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Editorial

Pulmonary hypertension due to chronic pulmonary thromboembolism. An evolving disease

La hipertensión pulmonar secundaria a tromboembolia pulmonar crónica. Una enfermedad en evolución

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Despite the therapeutic advances of the past 20 years, many forms of pulmonary hypertension still have a poor prognosis.[1] The most significant therapeutic advances relate to the treatment of chronic thromboembolic pulmonary hypertension (CTEPH),[1] for which surgical pulmonary thromboendarterectomy (PTE) can potentially be curative. Recent pharmacological treatments for pulmonary arterial hypertension have also led to a 5-year survival of above 80%.[2] CTEPH is classified as group 4 pulmonary hypertension and is characterized pathologically by organized thromboembolic material and abnormal vascular remodeling initiated and potentiated by a combination of defective angiogenesis, deficient fibrinolysis, and endothelial dysfunction.

Two interesting aspects of CTEPH are, first, that the classical risk factors for venous thrombosis do not appear to increase its risk, and second, that there are clear geographical differences in its epidemiology. This highlights the importance of having epidemiological data for each country or region. An international CTEPH registry (for Europe and Canada) indicates that 75% of patients have a clear history of acute pulmonary embolism, whereas in Japan this is only present in between 15% and 33%. Japan also has a female predominance (80%), unlike the USA and Europe.

In published prospective studies on CTEPH, with diagnosis confirmed on right heart catheterization, the incidence of CTEPH after symptomatic pulmonary embolism ranges from 0.4% to 6.2%, with a mean incidence of 3.4%. Precise determination of the incidence of CTEPH is difficult. It is likely that CTEPH is underdiagnosed, while the incidence of acute pulmonary embolism is probably overestimated. The nonspecific nature of the symptoms, the variability in history of acute pulmonary embolism, the experience required for correct interpretation of the computed tomography pulmonary angiography, and the infrequent use of ventilation-perfusion scans despite the recommendations in the guidelines all contribute to this problem.[3]

Recently, the cutoff for a diagnosis of pulmonary hypertension has been set at a mean pulmonary arterial pressure of 20 mmHg, with a pulmonary capillary pressure of $\leq$ 15 mmHg and vascular resistance $>$ 3 UW. This new cutoff will affect the epidemiology of all types of pulmonary hypertension, including that of CTEPH, reported in the literature.

Currently, the recommended treatment for CTEPH, due to being most effective, is surgical PTE. This treatment is potentially curative and can practically normalize pulmonary hemodynamics. However, up to 40% of patients are not candidates for this surgical treatment; balloon pulmonary angioplasty (BPA) can be a good treatment option for such patients.

BPA has acquired an important role in the therapeutic algorithm, since it was reported in 2012 in Japan that this type of treatment improved hemodynamics, reduced symptoms, increased exercise capacity, and improved right ventricular function.[4] In a retrospective analysis, the benefits of BPA appeared to be maintained in the mid-term,[5] a finding that was subsequently confirmed in European publications.[6] However, the low rate of complications reported in these studies with BPA reflect not only that the experience is very short, but also that it comes from centers with more experience in this area. Although the results of BPA are promising, the published studies are from expert centers and are probably not generalizable. Even with the best techniques, there remains a clear learning curve for the safe and effective performance of BPA. The benefit of BPA for patients with disease that is technically operable but who are not candidates for surgery due to other comorbidities is not yet established.[7]

In BPA, chronic vascular obstructions are observed in medium to large vessels as well as microvascular arterial disease that develops over time. The hemodynamic and clinical improvement observed with BPA (6-minute walk test, pulmonary arterial pressure, and pulmonary vascular resistances) are probably related to the removal of the macrovascular obstruction. Treatment of macrovascular obstruction is associated with reduced disease progression and improved prognosis across the whole spectrum of thromboembolic pulmonary disease. This is seen in patients with CTEPH who undergo PTE either as a surgical or percutaneous treatment of the acute pulmonary embolism.[8] This could explain, at least partially, the fact that PTE in CTEPH improves survival, while pulmonary vasodilators do not. Nonetheless, pulmonary vasodilators improve the functional capacity of patients with inoperable CTEPH by treating the microvascular disease. The

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relatively small improvement observed with pulmonary vasodilators in comparison with BPA suggests that macrovascular obstruction predominates in the pathophysiology of CTEPH. In summary, BPA and pulmonary vasodilators offer a functional and hemodynamic improvement in patients with inoperable CTEPH. BPA offers a clearer improvement but at the expense of the risks inherent to an invasive treatment. Still, high-quality randomized studies are needed to precisely determine the usefulness of BPA and pulmonary vasodilators in the treatment of inoperable CTEPH.

