The Lung Function Laboratory to Assist Clinical-Decision Making in Pulmonology: Evolving Challenges to an Old Issue

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Abstract

The lung function laboratory frequently provides relevant information to the practice of Pulmonology. Clinical interpretation of pulmonary function and exercise tests, however, has more recently been complicated by temporal changes in demographics (higher life expectancy) and anthropometric attributes (increased obesity prevalence) and the surge of polypharmacy in a sedentary population suffering from multiple chronic-degenerative diseases. In this narrative review, we concisely discuss some key challenges to testing interpretation which have been impacted from these epidemiological shifts: a) the confounding effects of advanced age and severe obesity, b) the contemporary controversies in the diagnosis of obstruction (including asthma and/or chronic obstructive pulmonary disease), c) the importance of considering the lung diffusing capacity for carbon monoxide (D_{LCO})/"accessible" alveolar volume (diffusing coefficient, K_{CO}) in association with D_{LCO} to uncover the cause(s) of impaired gas exchange, and d) the modern role of the pulmonary function laboratory (including cardiopulmonary exercise testing) in the investigation of undetermined dyspnea. Following a Bayesian perspective, we suggest interpretative algorithms which consider the pre-test probability of abnormalities as indicated by additional clinical information. We, therefore, adopt a pragmatic approach to help the practicing pulmonologist to apply the information provided by the lung function laboratory to the management of individual patients.

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Clinical Interpretation of PFTs: An Ever-Evolving Endeavour

The advances in applied respiratory physiology and its clinical application (i.e., pulmonary function tests (PFTs) and exercise tests) preceded the dawn of pulmonology.[1] Temporal changes in demographics (e.g., the "oldest-old")[2] and anthropometric attributes (e.g., super- and super-super obesity)[3], novel knowledge on the pathophysiology and structural bases of lung disorders, and the surge of polypharmacy and co-morbidities in extremely sedentary subjects [4] have created additional layers of complexity to testing interpretation. Under the influence of these evolving confounders, old questions such as the diagnosis of airway disease, the clinical relevance of highly-sensitive (but non-specific) tests such as the lung diffusing capacity for carbon monoxide (D_{LCO}), and the actual role of the lung function lab in untangling the cause(s) of undetermined dyspnea have gained new momentum. Following a Bayesian approach (i.e., the interpretation of a given test result is modulated by the prior probability of disease to generate a posterior probability), we herein provide a brief perspective on the best interpretative strategies to answer these contemporary clinical questions.

Careful consideration of the pre-test probability of abnormality is key to a meaningful interpretation of lung function and exercise tests in clinical practice.

Interpreting PFTs in the Obese and in the Elderly

The Aged Lung

The fraction of elderly people (older than 65) relative to the total American population has increased by ~50% from 1950 (8.2%) to 2000 (12.6%). It is anticipated that by 2050 one out of five Americans will be classified as "old"; moreover, one out of four of these subjects will be in the "oldest-old" range (>85 years).[2] Ageing is a known risk factor for chronic respiratory and systemic degenerative diseases [5] which can interfere with lung

function.[6] Thus, the frequency at which elderly subjects undergo PFTs is expected to keep on rising in the coming decades.

Ageing is associated with loss of lung elastic recoil and alveolar attachments to the small airways, [7] both conspiring to decrease the expiratory flows (and forced expiratory volume in one second (FEV_1)) while increasing the volume associated with the start of small airways closure (closing capacity (CC)).[8] Reduced chest wall compliance due to rib cage stiffening balances the inward recoil of the lung [7] at higher functional residual capacity (FRC).[9] As CC rises more than FRC during aging, early small airway closure causes ventilation distribution inequalities and gas exchange inefficiency. [10] The volume remaining in the lung when most of the small airways are closed also increases (residual volume, RV), particularly upon forced expiration.[10] Gradual increase in FRC and RV with minimal changes in total lung capacity (TLC) leads to lower inspiratory capacity (IC) and "slow" VC (SVC).[8] Regular airspace dilatation without clear-cut alveolar destruction and reduced density of the membranous bronchioles suggest coalescence of smaller into larger alveoli,[11] reducing the functional surface for gas exchange while increasing the areas of high ventilation-perfusion relationship.[12] **Table 1** highlights some consequences of these physiological modifications brought by senescence which should be carefully considered to avoid testing misinterpretation in the elderly.

Several functional alterations associated with ageing are similar to those induced by airway disease, including low expiration flows, ventilation distribution abnormalities and gas trapping. Thus, care should be taken to avoid over-diagnosis of airway disease in the elderly (or over-estimation of impairment caused by pre-existing disease).

Obesity: The Great Mimicker (and Concealer)

Pandemic obesity (body mass index (BMI) ≥ 30 kg/m^2) has further worsened in the past 20 years. [13] Among the obese people in America, the extreme obese (super-obesity (BMI between 50 and 59 kg/m^2) and super-super obesity (BMI ≥ 60 kg/m^2)) had the fastest rate of increase. [13] Obesity is a common cause of exertional dyspnea [14] and a risk factor for chronic cardiopulmonary diseases [6] ; in addition, more obese subjects than ever undergo bariatric surgery, a procedure in which PFTs are part of the risk assessment [15]. Thus, the need for a sound knowledge on the effects of obesity *per se* on PFTs and exercise testing results will only increase.

