in 17 of 21 participants along the 10 training sessions evaluated. Large inter-individual differences in $\bar{x}DL_{CO}$ are also showed after swimming exercise, including 6 subjects showing a large decrease (−5.6–11.2%), 11 subjects with a small decrease (−0.4–3.1%) and 4 subjects showing a slight increase (+1.3–2.2%). Therefore, at least 6 of 21 participants of the study suffer a post-training diffusion limitation consistently more pronounced than the repeatability of DL_{CO} in healthy adults (±3.1%).[12]

Several causes has been proposed to explain this decrease, including the redistribution of central blood volume to peripheral areas[13] and the development of an exercise-induced pulmonary oedema.[4] Beside, the changes in Hb during training were not considered, which could account to some extent for the differences in DL_{CO} after training. The first possible explanation is the redistribution of the blood flow to the peripheral tissues after the training through a significant redistribution of fluid shift from the thorax to the peripheral vascular space.[13] In our study, we measured DL_{CO} less than 10 min after exercise and the decrease in DL_{CO} occurs despite a slight increase in the alveolar volume after training, which conflict with this hypothesis. The second possible explanation is the presence of swimming-induced pulmonary oedema (SIPO) during exercise which has been related to the ultra-structural mechanical stress in the pulmonary capillaries under a condition of high pulmonary artery and capillary pressures[14] such as swimming exercise. Currently there is no evidence as to why certain individuals are susceptible to SIPO, although symptoms normally resolve rapidly within 48 h[7] and do not provoke the development of clinically relevant pulmonary oedema which remains as a rare event.[15]

In summary, this study shows that swimmers experience subclinical decrease in lung diffusing capacity after training, although elite swimmers have larger lungs and higher diffusing capacity than the general population. Therefore, the swimming-induced decrement in DL_{CO} is a transient phenomenon that does not lead to chronic impairment in pulmonary gas exchange. In fact, we suggest that the highly developed pulmonary function of the elite swimmers could be the result of repeated stress to the alveolar-capillary barrier during training. We also found large inter-individual variability, including some swimmers with a large decrease in lung diffusing capacity after exercise. Therefore, doctors and coaches should pay attention to the individual changes in alveolar-capillary diffusing capacity among elite swimmers exposed to highly demanding training regimes.

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Therapeutic adherence of COPD patients according to levels of involvement in health education in their sites☆

Adhesión terapéutica de los pacientes con EPOC según los niveles de implicación en educación sanitaria de sus centros

To the Editor:

According to recent data obtained from the RE-TAI study, 48.5% of patients with chronic obstructive pulmonary disease (COPD) in Spain have poor therapeutic adherence[1] (determined by the Test of Adherence to Inhalers [TAI]).[2] When the TAI data were combined with information from pharmacy refill rate (PRR) electronic records, the percentage of patients with poor adherence increased to almost 55%.[1]

Factors influencing therapeutic adherence are heterogeneous and include, but are not limited to, patient education, inhaler ease-of-use, and the complexity of the therapeutic regimen.[3,4] Lack of adherence is, in turn, associated with poor disease control and reduced quality of life, and an increase in the use of resources and costs.[3] Consequently, acting on factors such as health education that improve the therapeutic adherence of COPD patients can contribute substantially to an improvement in the disease. It is estimated that reductions in morbidity and mortality among respiratory patients who followed an education program were due primarily to their increased therapeutic adherence. No studies have been conducted to evaluate differences in

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Table 1
Responses from participating centers to the Educational Involvement (EIE) scale.

Item	Sites, n (%)				
	Never	Almost never	Sometimes	Almost always	Always
1. Is the nursing staff involved in the education of respiratory patients?	2 (9.5)	2 (9.5)	5 (23.8)	9 (42.9)	3 (14.3)
2. Are the patient's preferences or opinions taken into account when prescribing a new inhaler?	0 (0)	1 (4.8)	2 (9.5)	15 (71.4)	3 (14.3)
3. Does the patient receive supplementary written information (brochures, books, etc.) about their disease?	0 (0)	3 (14.3)	11 (52.4)	6 (28.6)	1 (4.8)
4. Is any additional method used to determine the patient's therapeutic adherence, e.g., questionnaires (TAI, Morisky-Green) and/or PRR?	0 (0)	5 (23.8)	3 (14.3)	9 (42.9)	4 (19.0)
5. Do patients receive an individual written action plan?	1 (4.8)	5 (23.8)	9 (42.9)	3 (14.3)	3 (14.3)
6. Is the patient taught how to use the inhaler?	0 (0)	0 (0)	1 (4.8)	5 (23.8)	15 (71.4)
7. Are placebo devices used to train patients in inhaled therapy?	0 (0)	1 (4.8)	2 (9.5)	5 (23.8)	13 (61.9)
8. Is the inhalation technique regularly monitored in each patient?	0 (0)	0 (0)	5 (23.8)	8 (38.1)	8 (38.1)

