Functional respiratory assessment: some key misconceptions and their clinical implications

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Dear editors,

There are few specialties in which the functional evaluation assumes the same pivotal role as in respiratory medicine. Although the patterns of abnormalities exposed by pulmonary function tests are not pathognomonic, they are frequently helpful to narrow the diagnostic alternatives. In the right clinical context, the absence of functional abnormality might be reassuring. Testing results can provide useful information for the longitudinal assessment of patients with known respiratory diseases; moreover, they might have an auxiliary role on risk stratification and prognosis estimation. Unfortunately, there has been a progressive abandonment of applied respiratory physiology in favour of basic sciences and molecular medicine. Accordingly, controversial issues on pulmonary function tests interpretation are much less discussed nowadays compared with a few decades ago. It should also be recognised that some key concepts in the interpretation of spirometry, 'static' lung volumes and cardiopulmonary exercise testing are still based on physiological constructs rather than evidence from prospective trials. With the intent of igniting some critical reflections on the current role of the laboratory of lung function tests on clinical decision making in our field, I herein challenge some deeply entrenched interpretative beliefs. They have been selected based on our long-standing interaction with learners and seasoned pulmonologists. In each scenario, I discuss the reasons why a given statement might be misleading, and the potential clinical consequences of testing misinterpretation. If feasible, I suggest some strategies to avoid the underlying pitfalls.

NORMAL FORCED EXPIRATORY VOLUME IN 1 S (FEV_1)/FORCED VITAL CAPACITY (FVC) RATIO RULES OUT OBSTRUCTIVE AIRWAY DISEASE

There is little disagreement that, in the right clinical context, a FEV_1/FVC ratio <the lower limit of normal (LLN) rules in obstruction (though, by definition, 5% of normal subjects have an FEV_1/FVC ratio <LLN). However, if the small airways close precociously during the forced expiratory manoeuvre in a subject with airway disease, FVC might decrease more (or to the same extent) than FEV_1 does, leading to a normal FEV_1/FVC ratio. Thus, obstruction in the absence of restriction (normal total lung capacity (TLC)) can coexist with preserved FEV_1/FVC ratio but (usually mildly) reduced FVC and FEV_1.[1] We found that using the 'slow' VC (SVC) instead of FVC is useful to uncover airflow limitation in obese subjects and those aged less than 60; conversely, it may lead to a false-positive result in the elderly since FVC decreases more than SVC with ageing.[2] If TLC decreases appreciably in an obstructed subject with high residual volume (RV) but coexistent restriction (including, as we recently described, those with body mass index ≥50 kg/m^2),[3] FEV_1/FVC ratio might be normalised. The LLN might not always be the best benchmark to judge the normalcy of the FEV_1/FVC ratio: a sizeable fraction of smokers with this ratio between 0.7 and the LLN does present with resting and exercise abnormalities consistent with chronic obstructive pulmonary disease (COPD).[4] In fact, large population-based studies showed that a sizeable portion of smokers with respiratory symptoms and imaging abnormalities do not manifest spirometric obstruction as defined by a low FEV_1/FVC ratio.[5–7] FEV_1 has also inherent limitations in reflecting patchy, early small airway disease, given it does not typically include the lowest lung volumes where elastic recoil is lowest (see also the section Low mid-expiratory flows indicate small airway disease). In this context, it is important to remember that airflow obstruction may coexist with a normal FEV_1, for example, spirometric stage 1 COPD according to the Global Initiative for Obstructive Lung Disease criteria.[8]

LOW MID-EXPIRATORY FLOWS INDICATE SMALL AIRWAY DISEASE

Although the mid-expiratory flows may decrease in the presence of small airway disease, they may also diminish when the larger airways are obstructed. If the forced expiratory flow between 25% and 75% of FVC ($FEF_{25\%-75\%}$) decreases in tandem with FVC, a low $FEF_{25\%-75\%}$ might be secondary to lower dynamic lung volumes regardless of the presence (or not) of airway obstruction. $FEF_{25\%-75\%}$, however, is poorly repeatable and highly dependent on effort[9]: extra-attention must be paid by the technician and interpreter to assure maximal effort and repeatability criteria.[1] Moreover, it markedly decreases with age,[10] bringing uncertainties on its interpretation in the elderly. The negative view of the mid-expiratory flows should be tempered with the fact that many patients with mild asthma and/or COPD do present with isolated decrements in $FEF_{25\%-75\%}$. A low $FEF_{25\%-75\%}$/ FVC ratio, a surrogate measure of airway size relative to lung size (dysanapsis), might be useful to suggest airflow limitation in a subject with a high pretest likelihood of airway disease. Interestingly, dysanapsis, as objectively determined by chest CT, has been associated with greater COPD risk.[10] Instead of characterising an isolated low $FEF_{25\%-75\%}$ as indicative of 'small airway disease', a short descriptive sentence (eg, reduced flows at mid lung volumes) might be preferable.

