Respiratory Function Testing in the Era of Precision Medicine

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Abstract

Precision medicine aims to deliver treatments tailored to the individual patient with the most appropriate and the best management possible, and with a balance between patients’ outcomes and socio-economic savings. In this scenario, what is the role of respiratory function testing delivered by Lung Units within the different National Health Systems? In our personal view, we believe that respiratory function testing should be considered a pillar proceeding to Precision medicine.

After underscoring the mandatory role of respiratory function testing for the diagnosis of a significant group of respiratory diseases (i.e. Asthma, COPD, IPF, OSAS), we describe its major contribute in the “phenotypic” recognition of treatable traits of airway obstructive disease. But we point out also that the selection of patients for advanced therapies (omalizumab, pirfenidone, nintedanib) or approaches (i.e. lung volume reduction, bronchial thermoplasty) strongly depends on data derived from Respiratory Function Testing. Finally, we highlight that new technologies or applications in respiratory pathophysiology are opening new horizons for a precision medicine approach.

Introduction

Precision Medicine (PM) aims to deliver “a treatment targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations” [1]. PM products should be tailored to the individual patient with the most appropriate and the best management possible, and with a balance between patients’ outcomes and socio-economic savings [2-4]. It requires the use of the stratification process, such as the discrimination of patients according to a specified disease into subgroups based on particular characteristics: of patients who respond more frequently (or better) to a particular treatment, and with a decreased risk of side effects. It also implies new diagnostic tools [5-8], rapidly evolving. Usually, the PM approach provides substantial benefits in well-characterized patients with severe disease, and in a specialized setting [1,4,9-11].

The Role of Lung Function in Patients’ Phenotyping

When proceeding to PM, one should ask what is the role of respiratory function testing, intended as the global evaluation of respiratory function which can be delivered by Lung Units within the different national health systems.

Asthma

In Respiratory Medicine, the functional approach is mandatory for the diagnosis and the follow-up of different diseases (Table 1). Indeed, UK NICE (National Institute for Health and Care Excellence) guideline on asthma diagnosis and monitoring recommended routine spirometry (with reversibility testing when obstruction is detected) for all individuals with suspected asthma, based on health economic modeling as this is the most cost-effective clinical strategy [12]. When assessing the bronchial response to inhaled β2-agonist and/or anticholinergic drugs, an increase in FEV1 >400 mL vs. baseline is strongly suggestive of asthma [13]. Monitoring asthmatic patients by spirometry is a key element of the “future risk” assessment, and the unique possibility to detect the “accelerated decline” (>30 mL/yr) phenotype, or the “fixed obstruction” phenotype, and their response to inhaled corticosteroids [14,15].
**Table 1: Characteristic of pulmonary diseases for which Respiratory Function Testing is mandatory for their diagnosis [14,16-17,24-26,57-59].**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevalence</th>
<th>Mandatory for diagnosis</th>
<th>Appropriate treatment</th>
<th>Single cost of treatment, €/yr</th>
<th>Estimated global cost of treatment, Million €/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>8% to 10%</td>
<td>FEV1/FVC&lt;LLN, FEV1/VC, PD25</td>
<td>GINA 3-4 (50% of asthma) at least LABA/ICS</td>
<td>700</td>
<td>28-35</td>
</tr>
<tr>
<td>COPD (ERS/ATS 2005)</td>
<td>5% to 10%</td>
<td>FEV1/FVC &lt; LLN</td>
<td>GOLD 2-4 (85% of COPD) at least LABA or LAMA</td>
<td>600</td>
<td>25-51</td>
</tr>
<tr>
<td>COPD (GOLD 2016)</td>
<td>10% to 22%</td>
<td>FEV1/FVC&lt;0.70</td>
<td>GOLD 2-4 (85% of COPD) at least LABA or LAMA</td>
<td>600</td>
<td>35-72</td>
</tr>
<tr>
<td>Respiratory Failure</td>
<td>0.10%</td>
<td>PsO2 ≤ 55 mmHg, PaCO2 ≥ 45 mmHg</td>
<td>LTOT</td>
<td>3000-6000</td>
<td>3-6</td>
</tr>
</tbody>
</table>

