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EDITORIAL

The natural history of acute and chronic thromboembolic disease: the search for the missing link

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In the USA, and worldwide, acute venous thromboembolism remains a major cause of morbidity and mortality. It is estimated that 600,000 episodes of acute pulmonary embolism occur each year in the USA that result in 50,000–100,000 deaths [1]. Despite the magnitude of the disease and extensive investigative efforts into its pathogenesis, diagnosis and therapy over the last four decades (1960–2000), the late natural history of those who survive an embolic event has not been well characterized. Data based predominately on clinical follow-up suggest that thromboembolic resolution with restoration of normal gas exchange and exercise tolerance occur in the overwhelming majority of patients who experience an acute embolic event [2]. Characterization of the anatomic and haemodynamic outcomes following acute thromboembolism, however, has been far less comprehensive [3]. Serial angiographic studies have been limited to a relatively small number of patients. Even in these, however, only partial resolution is apparent in many patients as long as 21 days after the acute event [4, 5]. When serial perfusion scans have been performed, ~15% to 25% of patients show only partial resolution as defined by persistent abnormal perfusion patterns on lung scans performed several months after the primary embolic event [6, 7]. These figures may misrepresent the degree of thromboembolic resolution since perfusion scanning in chronic thromboembolic disease may understate the actual extent of angiographic obstruction [8]. The frequency with which evidence of prior pulmonary embolism can be found on careful dissection of the pulmonary arteries suggests that asymptomatic events may occur commonly and that complete thromboembolic resolution following an acute embolic event may represent the exception rather than the rule.

Haemodynamic follow-up data following acute thromboembolism have been equally sparse. Early resolution of pulmonary vascular obstruction occurs by two mechanisms: mechanical changes in thrombus location and endogenous thrombolysis. Following these early events, organization and recanalization further alleviate the degree of pulmonary vascular obstruction [1]. As noted previously, most sequential data regarding resolution in humans are based on perfusion scans, not angiographic or haemodynamic data. Although reperfusion can occur with restoration of as little as 20% of the normal luminal diameter, these areas may continue to serve as high resistance areas that contribute to elevations of pulmonary artery pressure. Significant organized residuals, and therefore abnormal pulmonary haemodynamics at rest or with exercise, may persist in patients whose scans return to normal. That this may be the case is suggested by the experience with pulmonary angioscopy at University of California, San Diego (UCSD) Medical Center (CA, USA). Evidence of web formation, recanalization and luminal narrowing can be encountered in areas of vascular distribution associated with normal angiographic and perfusion scan findings.

How often such residuals persist and how often mild degree of postembolic, subclinical pulmonary hypertension occurs is not known. Recent information, however, has shed some light on the question. In a recent study, 1-year echocardiographic follow-up and 5-year clinical follow-up of 78 patients hospitalized with acute pulmonary embolism were reported [9]. An early dynamic phase followed by a protracted stable phase of pulmonary artery pressure decline after an acute thromboembolic event was identified. The time to achieve the stable phase was 38 days and was independent of whether the therapeutic intervention was thrombolytic therapy or heparin. In patients with a pulmonary artery systolic pressure >50 mmHg at the time of diagnosis of the acute episode, the risk for persistent pulmonary hypertension increased three-fold; four patients (5.1%) developed chronic pulmonary hypertension and three subsequently underwent successful pulmonary thromboendarterectomy.

In contrast to acute venous thromboembolic disease, in which the early natural history has been well defined, the early haemodynamic progression of chronic thromboembolic pulmonary hypertension (CTEPH) remains uncertain [10]. The symptomatic history has been well described [11]. Following a documented venous thromboembolic event, symptomatic recovery occurs although often not to a level equivalent to that prior to the acute event. In patients without a documented acute thromboembolic event, many can provide a history consistent with that diagnosis. They may describe an episode of pleurisy, lower extremity muscle strain, or prolonged, atypical pneumonia. Or, they may describe a hospitalization or surgical procedure from which they never fully recovered. That an episode of venous thromboembolism is not diagnosed, or is misdiagnosed, is not surprising given recent data that confirm the often subtle clinical presentation of a venous thromboembolic event and the frequency with which misdiagnosis occurs [12, 13]. Following a period of clinical

