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EDITORIAL

Your racing horses will help you to quit: a lesson for COPD and α_1-antitrypsin deficiency research

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The more we learn about spirometry, the more we could be challenged. *Au contraire*, farmers are proficient about horses and are experienced in identifying young thoroughbreds with potential talent. They refer to the horse-racing effect by saying that, if you train a fine, young stallion, you might well end up with a winner; and that horses who are leading a race, at a point closer to the finish line, are more likely to win it than those leading at earlier parts of the track. Mathematically, this effect is referred to as co-linearity; your baseline position determines your likely future position. In respiratory medicine, we know about the horse-racing effect from the famous pulmonary curves of FLETCHER and PETO [1], a model postulated 40 yrs ago but not yet validated. It could be assumed that by serially testing with spirometry those at a high risk of chronic obstructive pulmonary disease (COPD), such as heavy smokers, you could identify an increased slope of forced expiratory volume in one second (FEV1) decline. This increased decline could be used as a screening tool for those who finally develop the disease. In 1981, this was named as the lung function horse-racing effect [2]. As stated by FLETCHER and PETO [1], ''In a race between fast and slow horses … one would expect to find the faster horses out in front halfway through the race''.

In the current issue of the *European Respiratory Journal*, DAWKINS *et al.* [3] report on a 3-yr prospective follow-up study of FEV1 and transfer coefficient of the lung for carbon monoxide (*K*CO) in a group of 101 patients with PiZ α_1-antitrypsin deficiency (α_1-ATD). DAWKINS *et al.* [3] found that FEV1 decline was greatest with moderate disease; in contrast, *K*CO decline was greatest in severe disease. Furthermore, the factors associated with decline in FEV1 and *K*CO differed. FEV1 decline had significant associations with bronchodilator reversibility (BDR), lower body mass index (BMI), male sex, exacerbation rates and poor quality of life; whereas *K*CO decline had significant associations with baseline FEV1 and computed tomography (CT) scan indices, particularly with the lower zone-expiratory CT scan voxel index.

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FEV1 decline has been considered the gold standard for disease progression; thus treatments aiming to improve prognosis should reduce the rate of FEV1 decline. From their results, DAWKINS *et al.* [3] suggest that to demonstrate an effect of treatment on the rate of FEV1 decline in α_1-ATD patients (and probably also in COPD), patients with a baseline FEV1 between 50–80% predicted, frequent exacerbations and, if possible, with BDR and low BMI should be selected. Finding a significant number of α_1-ATD patients with these characteristics may be difficult, while any positive results would only be general to this selected population with a faster FEV1 decline.

A further problem is that the rate of FEV1 decline observed in patients with α_1-ATD has been decreasing significantly over the years, even without the use of replacement therapy. In a series published in 1995, the mean rate of FEV1 decline was 81 mL·yr^{-1} [4]; however, in 1997 another study provided an estimate of 75 mL·yr^{-1} [5]. In 1998, the US National Institutes of Health (NIH) registry observed a mean decline in patients not on replacement therapy of 59 mL·yr^{-1} [6]. The study of DAWKINS *et al.* [3] observed a mean decline of 49.9 mL·yr^{-1}, and a recent study on 144 patients followed for 30 months in 2007 gave an estimate of only 39.5 mL·yr^{-1} [7]. This reduction in the rate of FEV1 decline may be due to improvements in general disease management, and probably due to new COPD treatments in particular. An important consequence is that it will be difficult to demonstrate a significant further reduction in the rate of FEV1 decline for any new treatment, considering that a normal never-smoker without α_1-ATD has a rate of FEV1 decline of ~30 mL·yr^{-1}.

However, the parenchymatous component of lung disease in α_1-ATD patients in the form of basal emphysema is probably best reflected by the loss of *K*CO [8] and of lung density demonstrated by high-resolution CT scans [9]. Guidelines to standardise the diffusing capacity of the lung for carbon monoxide (*D*L,CO) are available to reduce interlaboratory variability [10]. However, uncertainty remains regarding the appropriateness of *D*L,CO correction for lung volume because of their nonlinear relationship [11]. DAWKINS *et al.* [3] provide new evidence that *K*CO decreases more rapidly in patients with the most severe disease (FEV1 <30% pred). Previous work from the same group demonstrated that a CT scan can be used to measure the progression of emphysema in α_1-ATD across a wide spectrum of disease severity [9]. Together, these findings suggest that: 1) in very severe patients there is progressive parenchymal destruction, despite the absence of an accelerated FEV1 decline; and 2) rate of decline in *K*CO and/or changes in

lung density measured by a CT scan [12, 13] could potentially be used as outcomes for intervention trials in severe and very severe patients, instead of FEV1 decline.

These results suggest that guidelines of replacement therapy for α_1-ATD should be reworded. In the most recent American Thoracic Society/European Respiratory Society guidelines it is correctly stated that a significant effect of treatment on the rate of FEV1 decline has only been observed in moderate patients [14]. However, this wording has led many physicians to interpret the lack of demonstration of an effect on FEV1 decline in very severe patients as synonymous with a lack of efficacy on the disease progression. Occasionally, this might lead to replacement therapy not being recommended for very severe patients, or even interrupted in the course of the disease when FEV1 falls below 30% pred, despite the recommendation that patients with very poor lung function, already being treated, should remain on the treatment [14]. These new data on the progression of lung disease (impairment in *K*CO and lung density) in very severe patients, together with the observed improvement in mortality in the NIH registry in patients receiving replacement therapy [6], should be enough to recommend this treatment in very severe patients with a similar level of evidence for moderate patients, although in neither case, unfortunately, with level A evidence as yet [15].

The natural history of airflow obstruction is a hot topic [16], and *K*CO decline is also of fundamental interest both to α_1-ATD and COPD research. Lessons should be identified as there is a wide research gap to assess outcomes and markers [17], and there are ongoing, large cohorts aimed to confirm or identify new biomarkers and end-points in COPD [18, 19].

As mentioned previously, in COPD or α_1-ATD patients the horse-racing effect refers to subjects observed to have a lower-than-average lung function at one measurement, and allegedly having a faster decline in lung function in longitudinal follow-up. However, BURROWS *et al.* [20] have already suggested that this was difficult to test true, as the horse-racing effect can produce some visual illusions [21]. By carefully studying the graphs of DAWKINS *et al.* [3] it can be envisaged that FEV1 decline shows no evidence of a horse-racing effect. It can't; the more severe COPD becomes, the harder it is to collect lung function data serially as patients get older, suffer from more comorbidities and are either exacerbated or already deceased at the time of testing, with little chance to co-operate. Even if the patients co-operate, the stringent quality control requirements set by current lung function guidelines, before and after bronchodilation, often label readings to calculate slope of FEV1 decline as low quality and not good enough to be assessed for the most interesting patients, so this information is disregarded. Serial spirometry produces right censoring of the most informative lung function, which is an inherent limitation of serial lung function testing and of any calculation of FEV1 decline.

Recently, acyclic graphs have been proposed to overcome this horse-racing effect bias [22]. Perhaps easier for the mere mortal, and for the time being, a single spirometry, rather than serial spirometry, to identify rapid decliners appears to be a more efficient way to screen for chronic obstructive pulmonary disease and convince these smokers to quit [23]. The search of biomarkers and end-points in α_1-antitrypsin deficiency and chronic obstructive pulmonary disease must go on…

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