Higher lung-chest wall elastic recoil may increase the expiratory flows in mild-to-moderate obesity.[16] FRC decreases exponentially in the early stages of obesity; thus, ERV decreases while IC increases in tandem with BMI.[17] Despite the fact that volume extremes (i.e., RV and TLC) may only change in very severe obesity,[18] [18] FVC frequently underestimates the relatively preserved SVC as the small airways might be compressed (and/or collapse) at the end of forced expiration.[19] Similar to ageing, therefore, FEV_1/FVC may be higher than FEV_1/SVC.[19, 20] As a consequence of early airway closure, CC may be higher than FRC; [21] thus, the dependent small airways may close even during tidal breathing. [21] Increased intra-thoracic blood volume and basal lung perfusion may increase lung diffusing capacity for carbon monoxide (D_{LCO}) at a given (low) lung volume; thus, K_{CO} (D_{LCO}/"accessible" alveolar volume (V_A)) increases exponentially as V_A decreases (***The Basis of Pulmonary Gas Transfer as Assessed by D_LCO***). [22] Hypercapnia may arise in the morbidly obese range secondary to a complex interplay between mechanical ("can't breathe") and chemical ("won't breathe") factors. [23] The need for displacing a higher body mass against gravity increases the metabolic/gas exchange, ventilatory, and cardiovascular costs of performing a given external work on exercise.[24] Higher flow of less oxygenated mixed venous blood through poorly ventilated alveoli in the lung bases (in addition to hypercapnia, if present) may lead to exertional hypoxemia.[24] Exercise intolerance then arises due to highly variable combinations of breathlessness and heightened sense of leg

discomfort.[14] **Table 2** summarizes some effects of obesity on the interpretation of PFTs with special consideration to their potential practical consequences.

Depending on the clinical context, obesity may either conceal or mimic airway disease and restrictive lung disease. Thus, the concept that lung function and exercise tests should be interpreted in light of additional clinical information is particularly important for testing interpretation in the obese.

Old Controversies in the Diagnosis of Obstruction: The New Players

Is There Airflow Limitation or Is It Just Ageing?

The prevalence of chronic obstructive airway disease (COPD) will increase markedly in the next few decades. [25] The importance of early diagnosis of COPD is now better recognized. [26] As the disease is more frequent in the elderly (who presents with naturally lower FEV_1/FVC compared to younger subjects) (***The Aged Lung***) (**Figure 1**) [27] , the trend of a false positive test using the fixed criterion of <0.7 [28] is of greater concern compared to previous. The lower limit of normal (LLN) based on the distribution of the residuals has a sounder statistical rationale;[29] however, it has not performed consistently well in avoiding false-negatives in the oldest-old and symptomatic (ex-) smokers.[28] A recent study found that the fixed ratio discriminated COPD-related hospitalization and mortality that was not significantly different or was more accurate than the LLN.[31] Whatever the chosen FEV_1/FVC criteria, the lower the FEV_1 the higher the probability of true obstruction — provided the low FEV_1 is not caused by a low FVC, i.e., restriction.[29, 30]

It should be recognized that many smokers with FEV_1/FVC ratio ≥ 0.7 (and the LLN) may report activity-related dyspnea, showing structural changes (emphysema and airway wall thickening) similar to that showed by their counterparts with lower values. [32] Some of them may have a low FEV_1 (more recently termed "preserved ratio-impaired spirometry (PRISm)") but others do not, i.e. abnormalities found on imaging but not on spirometry.[31] In PRISm subjects, a low FEV_1 is fundamentally related to a

low FVC which, in turn, may reflect the constraining effects of obesity (***Obesity: The Great Mimicker (and Concealer)***), loss of dynamic volumes secondary to an early closure of the small airway disease and/or the effects of co-morbidities.[31] Thus, FVC might underestimate SVC; consequently, the low denominator would lead to a preserved FEV_1/FVC, despite the presence of airway disease. [32] Indeed, SVC has been found to enhance the yield of spirometry in detecting mild airflow obstruction in younger and obese subjects; however, a low FEV_1/SVC but preserved FEV_1/FVC may represent a false positive for airway disease in the elderly. [33]

The fixed ratio versus LLN conundrum [34] is unlikely to be ever decided with a clear victor since none of them are unequivocally superior to the other in all cases. In fact, FEV_1/FVC, or any other ratio expressing flow-volume relationships, does not behave as a dichotomous variable.[35] Thus, FEV_1/FVC interpretation might be better understood by following a Bayesian approach, taking into consideration the pre-test probability of abnormality on an individual basis (**Figure 2**). In subjects with equivocal findings on spirometry (e.g., $0.7< FEV_1/FVC>LLN$, PRISm with a high pre-test probability of COPD), high lung volumes on body plethysmography (particularly RV) might help confirming an obstructive airway disease. [36] Body plethysmography might also be helpful in clarifying whether a low FEV_1/FVC associated with a low FVC is related to a low "ceiling" ($\Downarrow$ TLC, i.e., associated restriction) or a high "floor" ($\Uparrow$ RV). [37]

FEV_1/FVC is not a dichotomous variable, particularly under the modulating influence of ageing, obesity and multiple co-morbidities. In many subjects, therefore, the presence (or not) of airflow limitation due to airway disease should be established on an individual basis in view of additional clinical and physiological findings.

Is It Asthma and/or COPD?

