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EDITORIAL

Chronic thromboembolic pulmonary hypertension: a tribute to pulmonary endarterectomy

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Our understanding of chronic thromboembolic pulmonary hypertension (CTEPH), in terms of both its natural history and pathophysiology, has greatly improved since the landmark descriptions given by MOSER and BRAUNWALD [1] more than 40 yrs ago. At that time, small case series were available, depicting the clinical features of patients suffering from ''long-standing thromboembolic pulmonary hypertension'', ''chronic massive thromboembolic obstruction'' or ''chronic obstruction of large pulmonary arteries''. These patients shared a history of long-term dyspnoea on exertion with normal spirometry values, evidence of pulmonary hypertension, and right ventricular dysfunction in association with the presence of marked defects at the ventilation/perfusion scan; the occurrence of a single or multiple venous thromboembolism episodes, usually several years previously, was constantly mentioned in the diagnostic work-up [2–5]. The success of a surgical procedure, namely pulmonary endarterectomy, has transformed this lethal disorder into a potentially curable form of pulmonary hypertension [1]. As a consequence, the referral of cases suitable for surgery has gradually increased with time: at the University of San Diego (San Diego, CA, USA) there were 41 operated cases in 1980, rising to 323 cases in 1992 [6, 7]. This has enabled us to broaden our knowledge, with the help of further involvement from European centres [8–11].

Forty years ago, the frequency of CTEPH was estimated to be 0.1% of patients who survived an episode of pulmonary embolism [12]. Keeping in mind that an accurate estimation of the true frequency of CTEPH cannot be appraised by such case studies, researchers designed prospective descriptive follow-ups of patients recovering from an acute episode of pulmonary embolism. In the study by RIBEIRO *et al.* [13], systolic pulmonary arterial pressure, as estimated by echocardiography, exceeded 30 mmHg at 1 yr in 34 out of 78 patients, and a pulmonary endarterectomy was indicated in three of the patients at 12, 24 and 44 months. In the largest published prospective cohort, PENGO *et al.* [14] followed-up pulmonary embolism patients every 6 months during the first 2 yrs; patients with unexplained dyspnoea at rest or on exertion underwent echocardiography and CTEPH was considered to be present if the systolic and mean pulmonary artery pressures exceeded 40 and 25 mmHg, respectively. Based on this screening, PENGO *et al.* [14] found a cumulative incidence of symptomatic CTEPH of 3.8% at 2 yrs (95% confidence interval (CI) 1.1–6.5). These data suggested that CTEPH following acute pulmonary embolism is much more common than was previously reported [15].

Data from patients referred for possible pulmonary endarterectomy have not shown a systematic link between acute pulmonary embolism and CTEPH, as a documented history of prior venous thromboembolism events is missing in about 50% of CTEPH cases from such series [16]. Although possible asymptomatic pulmonary embolism cannot be excluded, the unique embolic origin of CTEPH has thus been questioned. This disturbing finding, in addition to the histopathological evidence of *in situ* arteriopathic changes in the resistance vessels of both involved and uninvolved pulmonary vascular areas, has prompted researchers to study overlapping of histopathology, predisposing factors, clinical signs and symptoms between CTEPH and idiopathic pulmonary arterial hypertension [12]. An original depiction of CTEPH has emerged, individual to that of idiopathic pulmonary arterial hypertension or of a venous thromboembolic disease.

A better understanding of this complex field is provided by two original contributions published in the current issue of the *European Respiratory Journal*. BONDERMAN *et al*. [17] gathered data retrospectively from three European referral centres for CTEPH covering four countries (Austria, Czech Republic, Germany and Slovak Republic). They compared 433 CTEPH cases with 254 non-thromboembolic pulmonary arterial hypertension patients from the same centres. Besides previously identified conditions associated with CTEPH, such as splenectomy or ventriculo-atrial shunt (both risk factors showing the highest odds ratios (ORs)), two possible associated conditions emerged, namely thyroid replacement therapy (OR 6.10, 95% CI 2.73–15.05) and history of malignancy (OR 3.76, 95% CI 1.47–10.43). The authors also found higher than previously published reported rates of history of and recurrence of venous thromboembolism (69 and 52%, respectively) in CTEPH patients.

The contribution of CONDLIFFE *et al*. [18] is based on the CTEPH UK national registry. The authors retrieved data regarding 236 patients who underwent pulmonary endarterectomy and 148 nonoperable patients; the main objective was to assess predictors of survival in both groups. In the operable patients, gas transfer and exercise capacity emerged as potential

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predictors, together with pulmonary resistance, a previously underlined prognostic factor. In the nonoperable patients, cardiac index and exercise capacity were the independent predictors. Among the previously described clinical risk factors for the development of CTEPH, interestingly enough, the history of venous thromboembolism was significantly less frequent in nonoperable patients than in patients who underwent pulmonary endarterectomy (49 *versus* 62%; p=0.01), supporting the hypothesis that in a certain number of patients a process of *in situ* thrombosis may occur.

Given the rich body of data gathered by these partly retrospective studies, the next step is a prospective one: the authors involved in these two studies are now involved in the recently launched international registry on CTEPH, the first collaborative work which aims to improve our understanding of the disease on a large scale [19]. This prospective observational registry will identify potential risk factors, characterise CTEPH history and evaluate long-term survival. The heterogeneity of CTEPH will thus be explored in depth. The history of venous thromboembolism, using a validated and standardised questionnaire based on the clinical symptoms of pulmonary embolism, the results of investigations and the duration of anticoagulation with respect to a reported episode deserve special attention [20]. Thanks to the recent fundamental outbreaks in the field of pulmonary arterial hypertension, the identification of cellular, molecular and genetic mechanisms will be facilitated [21]. An adequate assessment of patients who might benefit from endarterectomy, as well as of those who might benefit from medical treatment will be performed. Randomised trials comparing different therapeutic strategies in well-classified patients will be possible subsequently.

Another line of research could be undertaken through exploration of the underlined links between chronic thromboembolic pulmonary hypertension and the history of venous thromboembolism [15]. Cohort studies of unselected patients recovering from a proven episode of acute pulmonary embolism have the potential to adequately assess the incidence rate of chronic thromboembolic pulmonary hypertension. If confirmed, the fairly high chronic thromboembolic pulmonary hypertension incidence rate in patients with pulmonary embolism might set a new therapeutic challenge; until recently, the main end-points when evaluating different treatment regimens with respect to an acute episode of pulmonary embolism, in terms of the duration of anticoagulation or the types of molecules (new anticoagulant, fibrinolytics *etc.*), were recurrent venous thromboembolism episodes and major bleedings [22, 23]. It is also worth considering the occurrence of chronic thromboembolic pulmonary hypertension in the benefit–risk balance of anticoagulant therapy. Careful referral to specialised centres and inclusion in the international registry, as well as the long-term follow-up of patients recovering from acute pulmonary embolism are complementary approaches towards a better understanding of this intriguing disease.

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