PRR, Prescription refill record; TAI, Test of adhesion to inhalers.

therapeutic adherence in patients from sites which provide varying educational support. The aim of this study was to determine whether COPD patients treated in sites with greater involvement in education have better therapeutic adherence.

The RE-TAI project was an observational, cross-sectional study that included 410 COPD patients from 21 sites (11 respiratory medicine, 5 internal medicine, and 5 primary care). Demographic characteristics were collected and the TAI was completed in a single visit. Subsequently, principal investigators at the participating sites completed the Education Involvement Scale (EIE), an *ad hoc* questionnaire composed of 8 questions scored between 1 (never) and 5 (always). The relationship between the EIE score and the percentage of patients with intermediate or good adherence (TAI $10 \geq 46$) was analyzed with a univariate analysis. A multivariate analysis was performed to determine which variables (demographic and clinical) were independently associated with high adherence.

EIE scores per site ranged from 25 to 38, with a median (Q1-Q3) of 32 points (26–33) and a mean (SD) of 30.5 (4.1). More than 75% of sites reported that they always or almost always take patient preferences into account when prescribing the inhaler, instruct patients in its use using placebo inhalers, and monitor inhalation techniques (Table 1). Almost 62% of sites reported always or almost always using questionnaires or PRR to determine therapeutic adherence.

Univariate analysis showed that intermediate or good adherence was significantly associated with the EIE score (OR: 1.09; 95% CI: 1.03–1.15; p = 0.002), while multivariate analysis showed that intermediate or good adherence was associated with a higher EIE score (OR: 1.08; 95% CI: 1.02–1.15; p = 0.011) and also with the number of inhalers used by the patient (OR: 1.53; 95% CI: 1.06–2.22; p = 0.024).

This study confirms that the degree of involvement of sites in their patients' education may affect adherence to inhaled treatment in COPD patients. Other studies also suggest that certain strategies for patient empowerment, health education, and monitoring compliance increase adherence to inhaled treatment in these patients.[5–9] Clinical practice guidelines also emphasize the importance of health education.[10,11] These measures contrast with some observations from our study: e.g., no personalized action plans or written information, the involvement of nursing staff, or evaluation of therapeutic adherence using specific questionnaires or PRR. The heavy burden of care, the characteristics of COPD patients (age, comorbidities, polypharmacy, etc.), or even the lack of data from specialists on the use of inhalers[12] could explain why there is such room for improvement in our country. Despite all this, COPD patients show a higher rate of unwitting non-compliance than, for example, asthmatic patients.[13] Therefore, educational measures such as written self-management plans or visual aids, training in inhaler use, or audiovisual materials may be good strategies for improving adherence.[5]

This study has some limitations. The EIE used to assess the degree of health education in participating sites has not been previously validated. Moreover, only the principal investigator in each participating site completed the EIE, thus avoiding interpersonal differences between the different investigators who were able to recruit patients. The EIE has not been previously validated. The small series did not allow for comparisons between specialties. We intend to carry out a new, prospective study in a larger series that will include unbiased sites. Objectives will also include comparison between specialties. However, these potential limitations do not undermine the results obtained to date.

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Massive Pulmonary Thrombosis Following Haemoptysis in Type IV Ehlers–Danlos Syndrome

Trombosis pulmonar masiva tras hemoptisis en el Síndrome de Ehlers–Danlos tipo IV

Dear Editor:

Ehlers–Danlos syndromes (EDS) are a group of rare genetic disorders that affect connective tissue, characterized by joint hypermobility, skin hyperextensibility, and tissue fragility. The majority of the currently recognized 13 EDS subtypes[1] are due to gene variants leading to impaired synthesis or structural abnormalities of different collagen types. Type IV or vascular EDS (EDS-IV) is an autosomal dominant multisystem disease caused by defects in type III collagen, encoded by the *COL3A1* gene, in chromosome 2 (2q32.2).[1] Type III collagen is a major constituent of the interstitial matrix in many tissues, including blood vessels. Accordingly, aneurysms and rupture of large arteries, spontaneous bowel perforation and uterine rupture during pregnancy are life-threatening complications of EDS-IV. EDS-IV is the most severe form of EDS, with most individuals dying before the 5th decade.[1] Pulmonary involvement may occur without extrathoracic manifestations,[2–6] and the diagnosis of such cases may be made only at post-mortem examination.[6] Spontaneous pneumothorax or haemopneumothorax are the most frequent complications, but cavitary lesions, haemoptysis and pulmonary haemorrhage have also been reported.[2–6]