This question is a common indication for PFTs, particularly when the tests are requested by generalists. More recently, there has been a marked increase in the awareness of disease coexistence, i.e., asthma-COPD overlap (ACO). [38] Thus, the pulmonologist is frequently under pressure to provide a clear-cut response. Key fundamental concepts that the specialist should be aware to minimize misinterpretation are:

- The likelihood of a significant relative (Δ%) response to a short-acting bronchodilator (BD) (e.g. $\Delta FEV_1 \geq 12\%$) is inversely related to its baseline value whereas the opposite is true for an absolute change (e.g., ≥200 mL). [39] Thus, expressing changes as % *predicted* FEV_1 (e.g., ≥ 10%) seems a more logical approach.[39] Another strategy assumes that the FEV_1 and FVC response to a BD is a continuous variable in patients with COPD (minimal (>0.00% to ≤9.00% or >0.00 L to ≤0.09 L), mild (>9.00% to ≤16.00% or >0.09 L to ≤0.16 L), moderate (>16.00% to ≤26.00% or >0.16 L to ≤0.26 L), and marked (>26.00% or >0.26 L) responses).[41] None of these criteria for a positive response, however, has shown sufficient discriminative properties to separate asthma from COPD;
- Whatever the chosen criteria, a positive FEV_1 response may rather reflect volume recruitment, i.e., an increase in FVC due to larger decrements in RV than TLC. This is more commonly seen in COPD [36] but may also occur in asthmatic patients showing relevant gas trapping;
- A large improvement in FEV_1 deemed suggestive of asthma (e.g., ≥0.4 L and/or ≥20% baseline) might be seen in COPD patients showing a proportional volume response, i.e., pre- and post-BD FEV_1/FVC do not change appreciably. Frequent overlooking of this phenomenon may have artificially increased the prevalence of ACO[3 9];
- A volume response (e.g., ΔIC>200 mL, Δ(F)VC > 15%) might be more relevant to symptom improvement than a flow response. i.e., a significant increase in FEV_1 but not in FVC. Thus, both variables should be looked at after BD;[36]

• A positive methacholine challenge test is not diagnostic of asthma and despite a high negative predictive value, [40] it does not consistently rule out asthma in subjects who are asymptomatic at the time of testing; and

• Whereas a low D_{LCO} is rarely seen in asthma (unless there is another cause for impaired gas exchange) (***Considering K_{CO} in Addition to D_{LCO}***), a normal DL_{CO} may occur in a COPD patient showing the dominance of chronic bronchitis over emphysema.

In summary, apart from the fact that, by definition, spirometric normalization after a BD is not consistent with COPD (or asthma with chronic airflow limitation), any other result should be carefully interpreted taking into account the clinical context. Currently, the role of PFTs in suggesting ACO remains elusive though a preserved DL_{CO} in a subject with known COPD showing a large flow response which varies substantially over time may raise the suspicion of associated asthma.

Only in some specific scenarios, the PFTs results can help in discriminating asthma from COPD. Whereas a (large) flow response leading to spirometric normalization is unlikely to be seen in a patient with COPD, a low D_{LCO} is not consistent with asthma. In all other circumstances, clinical input if of foremost relevance.

D_{LCO} is a Poorly Specific but Highly Valuable PFT

There remains substantial misunderstanding of the physiological meaning of DL_{CO} and its derived measurements.[41] Its poor specificity has also contributed to a negative view in modern-day pulmonology which values tests with pathognomonic properties. More recently, there has been a rebirth of interest in DL_{CO} as this test has been found:

• The closest correlate of exertional dyspnea across the spectrum of COPD severity;[42]

• Sensitive to detect relatively minor dysfunction caused by diseases growing in prevalence, e.g., pulmonary vascular and interstitial diseases; [43] and

• Useful in the functional assessment of candidates for lung resection surgery secondary

to cancer [44] and to estimate the risk of complications of non-pharmacological treatments for COPD, e.g., lung volume reduction surgery or with endobronchial coils and bullectomy.[45] A very low D_{LCO} (e.g., ≤20% predicted) may indicate – in the right clinical context – that lung transplantation is the only non-pharmacological alternative. [45]

The Basis of Pulmonary Gas Transfer as Assessed by D_LCO

In light of the fact that most practitioners are not particularly familiar with the physiological (and mathematical) nuances of D_{LCO} measurements, a brief overview might prove useful. Thus, when a small amount of a highly diffusible gas as CO is inhaled, the membrane diffusing capacity (D_M) represents all steps preceding gas binding to hemoglobin (Hb). Accordingly, it is strongly related to the level of lung expansion (as concomitantly estimated by V_A) since greater inflation leads to airspace expansion and unfolding of the alveolar surface. [46] The diffusing capacity of the blood, in turn, depends on the microvascular ("capillary") blood volume which makes contact with CO (V_c) and the rate of CO reaction with Hb. [47] A large fraction of the D_{LCO} signal (~ 80%) derives from the blood phase, i.e., the number of red cells traversing the lung microvasculature at a given point in time and/ or the number of open capillaries. [48] It is instructive, therefore, to consider that K_{CO} (D_{LCO}/V_A) is proportional to V_c/D_M.