Estimated for every million of habitants, based on prevalence

"Estimated by multiplying 25-51 for 1, 41 [25]

**Legend:** LABA: Long Acting Beta Agonist; ICS: Inhaled Corticosteroids; LAMA: Long Acting Muscarinic Antagonist; LTOT: Long Term O2 Therapy; AHI: Apnea Hypopnea Index

**Chronic obstructive pulmonary disease (COPD)**

In addition, COPD diagnosis is linked to the detection of chronic airflow limitation (or better, airway obstruction). Performing spirometry is the first step to calculate the FEV1/FVC (VC) ratio, whatever the threshold selected, either the FEV1/VC Lower Limit of Normal (LLN) by the ERS/ATS document on spirometry interpretation [16], or the post-bronchodilator FEV1/FVC <0.7 fixed ratio by the GOLD document [17]. However, in the PM era, it should be pointed out that the FEV1/FVC fixed ratio leads to underestimate the prevalence of airflow limitation in younger people, and to overestimate it in subjects older than 45 years, yielding a 75% to 80% of false positive rate in 80-year-old healthy subjects [18-21]. Scholes et al. [22] reported a different prevalence of airflow obstruction in 40 years to 95 years old in England and Wales by selecting the FEV1/VC <LLN criteria (22.2% vs. 13.1%). Recently, Miller and Levy [23] demonstrated that up to 13% of people who received a diagnosis of COPD based on FEV1/FVC fixed ratio have been found to be misdiagnosed. Moreover, Luoto et al. [24] found an incidence of airflow limitation per 1000 person-year of 18.1 using the fixed ratio and 11.7 with the LLN, corresponding to a 1.41-fold higher incidence rate using the first criterion. Nevertheless, COPD is largely underdiagnosed [25] and spirometry largely underused [26], particularly among people with early stages of the disease, when preventive strategies are requested.

Once the diagnosis of COPD is established, the FEV1 represents the first and the most used variable adopted for the mortality risk assessment [27]. When combined with other variable in a multidimensional graded system as the BODE index [28], the survival prediction accuracy improves. And when combined with hospitalizations and exacerbations in the BODECOST Index, an implementation of del BODE Index, it is useful also in predicting the economic impact of COPD [29].

Agusti et al. [30] have recently proposed an intriguing precision medicine strategy for the management of patients with chronic airway obstruction disease based on the identification of "treatable traits" in each patient [9].

These traits can be "treatable" based on "phenotypic" recognition, or on deep understanding of the critical causal pathways (e.g. true "endotypes"). In this approach, respiratory function testing has, again, a central role to define different "traits of treatable diseases": 1) airflow limitation due to smooth muscle contraction; 2) airflow limitation due to emphysema; 3) chronic bronchitis, and 4) chronic respiratory failure. In the first case, the documentation of airflow calibre variability, spontaneously or pharmacologically-induced, defines the role of airway smooth muscle. In the second case, measuring lung volumes and CO diffusing capacity is the best cost-effective procedure to detect emphysema [16]. In the third case, measuring lung volumes allows to detect an isolated Residual Volume increase (RV), considered as an early airway impairment, that can be present in chronic bronchitis otherwise not included in the COPD definition [17,31]. An increased RV may be the earliest functional abnormality in heavy smokers with chronic bronchitis [32] without any significant changes in FEV1 and FEV1/FVC ratio [33]. In a recent series of 1000 patients with a clinical diagnosis of COPD, almost 14% could not be classified as obstructed based on a FEV1/FVC ratio within the normal range, despite having a reduced FEV1 [31]. This pattern may occur in early-stage COPD, due to an isolated increase in RV, and needs to be differentiated from restriction by lung volume measurements [16]. Finally, in the fourth case, it is well-known that chronic respiratory failure is defined only by another respiratory function test, i.e. arterial blood gas analysis. Therefore, respiratory function testing still represents the "core" of the recently proposed PM strategy in patients with chronic airway obstructive disease [30].

