Pulse oximetry oxygen saturation during the 6-min walk test: a limit for stopping the test without resuming it

To the Editor:

We read with interest the systematic review on [1] and the new procedures for [2] field tests for chronic respiratory diseases. However, we would like to raise some concerns regarding the indications given when oxygen desaturation occurs during the 6-min walk test (6MWT).

The technical standard reports that one of the reasons that should lead the examiner to stop the 6MWT is a fall in pulse oximetry oxygen saturation (\(S_{\text{PO}}2\)) to <80% and suggests resuming the test after the \(S_{\text{PO}}2\) recovers to >85%. This suggestion is based on a single study only [3] that reports instruction to resume walking if \(S_{\text{PO}}2\) rises above 80% (and not 85%), citing these two documents: "ATS statement: guidelines for six minute walk test" [4] and "ATS/ACCP Statement on cardiopulmonary testing" [5]. The former did not mention anything about the behaviour of \(S_{\text{PO}}2\) during the test, since its monitoring was optional; the latter examined a maximal exercise test, which is considerably different from a functional test such as 6MWT and, moreover, the indication to interrupt cardiopulmonary test is a fall in \(S_{\text{PO}}2\) to <80% when accompanied by symptoms and signs of severe hypoxaemia [4].

The self-paced nature of the 6MWT makes it a functional test that reflects the capacity for exercise in people suffering from chronic respiratory disease. Its validity depends on several methodological factors and controlling for confounders was shown to have an important impact on walked distance, even the tone of the voice was standardised. Therefore, introducing an additional variable such as resuming the test after a desaturation event might be a critical issue regardless of its standardised procedures and prognostic use.

Indeed, this introduces several biases to the procedure and the authors should clarify when the 6MWT has to be stopped after an \(S_{\text{PO}}2\) <80% is displayed on the pulse oximeter; moreover, they should define the minimum time needed to ask individuals to recommence walking after assessors see an \(S_{\text{PO}}2\) ≥85%. These time gaps undermine the repeatability of the test and, most importantly, are not well supported by scientific evidence.

Furthermore, we would like to question whether it is appropriate to interrupt the patient when certain levels of desaturation occur. Unless there are obvious signs and symptoms of severe hypoxaemia, are we sure that a self-paced test measuring physical functioning must be ceased even when \(S_{\text{PO}}2\) falls to <80%? As outlined in the technical standards, there are few data on the risk of not stopping subjects with significant desaturation and there are no studies that correlate desaturation during field tests with the incidence of adverse events. To this, we must add that in some diseases, such as interstitial lung disease [6], a significant percentage of individuals show awake and sleep average desaturation levels that can frequently be <85%, according to the severity of the clinical picture, which suggests that these subjects live under stressful cardiopulmonary conditions to which they respond with a sort of adaptation without considering it a life-threatening emergency.

Finally, we have to consider systematic error when measuring \(S_{\text{PO}}2\). The accuracy of \(S_{\text{PO}}2\) measurement is not equivalent to that of invasive arterial oxygen saturation (\(S_{\text{AO}}2\)), especially in sick patients, considering that empirical calibration of pulse oximeters is based on examinations of healthy volunteers [7]; this deviation of \(S_{\text{PO}}2\) from \(S_{\text{AO}}2\) is greater at saturations <80% [8]. The accuracy of a single measurement of \(S_{\text{PO}}2\) is 3–4% [7, 9] and considering the fact that the relevant clinical range of \(S_{\text{AO}}2\) is 80–100%, such an error could be of major significance. More crucially, digital clubbing, which is usually associated with greater severity of some lung diseases [10], is known to cause underestimation of \(S_{\text{PO}}2\) in cystic fibrosis [11]. In addition, signal corruption generally occurs during motion.

In conclusion, we are afraid that inaccurate (under)estimation of \(S_{\text{PO}}2\) might lead to a premature 6MWT cessation, twisting the functional meaning of the test itself and, potentially, causing a fundamental mistake over its rehabilitative and prognostic value. We hope that all the aforementioned points could be considered in order to return to performing a less equivocal 6MWT.
Guidance for the regulatory status of allergen extracts in clinical trials

To the Editor:

Following the introduction of the guidelines on clinical development and regulation of marketing authorisation for allergen extracts [1], there is an ongoing discussion on their regulatory status (i.e. authorised or unauthorised (off label)) when applied in interventional or observational clinical trials [2]. Since in most European Union (EU) countries, many allergen extracts either do not have a marketing authorisation or are not authorised for the intended application within a study protocol, it is often unclear which documents are needed for submission to an Independent Ethics Committee (IEC) and the Competent Authority.

Within clinical interventional or observational trials, allergen extracts can have different applications, i.e. as diagnostic tools (e.g. skin prick tests), as test or comparator products, as (standard) therapy, as challenge agents (e.g. nasal and inhalation provocation tests, inducing an immunological/physiological response) or as outcome measures. Depending on the application within a clinical protocol, allergen extracts can thus have different regulatory status requiring different product documentation (table 1) [3]. We present an overview of how to facilitate documentation for IEC and Competent Authority submission when an allergen extract is part of a clinical study.

Noninvestigational medicinal products (NIMPs) include agents other than the test product, the comparator product or placebo (the so-called investigational medicinal products (IMPs), and may be