In this context, it should be noted that when lung volume increases (⇑ V_A) D_{LCO} increases, but K_{CO} decreases exponentially. These effects are related to the fact that the beneficial consequences of a more extensive and thinner surface area for gas exchange more than outweigh the deleterious results of the compression and flattening of juxta-alveolar capillaries. In other words, V_c/D_M decreases.[48-48] Moreover, there is relatively less gain in surface area compared to volume at higher lung volumes. Conversely, when lung volume decreases (⇓ V_A) D_{LCO} decreases, but K_{CO} increases exponentially since the beneficial effects of less capillary compression by the smaller alveoli overcome the deleterious consequences of the smaller and thicker surface area for gas exchange. Thus,

V_C/D_M increases. [46] In addition, there is relatively more gain in surface area compared to volume at lower lung volumes. (**Figure 3**).

Importantly, however, the fraction of TLC accessed by the inhaled mixture (V_A) depends on how well the peripheral units receive air from the larger airways. [49] It follows that, in the presence of airway disease and poor distribution of ventilation (⇓ V_A/TLC), K_{CO} might be "preserved", despite substantial impairment in gas exchange efficiency. [50] This happens because:

- Only the better ventilated and perfused alveolar unities are sampled thereby providing a biased picture towards the more preserved areas of the lungs, and
- As discussed above, the large effect of a low lung volume on K_{CO}, i.e. 1 "unit" decrease in V_A leads to more than 1 "unit" increase in D_{LCO} (**Figure 3**).

The exquisite sensitivity of K_{CO} to V_A indicates that a failure to reach full inflation to TLC should prompt repetition of the manoeuvre rather than the application of any "volume" correction to D_{LCO}.

When analysed in conjunction, D_{LCO}, V_A and K_{CO} provide an integrated picture of the physiological mechanisms involved on pulmonary gas transfer, including ventilation distribution, the functional area for gas exchange and blood perfusion through the lung microvasculature.

Considering K_{CO} in Addition to D_{LCO}

The current recommendations for D_{LCO} measurements, endorsed by the American Thoracic Society and the European Respiratory Society, [51] ascribe a secondary role to K_{CO}.[52] Conversely, others defend a more prominent position to the latter variable.[48,49] We herein follow the line of reasoning that K_{CO} helps in the diagnostic differentiation of the cause(a) of a low D_{LCO} , provided V_A and V_A/TLC are *a priori* taken into consideration (**Figure 4**) (illustrative cases presented in the **On-Line Supplement**) [48-48 53]

Of course, D_{LCO} measurements should be analyzed in conjunction with other PFTs. Thus:

• If a low K_{CO} indicating inefficient gas exchange is associated with a preserved V_A, pulmonary vascular disease or right-to-left shunt might be suspected (provided the absence of anemia or recent smoking). This interpretation stems from the fact that a preserved V_A is neither consistent with a restrictive disease (⇓TLC) because V_A is, by definition, ≤ TLC nor with an obstructive airway disease since maldistribution of ventilation decreases both V_A/TLC and V_A (***The Basis of Pulmonary Gas Transfer as Assessed by D_LCO***).

• If a low K_{CO} is associated with a low V_A, V_A/TLC might also be low (<0.80 to stay in the conservative side)[54 55], indicating an obstructive airway disease with maldistribution of ventilation. In this scenario, K_{CO} might be falsely preserved (pseudo-normal) and no valid inferences can be made regarding the integrity and/or extension of the surface for gas exchange. However, if *despite* the ventilation distribution abnormalities (which, as mentioned, conspire to decrease V_A), a low K_{CO} signals extensive gas exchange impairment, e.g., emphysema.

• If a low K_{CO} is associated with a low V_A but preserved V_A/TLC (≥0.80), the implication is that TLC is also low. Thus, a low K_{CO} here points to intra-parenchymal restriction with impaired gas exchange efficiency. It is crucial to note, however, that a normal K_{CO} in this specific scenario should never be misinterpreted as indicative of "no interstitial lung disease (ILD)"[43 56] since D_{LCO} may decrease in tandem with the loss in lung volume caused by the disease. In fact, low D_{LCO}, preserved V_A/TLC and K_{CO} is the most common pattern found in patients with high-resolution computed tomography (HRCT) abnormalities suggesting idiopathic interstitial pneumonia.[56 58] Measurements of arterial blood gases and "wasted ventilation" might provide valuable complementary information to D_{LCO} and K_{CO} (**Figure 4**).

• A high K_{CO} indicates a predominance of V_C over D_M (**Figure 3**) either due to extra-parenchymal restriction or "extra-Hb" either inside or outside the lung vessels. The extra-parenchymal pattern may occur due to incomplete alveolar expansion on a

background of normal lung parenchyma (e.g., pleural, chest wall and neuromuscular disease) and/or discrete loss of units with over-perfusion of the remaining units, e.g., pneumonectomy, local infiltrates, atelectasis (**Figure 4**).[53] The potential confounding effects of ageing and obesity on the interpretation of D_{LCO} and K_{CO} are shown in **Table 1** and **Table 2**, respectively.

Starting K_{CO} interpretation from the TLC/V_A ratio helps in the differentiation of intra- and extra-parenchymal restriction from airway disease. It also minimizes the risk of labelling a preserved K_{CO} as evidence of "normality" in a patient with extensive ventilation distribution abnormalities.