A LACK OF SIGNIFICANT CHANGE IN FEV_1 AFTER AN INHALED BRONCHODILATOR (BD) INDICATES A NEGATIVE BRONCHIAL REVERSIBILITY TEST

Most physicians would read a spirometric test as 'positive' for bronchial reversibility only if FEV_1 increases, in absolute and relative terms, beyond a given threshold (more commonly ≥0.2 L and 12%, respectively). It should be emphasised, however, that in subjects with a self-reported physician diagnosis of asthma, absence of BD reversibility showed a negative predictive value of only 57% to exclude asthma.[11] In practice, it is also frequently forgotten that a BD may primarily act by recruiting lung volumes (ie, reducing RV more than TLC) rather than increasing flows in the airways which contribute the most to early expiration, that is, the larger ones.[1] It follows that changes in FEV_1 might not reach currently recommended cut-offs despite substantial lung deflation. The latter phenomenon might be inferred by significant increases in FVC, SVC

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or inspiratory capacity (IC) post-BD,[1 4] being particularly evident in patients with more advanced COPD.[12–14] Taking into consideration that increases in dynamic lung volumes after a BD enhances the likelihood of a positive clinical response (eg, less exertional dyspnoea),[5] a systematic analysis of these variables pre and post-BD is invariably useful.[1] A comment should also be made on the fact that a low FVC (either pre-BD or post-BD) in the presence of obstruction may reflect gas trapping and/or restriction (ie, a mixed defect). In the latter scenario, the severity of obstruction is frequently overestimated; thus, it is preferable to grade the severity of the entire ventilatory defect based on the decrease in FEV_1.[1]

NORMAL TLC RULES OUT A DISEASE WHICH CAUSES RESTRICTION

Functional restriction (low TLC) can be caused by parenchymal and extraparenchymal (pleural, chest wall, neuromuscular) diseases. However, a disease known to limit lung-chest wall volume may coexist with preserved TLC. For instance, it is a common clinical observation that patients with early/mild interstitial lung disease (ILD) may present with TLC >LLN but reduced FRC and/or RV. Some of them may also show mid-expiratory flows>the upper limit of normal (ULN) despite preserved FVC, occasionally associated with a high FEV_1/FVC. These subtle abnormalities may prove helpful to uncover (or confirm) incipient ILD in a patient with a high pretest likelihood of disease.

A HIGH RV/TLC RATIO EQUALS TO GAS TRAPPING

A high RV/TLC ratio is frequently considered a sign of small airway disease and gas trapping, particularly in a smoker. However, such a finding might reflect a disproportionate decrease in TLC compared with RV in some patients with restriction and/or insufficient exhalation due to expiratory muscle weakness[15] or chest wall/spinal deformities. Of note, RV becomes more dependent on the expiratory muscle strength in the elderly. In addition, loss of tonic activity of the abdominal muscles might shift upwards the end-expiratory lung volume; thus, even a low IC may lead to a relatively preserved TLC in a subject with weak respiratory muscles. The corollary is that, in the presence of a motor neuron disease and global respiratory muscle weakness, RV and RV/TLC might increase substantially despite the absence of airway disease.

DL_{CO} REFLECTS THE DIFFUSING CAPACITY OF THE LUNGS

There is a widespread notion that one can estimate the area of the alveolar-capillary membrane available for gas exchange, and its thickness, by measuring the 'lung diffusing capacity' of the lungs for carbon monoxide (DL_{CO}). This is untrue not only because DL_{CO} is meaningfully influenced by membrane thickness only in limited circumstances but, importantly, because it is modulated by inhomogeneities in ventilation and perfusion, and the blood volume in the units exposed to the inhaled gas at a given lung volume. Thus, it should not be erroneously assumed that a low DL_{CO} indicates diffusion limitation of O_2 across the alveolar-capillary membrane. The European terminology ('transfer factor' (TL_{CO})) is more appropriate but the fundamental misconception that TL_{CO} is a faithful metric of lung tissue destruction remains pervasive.

NORMAL K_{CO} INDICATES A PRESERVED ALVEOLAR-CAPILLARY INTERFACE

Dividing DL_{CO} by the alveolar volume (VA) (transfer coefficient, K_{CO}) does not provide the 'diffusing capacity corrected by lung volume': K_{CO} rises curvilinearly with reductions in lung volume at low lung volumes whereas K_{CO} (and DL_{CO}) change very little with reductions in lung volume at higher lung volumes.[16 17] Moreover, VA may grossly underestimate TLC depending on the severity of ventilation distribution abnormalities. It follows that a patient with significant parenchymal and/or airway abnormalities may present with a normal K_{CO}. It should also be emphasised that, owing to heterogeneity of ventilation and time-dependent effects of initial dilution and redistribution of inhaled gas, as well as subsequent early and discrete gas sampling during exhalation, VA is not a faithful measure of the volume of lung with normal structure, that is,K_{CO} should not be assumed to provide an assessment of the structure of the fraction of lung accessible to test gas. Judging whether the VA is, or not, a reasonable estimate of TLC (VA/TLC ratio ≥0.80–0.85) may help the interpretation of K_{CO}: a 'preserved' K_{CO} in the presence of a low VA/TLC ratio should not be misinterpreted as evidence of normality.[6 17] Another illustrative example is the effect of lung resection: despite less alveolar-capillary interface, capillary recruitment (increased blood volume) may normalise (or even increase) K_{CO}. A preserved VA is also useful to rule out restriction since, as mentioned, VA is a fraction of TLC.[18]