One interesting and much debated point is the differences in the natural history depending on the underlying disease. For example, although exertional dyspnea is relatively common after acute pulmonary embolism, even despite long-term anticoagulation, only some of these patients develop clear pulmonary hypertension, whereas in others no cardiopulmonary disease is found on diagnostic investigation. Surprisingly, there is a group of patients who show evidence of chronic thromboembolic disease (residual fibrothrombotic pulmonary vessel obstruction), but without pulmonary hypertension. In these patients, dyspnea could be explained by ventilatory inefficiency, abnormal pulmonary vascular response to exercise, poor right ventricular-pulmonary artery coupling, and diastolic right ventricular dysfunction.[9,10]

Although the epidemiological data on CTEPH are limited, with some discrepancies in the pathogenesis, an analysis of 25 publications based on 14 databases has provided quantitative epidemiological information for several different geographical areas.[11] The incidence of this disease is clearly different in Europe and USA than in Japan, where the incidence is lower. The mathematical projection models indicate that the incidence of CTEPH will continue to increase in the coming decade. This suggests that CTEPH is underdiagnosed and, in turn, undertreated. Consequently, any and all epidemiological information is needed and of great clinical usefulness for each geographical location, and should be monitored over time.[11]

In a recent article in *Revista Española de Cardiología,* Martínez-Santos et al. published an interesting study on patients with CTEPH based on data from the REHAP resgistry.[12] This is an unfunded, voluntary registry that was created in January 2007. Patients were prospectively included from 2007, and the analysis was retrospective.[12] It should be noted that BPA programs began in Spain in 2013 and that marketing of riociguat began in 2015. The REHAP registry provides useful information for everyday clinical practice. It contains demographic, clinical, and prognostic data on patients from 40 hospitals throughout Spain.

The key findings relate to the increase in this disease in the past decade and the clinical benefit from pulmonary angioplasty in patients who are not candidates for surgical treatment.

In the REHAP study, the criteria for the diagnosis of CTEPH was a mean pulmonary arterial pressure of $>$ 25 mmHg on right heart catheterization. This was the definition used until the latest guidelines,[13] in which a new cutoff of 20 mmHg was approved for the diagnosis of pulmonary hypertension. Therefore, the epidemiological data in the study by Martínez-Santos et al.[12] must be analyzed in this context. Although all the hospitals with a pulmonary hypertension unit have included patients in the REHAP study, we cannot rule out the possibility that patients with CTEPH treated in smaller hospitals may not be included in this registry. Nonetheless, we must acknowledge that such problems are inevitable with the creation of a multicenter national registry. As a significant strength, from a methodological perspective it is a study that prospectively included patients from 2007 to 2018. This is an important point, because the data was collected at the time of occurrence rather than from information recorded in the patient notes, making the quality of data more reliable and exhaustive.

From the analysis performed, the authors first present the characteristics and differences of the 1019 patients included, according to the treatment received (3 groups: BPA, surgical PTE, and medical treatment) and according to whether they had been referred to a tertiary referral center or not. No differences were observed between groups. To control the differences between subjects with interventional vs medical treatment, they used an adjustment model based on propensity scoring, which paired subjects with the same probability of receiving treatment, reducing the sample to 294 individuals. The analysis used was able to control for some of the differences between medical treatment and interventional treatment, although not for the calendar period. This variable was not used for the calculation of propensity scores and is very closely correlated with the type of treatment given, which could partly explain the observed survival differences.

As the authors noted, propensity score matching allowed them to determine the effect of medical treatment vs interventional treatment, as though simulating a clinical trial. However, for the correct interpretation of the results, it must be borne in mind that even a paired analysis does not eliminate differences in the time period. For this, it would have been necessary to include the year the treatment was delivered in the calculation of the propensity of receiving one treatment or the other, something which is often not possible for obvious reasons, as treatments are closely correlated with the calendar period. In addition, the use of propensity score matching techniques reduces the total number of subjects and, if the analysis is not stratified, the results are not completely corrected. Thus, the use of other techniques such as an inverse probability-weighted Cox model could have attenuated the differences. Nonetheless, although there are limitations that must be taken into account for the correct interpretation of the results, we must congratulate the authors for this work, which corroborates the improved diagnosis and prognosis of CTEPH in recent years.

It seems clear from the literature that the epidemiology of CTEPH varies in relation to geographical location and that its incidence is increasing, due to both changes in the hemodynamic definition of pulmonary hypertension and the increase in diagnostic sensitivity. The prognosis of CTEPH also changes over time with the introduction of new, more effective therapeutic options. All of this highlights the importance of studies such as that by Martínez-Santos et al.[12] which, despite the limitations inherent to this type of registry, provide data that is of great clinical relevance. As the Châtenay-Malabry-born French philosopher François-Marie Arouet, better known as Voltaire, once said, "*Le mieux est l'ennemi du bien*". We should value and use the information that we have available even if it is not as perfect as we would like it to be.

CONFLICTS OF INTEREST

None of the authors have any conflicts of interest.

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