Brave New World: The Changing Role of the PFT Lab in the Investigation of Undetermined Dyspnea

Undetermined chronic dyspnea (including disproportionate dyspnea, [59] dyspnea with multiple potential causes, [60] and dyspnea without any apparent cause) is a common indication for PFTs and exercise tests. Although a plethora of investigation algorithms have been proposed in the past five decades (as reviewed, for instance, in ref. [61]), few of them have considered the epidemiological shift in the population referred to functional assessment. For instance, the patient with isolated "respiratory" or "cardiovascular" cause of dyspnea is a rather uncommon client of modern PFT laboratories. Nowadays, patients may present with compounding abnormalities which individual contribution to dyspnea still remains unclear, e.g., exercise-induced diastolic dysfunction, atrial fibrillation, left atrial abnormalities, isolated respiratory muscle weakness, and chronotropic incompetence. [62]

Is CPET Really Useful in the Investigation of Dyspnea?

The test can provide valuable information on syndromic causes of dyspnea and poor exercise tolerance (i.e., cluster of abnormalities) (**Table 3**), [63] which should be associated with other pieces of information to effectively help in clinical decision making. [64] Thus,

CPET fundamentally aims to shorten the list of differential diagnoses which could explain patient's symptoms; alternatively, results might give reassurance that major dysfunction is not currently impacting on exercise responses. Nevertheless, there have been some recent advances in the field that, despite making the interpretation of the test more complex, improved its clinical usefulness:

- It has become clearer that the traditional concept of "ventilatory limitation" based solely on a low breathing reserve at peak exercise does overlook a large fraction of dyspneic subjects with relevant mechanical-ventilatory disturbances relevant to exertional dyspnea. As shown in **Figure 5A** and **Figure 5C**, for instance, a sizeable fraction of subjects limited by dyspnea may present with preserved breathing reserve; conversely, a low breathing reserve may not be consistently associated with dyspnea; [65]
- On the other hand, assessment of constraints to tidal volume expansion (with serial IC measurements) and increased ventilation ($\dot{V}_E$) as a function of metabolic demand (CO_2 output ($\dot{V}CO_2$)) have proved instrumental to uncover such abnormalities. **Figure 5B** and **Figure 5D** show that the presence of critical inspiratory constraints and high $\dot{V}_E/\dot{V}CO_2$ ratio (reflecting increased "wasted" ventilation and/or excessive afferent stimuli to $\dot{V}_E$) [65] [66] is consistently associated with severe dyspnea (**Figure 5C**) regardless of the breathing reserve (**Figure 5A**). [64] There is also potential benefits of assessing exercise flow-volume curves on this regard [67]: a detailed discussion on the topic, however, is beyond the scope of this review;
- A cluster of CPET findings indicative of combined metabolic-cardiovascular (e.g. a shallow ΔO_2 uptake ($\dot{V}O_2$)/Δwork rate, a plateau in O_2 pulse, an early lactate threshold and ventilatory-gas exchange abnormalities (high $\dot{V}_E$-$\dot{V}CO_2$, low end-tidal partial pressure for CO_2 ($P_{ET}CO_2$)) may raise the suspicion for pulmonary vascular disease in a subject with a high pre-test likelihood of disease; [68] and
- Non-physiological changes and increased variability in breathing pattern, frequently accompanied by varied degrees of alveolar hyperventilation, can be identified in patients with "dysfunctional breathing" thereby avoiding potentially iatrogenic and costly procedures. [63]

These encouraging advances should be tempered with the persistence of important limitations of non-invasive CPET. Due to space constraints, we refrain from discussing those related to technical issues, protocol selection and external validity among others. We will therefore focus on interpretative pitfalls in the context of unexplained dyspnea. For instance, CPET remains poorly sensitive to detect mild-to-moderate cardiocirculatory derangements, i.e., the abnormalities more likely to be found in a subject with undetermined dyspnea. [69] The interpretation of $\dot{V}O_2$/heart rate (O_2 pulse) has become more complex because the growing prevalence of patients whose exertional heart rate is under pharmacological (β-blockers) or non-pharmacological (pacemakers) control. [70] In some patients with unexplained exercise intolerance, an abnormally-low cardiac output is not mechanistically linked to intrinsic cardio-pulmonary disease but a failure to increase right atrial pressure, i.e., reduced pre-load.[71] Conversely, some "central" cardiovascular causes of dyspnea are not necessarily associated with impairment in stroke volume e.g. heart failure with preserved ejection fraction [72] [73], exercise-induced pulmonary hypertension [74] and right ventricle-to-pulmonary circulation uncoupling.[74] Due to the effects of obesity in increasing $\dot{V}O_2$ for a given work rate (**Table 2** and **Table 3**), peak $\dot{V}O_2$ might be within the limits of normal in a patient with severely reduced peak work rate; moreover, peak $\dot{V}O_2$ correction by total body weight may penalize obese subjects exercising on a cycle ergometer.[75] In fact, Kaminsky and colleagues found that subjects with lower peak work rate than peak $\dot{V}O_2$ % predicted were heavier and presented with a higher ventilatory response to exertion than their leaner counterparts.[76] These data suggest that some "extra-$\dot{V}O_2$"might come from the over-activated respiratory muscles, a common finding in the obese.