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stability, which may range from months to years, worsening exertional dyspnoea, hypoxaemia, and right ventricular dysfunction ultimately ensue. The degree to which this haemodynamic and symptomatic decline is related to recurrent embolic events, *in situ* thrombosis, changes in the pulmonary microvasculature, or loss of right ventricular adaptive mechanisms remains controversial and is one of the most fascinating enigmas surrounding this disease process. There is evidence, based on lung biopsy findings obtained at the time of thromboendarterectomy, that changes in the microvasculature, similar to that seen in other forms of pulmonary hypertension, may account for the progressive clinical decline [14].

It has been proposed that CTEPH represents an alternative natural history of acute venous thromboembolism. Although exact incidence figures are not available, it is likely, based on the number of embolic survivors and the number of patients referred for pulmonary thromboendarterectomy, that CTEPH of sufficient severity to require surgical intervention occurs in no more than 0.1% of patients who experience an embolic event [10, 11]. It is likely that the term "alternative" is imprecise and that CTEPH represents part of the normal spectrum of disease associated with pulmonary embolism: complete haemodynamic and anatomic resolution in a minority of patients, partial resolution associated with a normal clinical status in most, and progression to pulmonary hypertension in the remaining few.

In this issue of the *European Respiratory Journal*, EGERMAYER and PEACOCK [15] hypothesize that venous thromboembolism is unlikely to be a common cause of CTEPH and that, instead, the pathophysiological mechanism responsible for the disease is a primary pulmonary arteriopathy with secondary *in situ* thrombosis. Experience with this patient population at the UC, SD Medical Center suggests that this hypothesis, although intriguing, is flawed. At the UCSD Medical Center, pulmonary thromboendarterectomy has been performed in almost 1,200 patients since 1970, 985 patients over the last decade (1990–1999) alone with an overall in-hospital mortality rate during this latter time frame of 7.2%. Therefore, experience with the history and clinical presentation of these patients is extensive.

The thromboembolic basis for the disease is supported by several lines of clinical evidence. First, the majority of patients who have been referred with suspected chronic thromboembolic pulmonary disease over the last several years can provide a history not only of pulmonary embolic disease but of venous thromboembolism. This may be the result of a growing acceptance by clinicians that venous thrombosis and pulmonary embolism represent manifestations of a common disease entity and the consequent widespread utilization of lower extremity venous duplex imaging as a routine part of the diagnostic pathway in embolic suspects. Duplex ultrasonography findings in patients referred for thromboendarterectomy support this likelihood. In a review of the 245 patients undergoing thromboendarterectomy at UCSD Medical Center in 1996 and 1997, 48% had lower extremity duplex findings consistent with prior venous thrombosis, an incidence not dissimilar to that found in cases of acute pulmonary embolic disease [16–18]. To infer that a primary pulmonary arteriopathy is associated with pulmonary artery thrombosis and lower extremity venous thrombosis stretches the limits of credulity and neglects the conceptual advances made in the area of venous thromboembolism over the last few decades. Second, the haemodynamic outcome following thromboendarterectomy suggests that, in most patients, the distal pulmonary vascular bed is not involved with an arteriopathic process, or at least one of significant extent. In the overwhelming majority of operated patients, even those with severe levels of pulmonary hypertension, normalization or near-normalization of pulmonary haemodynamics has been achieved [19–22]. This would not be the case if central pulmonary artery thrombosis was a secondary response to increased downstream resistance. Furthermore, long term follow-up, albeit in a limited number of patients, has demonstrated that this improvement is sustained [23, 24].

