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When Harry Met Sally, or When Machine Learning Met Chronic Obstructive Pulmonary Disease

Our understanding of chronic obstructive pulmonary disease (COPD) is changing rapidly (1). Traditionally considered a self-inflicted disease caused by tobacco smoking and characterized by an accelerated rate of lung function decline with age (2), we now know that it is not always self-inflicted, as a substantial proportion of patients with COPD have never smoked (3), and both abnormal lung development and aging determine different lung-function trajectories that can lead to COPD in adulthood (Figure 1) (4–6). Accordingly, the concept of disease progression, traditionally linked to the decline in lung function over time, needs revision (1). For instance, not all patients exhibit rapid lung function decline (7, 8), different disease components can progress independent of each other (e.g., lung function and exacerbation rate), and multimorbid conditions can contribute to disease progression independent of lung function (1). In this issue of the *Journal*, Young and colleagues (pp. 294–302) applied modern machine learning (ML) methods to model disease progression in COPD (9). ML is a subset of artificial intelligence in which a computer system performs specific analysis using algorithms and statistical models without preestablished explicit instructions, relying only on observed patterns and inferences.

Young and colleagues (9) used an ML tool named Subtype and Stage Inference (SuStain), capable of "reconstructing long-term temporal progression of disease from cross-sectional data" (10). Using four computed tomography (CT) imaging features (two tissue measurements [emphysema and functional small airways disease] and two airway measurements [airway wall area and thickness]) determined in patients and control individuals participating in the COPDGene study (11), the authors asked SuStain to determine the subtypes of COPD (defined as "a group of subjects who share a particular trajectory of CT measurement evolution"), stages (defined as "the position on a subtype trajectory of an individual subject at a specific time, representing the degree of abnormality in imaging measurements"), and disease progression (defined as "change in stage with time, which occurs when an CT measurements becomes more abnormal relative to a control population") (9). Findings were validated cross-sectionally in the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-Points) cohort (12) and longitudinally in the same COPDGene cohort, using 5 years follow-up data (9). Finally, Young and colleagues also investigated whether SuStain observations in patients with COPD could be identified in a subgroup of smokers with normal spirometry.

Main results showed (9) that, cross-sectionally, SuStain identified two subtypes of patients in COPDGene. The most prevalent one (70%) was characterized by emphysema and peripheral airway disease being detectable "earlier" than central airway abnormalities (so authors named it Tissue→Airway), whereas the reverse occurred in the other subtype (Airway→Tissue). The clinical characteristics of these two subtypes were broadly similar, and in both, SuStain stages were related to airflow limitation severity (9). These observations were mostly reproduced in ECLIPSE (9), and these two subtypes remained consistent in 87% of COPDGene patients after 5 years of follow-up. Individual patients tended to progress in stage within each subtype, particularly GOLD 1–2 patients. Baseline SuStain stage correlated (weakly) with lung function decline during follow-up in both subtypes (9), and SuStain identified a subpopulation of control smokers (29%) with similar imaging abnormalities (subtypes) as those determined in patients with COPD (Tissue→Airway, 63%; Airway→Tissue, 37%), despite normal spirometric values. As in patients with COPD, these subtypes remained constant at 5-year follow-up, and SuStain stage was associated with lung function both at baseline and during follow-up (9).

This article is important, novel, intriguing, and a bit difficult to follow because of the large amount of complex data it includes. As with any good article, though, it raises many questions.

First, that COPD progression (a concept tightly related to a time axis) can be modeled from cross-sectional data (where the time axis is absent) is difficult to grasp. Admittedly, however, authors validate their cross-sectional results in COPDGene in an independent cohort (ECLIPSE) and, more important, explored changes over time using COPDGene follow-up data (9).

Second, that X occurs earlier than Y (time axis again) means that Y may occur later. Whether or not this happened here is unclear, but judging from the fact that 87% of patients remained classified in the same subtype after 5-year follow-up, it seems unlikely. If so, does SuStain really model disease progression or simply identify two different and time-stable phenotypes? Actually, these two subtypes look remarkably similar to those described by Burrows and colleagues many years ago (type A [Tissue] and type B [Airway]) (13). Is ML rediscovering the wheel?