Sub-maximal CPET variables are also not free from pitfalls: the lactate threshold is not always identified, particularly in mechanically limited patients. $\dot{V}E$-$\dot{V}CO_2$ decreases as critical mechanical constraints progress in tandem with COPD [66]; thus, a relatively-preserved $\dot{V}E$-$\dot{V}CO_2$ slope might give false reassurance despite the presence of severe

disease. A low $P_{ET}CO_2$ may indicate impaired perfusion of ventilated alveoli (e.g., pulmonary vascular disease) or a low $PaCO_2$ (e.g. psychogenic hyperventilation) - two conditions with radically dissimilar clinical implications. Arterial or capillary ("arterialized") blood gases might be helpful to uncover the mechanisms behind a low $P_{ET}CO_2$. In normal subjects with preserved pulmonary vasculature, exertional $P_{ET}CO_2$ increases more than $PaCO_2$; thus, $P(a\text{-}ET)CO_2$ becomes more negative as exercise progresses. If $P(a\text{-}ET)CO_2$ is a positive value, $P_{ET}CO_2$ has underestimated $PaCO_2$ due to poor capillary perfusion; conversely, a proportional decrease in $P_{ET}CO_2$ and $PaCO_2$ signals for alveolar hyperventilation (**Figure 4**).[68] Arterial sampling is also important in other circumstances such as uncovering mild-to-moderately reduced PaO_2 despite relatively-preserved SpO_2 and proper quantification of the physiological dead space, both important correlates of exertional dyspnea.[65,66]

There is a widespread trend to CPET over-interpretation in the dyspneic subject. By looking for cluster of abnormalities, however, the pulmonologist can identify syndromes of exercise limitation which may prompt (or negate) further investigations.

Combining Resting and Exercise Measurements: A Realistic Approach to Untangle the Cause(s) of Dyspnea

Nowadays, most patients referred to PFTs due to undetermined dyspnea have undergone several investigations, including transthoracic echocardiogram and HRCT. These pieces of information, in addition to subject's age, clinical information and medication list, should be carefully considered to estimate the pre-test likelihood of abnormality - and the sequence of further investigations (if any). **Figure 6** outlines a practical step-by-step approach for the investigation of undetermined which follows these premises.

There is no rigid algorithm for the investigation of undetermined dyspnea. Depending on the clinical context and availability of advanced methods, the principles of Bayesian inference should be used to judge the best investigative sequence on an individual basis.

The Importance of Recognizing the Limits of Certainty in the Interpretation of Lung Function and Exercise Tests

Several interpretative strategies PFTs and exercise tests are still modulated by empirical evidence as derived from clinical observation of individual cases. The importance of a Bayesian approach to testing interpretation, therefore, cannot be underestimated. The pulmonologist in charge of reading these tests should specifically avoid strong "diagnostic" considerations if he/she is unaware (as it is frequently the case) of the pre-test probability of disease. Such a cautious, non-committal attitude is important to avoid undesirable consequences of over-reading, such as futile or potentially iatrogenic investigations, excessive treatment and the psychological burden of false positive results. The overarching goal is to provide a cogent, integrated account of the pattern of abnormalities in light of population characteristics which, as discussed in the present review, are in constant change.

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Table 1. Selected effects of ageing on main PFTs results and their implications for testing interpretation. The effects are more pronounced in subjects older than 75, being further accentuated in the oldest-old (>85 years). The directional changes in a given test are listed by their frequency.

Directional changes	Main putative mechanism(s)	Potential interpretative consequences
Spirometry		
↓ FEV_1/FVC	Larger decrease in flows than lung volumes as age progresses	Unfounded concern for airway disease
↓ FEV_1	↓ lung elastic recoil, upstream (distal) displacement of the choke point *	Overestimation of impairment caused by pre-existing lung disease
↓ FVC	↑ RV and, secondarily, ↓ TLC	As above
↑ ΔSVC-FVC leading to ↓ FEV_1/SVC	↑ compressibility/collapsibility of the small airways in the forced maneuver	Unfounded concern for airway disease
↓ $FEF_{25-75\%}$	As above and ↓ diameter of the lower bronchioles	Unfounded concern for small airway disease
Airway resistance		
↑ sRaw	All above	Unfounded concern for airway disease
Body plethysmography		
↑ RV and ↑ RV/TLC	↑ closure volume, enlarged distal airspaces	Unfounded concern for airway disease or overestimation of impairment caused by pre-existing airway disease
↑ FRC, ↑ FRC/TLC	↑ closure capacity, upward shift of the TLC-RV equilibrium volume	As above
↓TLC	Dominance of chest wall stiffness relative to loss of lung elastic recoil	Unfounded concern for restriction or overestimation of impairment caused by pre-existing restrictive disease
Gas exchange		
↓ D_{LCO}	↓ anatomical-functional area for gas exchange, ventilation distribution inhomogeneity (↓ V_A)	Overestimation of impairment caused by pre-existing lung disease (including pulmonary vascular)
↓ PaO_2	As above	As above

Definition of symbols and abbreviations: ↑: increase; ↓: decrease; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; SVC: slow vital capacity; $FEF_{25-75\%}$: forced expiratory flow between 25% and 75% of FVC; sRaw: specific airway resistance; RV: residual volume; TLC: total lung capacity; D_{LCO}: lung

diffusing capacity for carbon monoxide; V_A: alveolar volume;; Pa: arterial partial pressure. * The point at which a critical airway transmural pressure develops when local flow velocity reaches the local speed of pressure wave propagation, leading to airway collapse.