An outstanding example of "phenotypic" recognition, useful for a PM approach in COPD, was reported by Pellegrino et al. [34]. During the expiratory effort requested for the FVC manoeuvre, part of Thoracic Gas Volume (TGV) is compressed and the amount varies depending on airway resistance and absolute lung volume [35]. In healthy subjects the difference between FEV1 measured at the mouth (FEV1-mo) and the simultaneous changes in the chest wall volume derived from body plethysmography (FEV1-pleth) is small (4%, the amount of Thoracic Gas Compression Volume: TGV). But, in obstructive lung disease, such a difference is large, being 100% or more in the case of high airway resistance and/or large total lung capacity, as occurs in emphysema [35]. Pellegrino et al. [34] reported, for a given airway resistance that FEV1-mo overestimate the magnitude of airflow limitation in subjects with dominant emphysema compared with those with dominant bronchitis: this may confound severity classification and prognosis [35]. Patients with predominant emphysema may be unnecessarily over-treated with inhaled bronchodilators and steroids simply because of the large effect of TGCV on FEV1. Therefore, body plethysmography represents a useful tool in COPD phenotyping, severity grading, and therapy establishing [36].

**Severe asthma**

Lung volume measurement is also part of severe asthma
evolution [37], as the severity of asthma appears to be linked to enhanced air trapping rather than the level of airflow obstruction. The European Network for Understanding Mechanisms of Severe Asthma (ENFUMOSA) study, comparing severe asthma with mild-to-moderate asthma, found that RV increased (parallel to a reduction in FVC) in severe asthmatic patients as compared with mild-to-moderate ones [38]. Again, the Severe Asthma Research Network (SARP) showed that severe asthmatic patients had prominent air trapping (detected as increased RV/TLC) over the entire range of airflow obstruction severity and that non-severe asthmatic patients did not exhibit significant air trapping, even at the more severe stage of airflow obstruction expressed as FEV1/FVC ratio [39].

**PM for advanced therapies and in other respiratory conditions**

It is noteworthy that respiratory function testing supports the selection of patients for advanced therapies or approaches with a high social burden (Table 2). It is the case of Omalizumab and Bronchial thermoplasty in severe uncontrolled asthma [40,41], or bronchoscopic lung volume reduction in heterogeneous emphysema with pulmonary hyperinflation [42,43], or Pirfenidone and Nintedanib in Idiopathic Pulmonary Fibrosis (IPF) [44-46], or Continuous Positive Airway Pressure (CPAP) in moderate-to-severe Obstructive Sleep Apnea Syndrome (OSAS) [47,48]. Indices of pulmonary function, such as FVC and CO diffusion capacity, are considered mandatory in IPF for the selection of candidate patients for pirfenidone or nintedanib [44-46], while the ≥ 10% FVC decline is now accepted by regulatory agencies as the standard to evaluate the diagnosis and severity assessment of OSAS that is a common and under diagnosed health-care consuming and eminently treatable condition [47,48,51].

As part of respiratory function testing, cardiopulmonary exercise testing is a useful tool in order to select advanced therapeutic strategies in severe-to-moderate heart failure and for the preoperative assessment in thoracic surgery [52,53].

Finally, oscillation mechanics and partitioning of CO diffusion lung components are opening new horizons for clinical applications. In asthma, day-to-day variability of respiratory resistance by Forced Oscillatory Technique proves to be a good predictor of functional deterioration, and DLCO/VA/V’A has demonstrated a higher sensitivity than DLCO/V’A to detect emphysema or pulmonary fibrosis [54-61].

### References


