced stage of CTEPH with high pulmonary hypertension and right ventricular overload decreased exercise tolerance may be accompanied by ischaemic chest pain and syncope. Only then may an enhanced and split-second sound be heard over the pulmonary artery valve and the systolic murmur of tricuspid valve regurgitation. Typical for CTEPH, but very rare, is the continuous or systolic murmur over lung fields described by Augers and Moser, which is a consequence of partial obstruction of the major pulmonary arteries or recanalisation of thrombi [34]. A chest X-ray is usually normal or can reveal other causes of chronic dyspnoea. A routine electrocardiogram can show

signs of right ventricular overload, especially in the case of high pulmonary pressure. In a population of 56 patients who had experienced APE in the past the highest incidences of negative T wave in the precordial V1–V5 leads, negative T waves in II, III and aVF, pulmonary P wave and right axis deviation > 90% were determined as 43%, 32%, 30% and 30% respectively. These ECG signs of right ventricular overload were of positive value in predicting CTEPH, which ranged from 80 to 100% [35]. Signs of right ventricular overload could be much better recognised and assessed by transthoracic echocardiography, whereas transoesophageal echocardiography can visualise proximal emboli. Continuous valve Doppler measurement of the peak velocity of the regurgitant jet across the tricuspid valve is the basis for the non-invasive assessment of systolic pulmonary artery pressure. This pressure correlates well with the pressure directly measured during pulmonary haemodynamics, although sometimes it can be underestimated [36, 37]. Pulmonary scintigraphy shows perfusion defects, although the greatest value of this study is to exclude CTEPH in patients with pulmonary hypertension when the result is negative [38]. Introducing modern multi-detector row spiral computed tomography increased considerably the possibility of recognising and assessing pulmonary emboli and the appearance of pulmonary vasculature, lung flow and lung parenchyma. Nevertheless, pulmonary angiography accompanied by pulmonary haemodynamics best confirms the diagnosis and establishes the surgical feasibility of CTEPH. It must, however, be remembered, that the appearance of an angiogram in CTEPH is different from that in APE. It is more complicated, reflecting chronic processes of recanalisation and organisation. Thus, apart from "cut-off" changes, webs, bands, and irregularly narrowed vessels can be seen [39].

CTEPH is frequently recognised as late as during the phase of overt right ventricular failure, when episodes of peripheral oedemas, hepatomegaly, ascites and jugular vein distension join the chronic dyspnoea and exercise intolerance. The survival of these patients is short, a few years at most, similar to survival in decompensated hipoxic cor pulmonale [40]. The prognosis at this stage can not be improved significantly by anticoagulation. The reason for this seems to be an irreversible remodelling of the pulmonary vessels which is not susceptible to anticoagulation, while thrombosis may play a less important role. Even in this advanced phase of CTEPH, patients with proximal emboli can be successfully operated on. However, their perioperative prognosis and haemodynamic improvement are worse then those operated on during an earlier phase of CTEPH [41].

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