Table 2. Selected effects of obesity on main lung function and exercise testing results and their practical implications to interpretation. These effects are more pronounced in morbid obesity (body mass index (BMI)≥40 kg/m^2), being particularly accentuated in massive obesity (BMI≥50 kg/m^2). The directional changes in a given test are listed by frequency.

Directional changes	Main putative mechanism(s)	Potential interpretative consequences
Spirometry		
↑ FEV_1/FVC	↓ FVC due to early closure of the small airways and/or ↓ TLC in severe obesity	Unfounded concern for restriction; the pseudo-restrictive ("PRISm") pattern
↑ ΔSVC-FVC leading to ↓ FEV_1/SVC	↑ compressibility/collapsibility of the small airways and/or ↓ FEV_1 due to compression of the larger airways in the forced maneuver	Unfounded concern for airway disease or overestimation of impairment caused by pre-existing airway disease
↓ $FEF_{25-75\%}$ but ↔ $FEF_{25-75\%}$ /FVC	↓ flows commensurate to ↓ volumes	Unfounded concern for small airway disease
↑ $FEF_{25-75\%}$ and $FEF_{25-75\%}$ /FVC	↑ elastic recoil of the lung-chest wall	Small airway disease might be missed; unfounded concern for early/incipient restrictive disease
Airway resistance		
↑ *s*Raw	Small airway compression, supraglottic obstruction due to fat deposition	Unfounded concern for airway disease
Body plethysmography		
↓ FRC	Downward displacement of the chest wall-lung equilibrium point, mass effect of fat deposition on the lower rib cage and abdomen	Airway disease might be missed or underestimation of impairment caused by pre-existing airway disease
↑ IC	↓ FRC but preserved TLC	The consequences of obstruction and/restriction on operating lung volumes might be obscured
↓ RV	Cephalic displacement of the diaphragm	Unfounded concern for restriction or overestimation of impairment caused by restrictive disease
↓ TLC	↑ lung-chest wall elastic recoil in those with BMI>50	As above

	kg/m^2	
Neuromuscular assessment		
ΔFVC seated- supine>15%	Cephalic displacement of the diaphragm; lower chest/lung compliance on decubitus	Unfounded concern for neuromuscular disease
Gas exchange		
↑ DL_{CO}	↑ blood flow in areas of preserved ventilation-perfusion	Overestimation of impairment caused by pre-existing lung disease (including pulmonary vascular)
↑ K_{CO}	K_{CO} ↑ exponentially as V_A ↓	As above
↓ PaO_2	Poorly-ventilated (dependent) airways, micro-atelectasis	Overestimation of impairment caused by any lung disease (including pulmonary vascular)
↑ $PaCO_2$	Alterations in ventilatory control and ↑ mechanical constraints	As above
6-min walking test		
↓ distance walked	Increased metabolic, ventilatory and perceptual costs of external work	As above
↓ Exertional SpO_2	↑ perfusion of poorly-ventilated airways with less oxygenated mixed venous blood	As above
CPET		
↑ impairment in peak work rate than peak $\dot{V}O_2$	↑ metabolic cost of work: upward displacement of the linear $\dot{V}O_2$-work rate relationship	Underestimation of exercise intolerance
↑ O_2 pulse	Chronotropic incompetence in the presence of metabolic /cardiovascular disease	Overestimation of cardiovascular performance
↔ or ↓ $\dot{V}_E$-$\dot{V}CO_2$	Ventilatory constraints and/or ↑$PaCO_2$ set-point	Underestimation of V_D/V_T ("wasted" ventilation)
Lack of physiological ↑ in IC as exercise progresses	Dynamic decrease in the maximal inspiratory level and/or stable EELV	Overestimation of functional impairment caused by pre-existing airway disease

Definition of symbols and abbreviations: ↑: increase; ↓: decrease; ↔: preserved; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; SVC: slow vital capacity; $FEF_{25-75\%}$: forced expiratory flow between 25% and 75% of FVC; sRaw: specific airway resistance; TLC: total lung capacity; FRC: functional residual capacity; RV: residual volume; IC: inspiratory capacity; DL_{CO}: lung diffusing capacity for carbon monoxide; K_{CO}: lung diffusion coefficient for carbon monoxide; V_A: alveolar volume; Pa: arterial partial pressure; SpO_2: oxygen saturation by pulse oximetry; $\dot{V}O_2$: oxygen uptake; $\dot{V}_E$: ventilation; $\dot{V}CO_2$: carbon dioxide output; $PaCO_2$: arterial partial pressure for carbon dioxide; V_D: dead

space; VT: tidal volume; EELV: end-expiratory lung volume.

Table 3. Key CPET findings useful to discriminate different patterns of dysfunction.