Third, the results of the study by Young and colleagues (9) have to be contrasted and reconciled with those of two other recent studies that also used ML methods (admittedly different from SuStain) in the same COPDGene cohort but provided different results: one identified four (not two) trajectories (14) and the other questioned the concept of disease subtypes in favor of a continuum of COPD manifestations or "disease axes" (15). To what extent are different ML methods complementary, concordant, or help us to better understand COPD progression? In fact, real-life (not
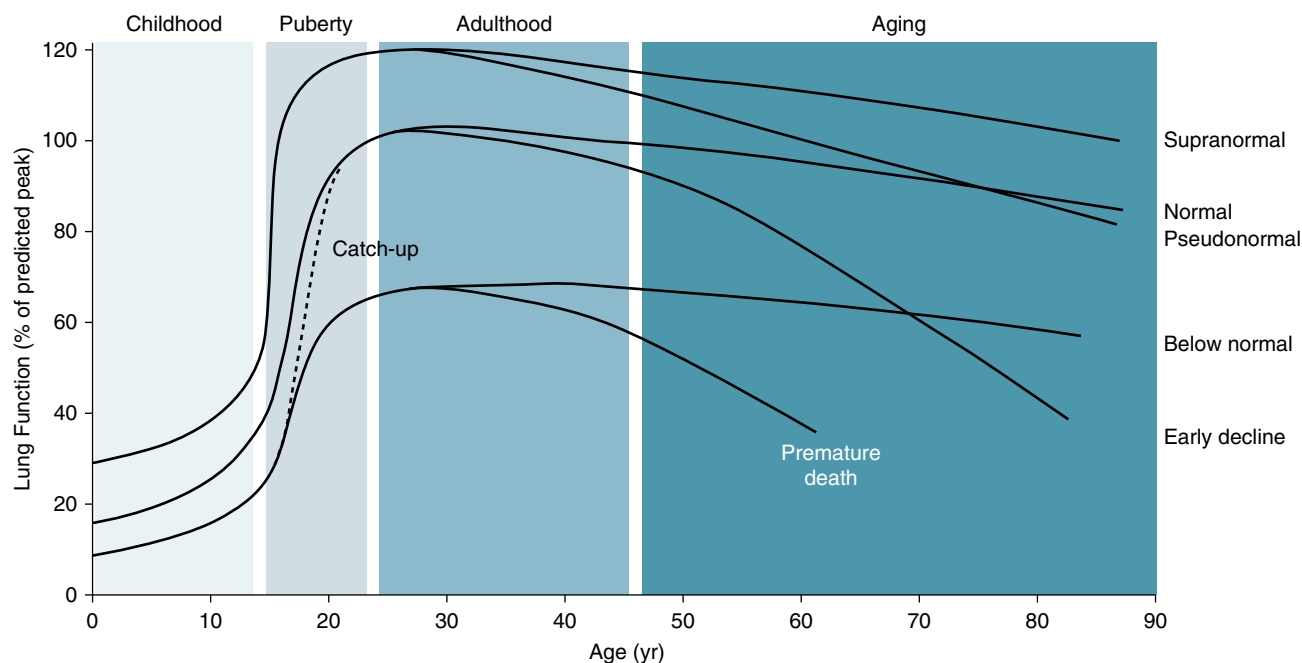
Figure 1. Potential lung function trajectories through life. Reprinted by permission from Reference 1.

modeled) data from the Tasmanian cohort (which includes serial spirometric data from patients aged 7 to 53 yr) recently reported the existence of 6 (not 4, not 2) different lung function trajectories (16). It is likely that the much longer period of follow-up in the Tasmanian cohort (46 vs. 5 yr) brings a more precise description of reality in which, we speculate, an infinite number of disease trajectories may exist (Figure 1).

Fourth, if the clinical characteristics of the two subtypes identified by Young and colleagues were similar, and both remained basically stable over time (9), what is their clinical relevance? In this context, it should be noted that other important components of disease progression, such as changes in exacerbation frequency or mortality, were not included in their analysis.