It is true that recurrent pulmonary hypertension does occur in a small number of patients undergoing thromboendarterectomy. However, this has been limited solely to those patients with significant residual pulmonary hypertension immediately following the procedure. The authors have yet to encounter a patient with normalization of their pulmonary haemodynamics following the procedure in whom recurrent pulmonary hypertension has developed in the absence of a documented recurrent venous thromboembolic event associated with inadequate levels of anticoagulation. It is also true that recurrent thromboembolism is unusual following thromboendarterectomy [25]. It must be emphasized, however, that an inferior vena caval filter is placed in all patients prior to the procedure and that lifelong anticoagulation is recommended. It is likely that physician and patient compliance with an anticoagulation regimen following the rigours of thromboendarterectomy is considerably more exacting than that encountered following an acute, uncomplicated venous thromboembolic event.

The hypothesis presented by ERGEMEYER and PEACOCK [15], therefore, may have little to do with the genesis of CTEPH but a great deal to do with its evolution. It has become increasingly apparent that, at least in certain patients, CTEPH represents more than simple mechanical obstruction of the large pulmonary arteries. The dissociation between the degree of angiographic obstruction and the haemodynamic consequences of that obstruction can be striking. Certain patients with relatively modest levels of central pulmonary artery obstruction determined by angiography can have severe pulmonary hypertension while others with a degree of central pulmonary vascular obstruction approaching 70% of the pulmonary vascular bed may have only moderate haemodynamic impairment.

One of the engrossing aspects of chronic thromboembolic disease, and in fact any form of pulmonary vascular disease, is why haemodynamic progression occurs in certain patients and not others and what factors determine the rate of progression. Among other possibilities, this haemodynamic evolution may involve an interplay among the percentage obstruction of the pulmonary vascular bed, the effects of circulating vasoconstrictors, immune-related events, the development of a hypertensive pulmonary arteriopathy, an individual genetic predispositon to pulmonary hypertension, and the hypertrophic and dilatory adaptations of the right ventricle [3]. Of course, similar questions may be asked about any form of pulmonary hypertension. What is the triggering mechanism, for example, involved in the genesis of pulmonary hypertension associated with

the use of anorexogenic agents and why, at some point in the haemodynamic evolution of the disease, does the pulmonary hypertension progress even after the offending agent is withdrawn?

The questions raised by ERGEMEYER and PEACOCK [15], therefore, are relevant to the clinical care of patients suffering from both acute and chronic thromboembolic disease. In regard to acute thromboembolic disease, a great deal more needs to be learned about the natural history of the disease process. The early detection of those with persistent pulmonary hypertension following an acute event would serve to identify patients at risk of further haemodynamic impairment and shed light on the pathophysiological mechanisms involved in the progression of their pulmonary hypertension. Unlike other forms of pulmonary hypertension, that typically present late in their course and long after a potentially inciting event has dissipated, the predisposing event in CTEPH can be identified and the natural history of the disease carefully followed.

In regard to chronic thromboembolic disease, the major cause of death (other than reperfusion pulmonary oedema) following pulmonary thromboendarterectomy is persistent postoperative pulmonary hypertension and right ventricular failure in patients for whom pulmonary thromboendarterectomy failed to achieve substantial improvement in pulmonary haemodynamics [10, 22]. This latter group includes patients whose disease involves a substantial component of distal, surgically-inaccessible embolic obstruction and patients who have developed severe, secondary pulmonary hypertensive changes in their distal pulmonary vascular bed. Partitioning the central component of the haemodynamic impairment from that which is not surgically amenable during the preoperative evaluation is an inexact science even in the most experienced of hands. The ability to do so with greater precision would help identify that cohort of patients with chronic thromboembolic disease in whom thromboendarterectomy is not indicated as well as those who might potentially benefit from a combined therapeutic approach, thromboendarterectomy to manage the central component of the disease followed by aggressive medical intervention (*e.g.* prostacyclin) to manage the distal component.

If the recent history of pulmonary hypertension has taught anything, it is that there are few absolutes associated with this condition. It is probable, however, that a better understanding of the late natural history of acute venous thromboembolism will provide insight into the early natural history of chronic thromboembolic disease and into the pathophysiological mechanisms of pulmonary hypertension as a whole.

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