Herein, we report the occurrence of severe haemoptysis associated with massive pulmonary thrombosis, with a fatal outcome, in a young adult male with EDS-IV. The patient's diagnosis was established by genetic testing in mid-adolescence, as soon as the family's pathogenic *COL3A1* (c.3517_3519del/p.(Gly1173del)) variant was identified. The patient had been free of significant EDS-related complications until the age of 17 years. The patient's father and one maternal aunt died from spontaneous aortic dissection/rupture, early in the 4th decade of life.

Our patient had a first hospital admission for haemoptysis at the age of 17. At the time, small areas of ground-glass opacities suggestive of alveolar haemorrhage were observed on chest computed tomography (CT). Over the next two years, he had occasional episodes of small-volume haemoptysis, often preceded by a tingling sensation in the head and neck.

At age 19, the patient needed hospitalization for large-volume haemoptysis. In the previous days, he had intermittent episodes of small-volume haemoptysis preceded by what he described as a "clicking" sensation in the head and, right-sided paraesthesia and mild motor weakness. The chest CT scan (late arterial phase) showed multiple bilateral ground-glass opacities suggestive of diffuse alveolar haemorrhage and large fluid-filled cavities with air-fluid levels suggestive of haemorrhagic cavitation (Fig. 1A/B). Brain and cervical magnetic resonance (MR) imaging, MR angiography of the carotid and vertebrobasilar circulations, including the supra-aortic arches, and electroencephalogram were unremarkable. Despite the decrease in the haemoglobin level relative to baseline (respectively 15.3 g/dL and 13.8 g/dL), the patient remained hemodynamically stable without respiratory failure. Cough suppressive and antifibrinolytic therapies were initiated. Since the patient did not have any bronchial artery hypertrophy on CT scan and due to the high risk of vascular manipulation, bronchial arteriography was not performed. The surgical risk was also very high; therefore, the patient was not a candidate for thoracic surgery at that time.

A pulmonary CT angiography obtained on day 7 of hospital stay showed extensive bilateral thrombosis and an enlargement of the haemorrhagic parenchymal cavitation, but no actively bleeding arteries (Fig. 1C/D). There were no signs of deep vein thrombosis on Doppler ultrasound examination of the lower limbs. Despite the striking radiological signs, the patient remained asymptomatic. Transthoracic echocardiogram did not show any signs of right ventricular dysfunction, and the Pulmonary Embolism Severity Index (PESI) score was 29 (class I), translating into a low mortality risk.[7] Given the high bleeding risk and the low overall risk stratification, hypocoagulation was not prescribed.

Two days later, the patient was admitted to the intensive care unit, following a syncope episode with echocardiographic evidence of right ventricular dysfunction. Anticoagulation with unfractionated heparin and inotropic support were instituted. After about 24 h of clinical stability, his haemodynamic condition suddenly deteriorated due to supraventricular tachycardia, followed by cardiac arrest that did not respond to advanced life support measures and thrombolysis. Autopsy was not performed.

To our knowledge, this is the first report of massive pulmonary thrombosis in a patient with EDS-IV seeking medical attention for recurrent haemoptysis. Arterial bleeding complications are typical of EDS-IV and several cases of severe haemoptysis, including with fatal outcomes, have been described.[2,4,6] Platelet dysfunction may additionally aggravate the constitutional haemorrhagic propensity.[8] Contrastingly, thrombotic events seem to be exceedingly rare in patients with EDS,[9] but have been reported in EDS-IV[10–12] and other EDS subtypes.[9,13] In one of the EDS-IV cases, the patient had renal infarctions caused by emboli from a thrombotic renal artery aneurysm, and hypocoagulation was not prescribed either, with a favourable outcome.[12]

Major treatment decisions taken in our patient were based on validated risk stratification algorithms for pulmonary embolism/thrombosis[7] and current clinical approaches to the management of haemoptysis.[14] The delay in starting anticoagu-