Fifth, what can we learn about the pathogenesis (endotypes) of these two subtypes in particular, and COPD in general? Why, according to SuStain, does the disease start in the parenchyma in the majority of patients (70%), but in the large airways (which are irrelevant in terms of airflow limitation) in a relative minority (30%)? This seems at variance with results obtained using micro-CT *ex vivo* in lung tissue samples of patients with COPD that indicate that peripheral airways are reduced in number before emphysema develops (17), although we acknowledge that SuStain cannot disentangle (and hence includes in the same subtype) parenchymal and peripheral airway changes (9).

Sixth, the observation that individual stage progression was more rapid in GOLD 1–2 than GOLD 3–4 patients (9) is in keeping with previous observations and may be consistent with patients belonging to different lung function trajectories (Figure 1) (1).

Finally, observations in smokers with normal spirometry suggest that SuStain can detect early COPD (9). This is an important observation that needs replication in other studies. ■

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High Pressure versus High Flow: What Should We Target in Acute Respiratory Failure?

In this issue of the *Journal*, Grieco and colleagues (pp. 303–312) compare high-flow nasal cannula (HFNC) oxygenation versus noninvasive ventilation (NIV) delivering high levels of pressure using a helmet (1). In this physiological study, 15 patients with acute respiratory failure ($Pa_{O_2}/Fi_{O_2} < 200$ mm Hg) were treated in a randomized crossover fashion by HFNC with a flow of 50 L/min or by NIV using a helmet with a high pressure-support level (10–15 cm H_2O) and a positive end-expiratory pressure (PEEP) of at least 10 cm H_2O, with each phase lasting 60 minutes. Compared with HFNC, NIV with a helmet markedly improved oxygenation and significantly reduced dyspnea, respiratory rate, and patient effort, whereas comfort and P_{CO_2} did not differ between the two techniques.

The management of acute hypoxemic respiratory failure in the ICU is challenging. In the most recent clinical practice guidelines, the use of NIV with a face mask was discussed, but the experts were unable to offer a recommendation (2). Patients with acute respiratory failure who have failed NIV are now known to have a vigorous respiratory drive, and such patients have a particularly poor prognosis (3, 4). Therefore, management to protect the already injured lung from the patient's vigorous spontaneous efforts (i.e., self-inflicted lung injury) is needed in this particular setting (5). Furthermore, synchronization between the patient's intense respiratory drive to breath and the pressure support delivered by NIV may result in high V_Ts that may worsen lung injury (5–8). Thus, controlling spontaneous efforts and V_Ts could be of key importance in the management of acute hypoxemic respiratory failure.

HFNC is an alternative to standard oxygen that enables improved oxygenation and comfort and decreases the respiratory rate and work of breathing without increasing V_Ts (9). In a large randomized clinical trial, HFNC significantly decreased mortality in patients with acute respiratory failure when compared with standard oxygen, as well as when compared with HFNC with the addition of intermittent sessions of NIV using a face mask, suggesting deleterious effects of NIV (10). A *post hoc* analysis of this study showed that large V_Ts (>9 ml/kg of predicted body weight) 1 hour after initiation of NIV were independently associated with intubation and mortality (11). This could highlight the importance of controlling patients' efforts and V_Ts to prevent the progression of acute respiratory failure.

As compared with the face mask, the helmet is an interface that appears to be more comfortable for patients (avoiding facial pressure points), enabling the delivery of more prolonged NIV sessions with higher levels of pressure (12). A randomized controlled trial that included patients with acute respiratory distress syndrome found a spectacular decrease in intubation and mortality rates with NIV performed using a helmet as compared with a face mask (13). In this trial, NIV with a helmet (vs. a face mask) enabled the delivery of higher PEEP levels, likely resulting in less spontaneous effort (as suggested by lower respiratory rates), lower intubation rates, and better survival. Although these results are encouraging, this study had major weaknesses, including a small sample of patients ($n = 83$), a single-center design, and particularly high intubation rates in the group treated with a face mask (13). However, these results suggest that NIV with a helmet could be a useful technique to manage patients' efforts through an effective delivery of higher pressures.