NORMAL MAXIMAL INSPIRATORY PRESSURE RULES OUT DIAPHRAGM WEAKNESS

The maximal 'static' inspiratory pressure (MIP) is not a reliable indicator of diaphragm strength. A normal value may be a consequence of overactivation of the accessory inspiratory muscles, leading to a normal MIP in the presence of substantial weakness. The sniff inspiratory pressure better reflects diaphragm strength[19] though it is also a volitional manoeuvre. Defining weakness based on MIP is not a trivial task[20]: we found that the threshold for an abnormal test result may vary up to 50% depending on the specific set of reference values (see Reference values unequivocally establish the range of normality).[21] Thus, an apparently normal MIP should be viewed with caution: if available, more elaborated, non-volitional measurements should be used to rule out weakness in a highly suspicious subject,[19] for example, known neuromuscular disease or hemidiaphragm elevation associated with a significant drop in FVC from seated to supine position.

A NEGATIVE METHACHOLINE CHALLENGE TEST (MCT) RULES OUT ASTHMA

Clinical interpretation of a MCT should consider the uncertaints around the threshold for a positive test, the effects of recent/ongoing treatment (including inhaled steroids) and whether the subject has or not symptoms suggestive of 'current asthma'. Thus, its measurement properties need to be interpreted in the light of 'current asthma' as opposed to 'ever asthma.'[22] Although most physicians are aware of the fact that a positive MCT is poorly specific and non-diagnostic for asthma, there is an over-reliance on a negative test to rule out the disease. In fact, a not-insignificant fraction of asthmatic patients might present with a negative MCT in the quiescent phase of the disease (even if the confounding medications are correctly discontinued before testing). The bronchoprotective effect of deep inhalations associated with the dosimeter method of delivering methacholine cannot also be underestimated.[23] A recent study involving 500 subjects with self-reported physician-diagnosed asthma found that MCT converted from negative to positive, with medication tapering in 19.1% participants, and spontaneously over time in 15.2% participants. Of 231 subjects with negative MCT, 12.1% subsequently received an asthma diagnosis from a pulmonologist.[11] It follows that repeating MCT when the

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patient is symptomatic might be required to confidently rule out asthma for whom a high clinical suspicion of asthma exists.

BREATHING RESERVE AT EXERCISE TERMINATION INDICATES THE ABSENCE OF VENTILATORY LIMITATION

Uncovering a role for the lungs to cause shortness of breath on exertion is an important endeavour to the pulmonologist. The traditional approach has been largely based on the comparison between ventilation at peak incremental exercise with the maximal breathing capacity, the latter being either measured in the maximal voluntary ventilation manoeuvre or estimated by the product of $FEV_1 \times 35$–40. In this context, a large difference between peak ventilation and the maximal breathing capacity ('breathing reserve') has been assumed to rule out ventilatory limitation to exercise. We have shown, however, that either in subjects under assessment for unexplained dyspnoea,[24] or in patients with COPD,[25] a preserved breathing reserve may coexist with limiting mechanical-ventilatory abnormalities exposed by the emergence of inspiratory constraints and poor submaximal ventilatory efficiency. Recently-published reference values for submaximal dyspnoea intensity at a given ventilation and work rate[26] now allow a better appreciation of the overall symptom burden. The corollary is that measurements of inspiratory constraints, ventilatory efficiency and submaximal dyspnoea should be an integral part of comprehensive cardiopulmonary exercise testing for the assessment of dyspnoeic subjects.

REFERENCE VALUES UNEQUIVOCALLY ESTABLISH THE RANGE OF NORMALITY

Reference values for pulmonary function tests usually encompass a large range of results. Even with the best prediction equations, there is some uncertainty about whether an individual's values are 'normal' or 'abnormal'. This is particularly true when the result is slightly above or below the chosen threshold, for example, the LLN or ULN. In fact, the limits of normal (usually based on the distribution percentile) can be adjusted depending on the prevalence of the disease in the target population and the desired sensitivity and specificity of the threshold. Large ranges of normal also make interpretation of a given test imperfect without prior tests for comparison. In this specific scenario, it is difficult to judge whether an individual's current normal value actually reflects a significant longitudinal decrease, being therefore suggestive of disease. Persistence of symptoms in a subject with apparently normal results at a given point in time should prompt serial testing. It should be recognised that reference values based on cross-sectional analyses may not match longitudinal change, that is, equations that fit the population at one point in time may not apply decades later. Reference values in one geographical region may not reflect the genetic mix, exposures and nutritional status of the populations in which they are used. We should also keep in mind that stringent selection of healthy individuals for some reference sets may not reflect the general population without pulmonary disease.

This non-exhausting list of common misconceptions on the interpretation of common resting and exercise measurements reminds us of the enduring relevance of clinical physiology applied to the practice of respiratory medicine.

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