	Physiological bases	Key CPET findings	CPET response modifiers & comments
Obesity			
	⇑ Metabolic cost of work	⇑ $\dot{V}O_2$ for a given WR	⇑⇑ in weight-bearing exercise
	⇔ Work efficiency	⇔ Δ $\dot{V}O_2$ / Δ WR	⇑ in extreme obesity
	⇑ Ventilatory cost of work	⇑ $\dot{V}E$ for given WR	⇓ in obesity-hypoventilation
	⇓ End-expiratory lung volume	⇑ IC	⇓ in respiratory muscle weakness
	⇑ Work of breathing	⇑ Dyspnea for a given WR	⇑⇑ in weight-bearing exercise
O_2 delivery/utilization impairment			
	⇓⇓ O_2 delivery as exercise progresses	⇓ Δ $\dot{V}O_2$ / Δ WR	"Plateau" in severe impairment
	⇑ Aerobic "inertia"	⇑ Time for $\dot{V}O_2$ increase at the onset	Influenced by training status
	Early shift to anaerobiosis	⇓ Estimated lactate threshold	Not always identified
	⇑ Reliance on HR to increase CO	⇑ Δ HR/Δ $\dot{V}O_2$	Might be obscured by β-blockers
	⇓ SV and/or ⇓ O_2 extraction	⇓ O_2 pulse	"Plateau" in severe impairment
Mechanical-ventilatory impairment			
	⇓ Breathing reserve	⇑ $\dot{V}E$ /MVV	MVV might overestimate ceiling
	⇑ VD/VT and/or ⇓ $PaCO_2$ set-point	⇑ $\dot{V}E$-$\dot{V}CO_2$ relationship	⇓ as mechanical constraints ⇑
	Dynamic hyperinflation	⇓ IC as $\dot{V}E$ increases	⇔ if IC already ⇓⇓ at rest
	Critical inspiratory constraints	⇑ VT/IC, ⇓ IRV, ⇑ EILV/TLC	Adequate IC maneuver is critical
	Tidal expiratory flow limitation	Tidal F-V loop "enveloping"	Trapezoid/concave shape
	⇑ Neural drive	⇑ Dyspnea-WR but ⇔ dyspnea-$\dot{V}E$	Relate to known sources of ⇑ drive
	Impaired lung mechanics	⇑ Dyspnea-WR and ⇑ dyspnea-$\dot{V}E$	Relate to inspiratory constraints
Gas exchange impairment			
	Hypoxemia	⇓ SpO_2, ⇓ PcO_2	⇓⇓ in walking than cycling
	Hypercapnia	⇑ $PETCO_2$, ⇑$PcCO_2$	⇑ as mechanical constraints ⇑

	⇑ V_D/V_T	⇑ $\dot{V}_E$-$\dot{V}CO_2$ relationship	As above
	Impaired pulmonary perfusion	⇓ $P_{ET}CO_2$	Influenced by breathing pattern
	Ventilation/perfusion mismatch	Less negative or even positive $P(c\text{-}_{ET})CO_2$	Trending more informative
Dysfunctional breathing-hyperventilation			
	Chaotic breathing pattern	⇑ variability in V_T-*f* relationship	Influenced by data averaging
	Hyperventilation	⇑ RER, ⇑ $\dot{V}_E/\dot{V}CO_2$, ⇓ $P_{ET}CO_2$	Trending more informative
	⇑ Neural drive	⇑ Dyspnea-WR but ⇔ dyspnea-$\dot{V}_E$	Relate to changes in $\dot{V}_E$

Definition of abbreviations and symbols: ⇑= increase; ⇓= decrease, ⇔= unaltered; $\dot{V}O_2$ = oxygen uptake; WR= work rate; $\dot{V}_E$ = minute ventilation; IC= inspiratory capacity; HR= heart rate; SV= stroke volume; CO= cardiac output; MVV=maximum voluntary ventilation; $\dot{V}CO_2$ = carbon dioxide output; V_T= tidal volume; IRV= inspiratory reserve volume; EILV= end-inspiratory lung volume; TLC= total lung capacity; F= flow; V= volume; SpO_2= oxyhemoglobin saturation by pulse oximetry; P_{ET}= end-tidal pressure; P_c = capillary (arterialized) pressure; *f* = breathing frequency; RER= respiratory exchange ratio.

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Figure Legends

Figure 1. Age related decrease in predicted (pred) and lower limits of normal (LLN) of the forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ratio in men and women. Note that a sizeable fraction of normal subjects older than 50 may present with $FEV_1/FVC < 0.7$ but above the LLN ("grey zone"). The arrows indicate the ages at which the declining LLN reaches the 0.7 threshold in men and women.

Calculated from data provided on: *Tan WC, Bourbeau J, Hernandez P, et al. Canadian prediction equations of spirometric lung function for Caucasian adults 20 to 90 years of age: results from the Canadian Obstructive Lung Disease (COLD) study and the Lung Health Canadian Environment (LHCE) study. Can Respir J. 2011;18(6):321-6*

Figure 2. A pragmatic approach for spirometry interpretation in a patient at risk for airflow limitation which considers the uncertainties surrounding the interpretation of "discordance" in post-bronchodilator (BD) forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ratio between 0.7 and the lower limit of normal (LLN). See the text for further elaboration.

Symbols and Abbreviations: ↓, reduced; ↔, preserved; (+), present; (-), absent; D_{LCO}, lung diffusing capacity for carbon monoxide; LH, likelihood; RV, residual volume; TLC, total lung capacity.

Figure 3. A schematic representation of the effects of changes in lung volume (*upper panels*) on the membrane (DM) and capillary (VC) components of lung diffusing capacity (*panel A*) and their consequences on the diffusion factor (DLCO) and the diffusion coefficient (KCO) (*panel B*). Note that DM increases linearly from functional residual capacity (FRC) to total lung capacity (TLC) (*panel A*) because of the increase in surface area and a thinner membrane as the alveoli are expanded. In contrast, VC predominates over DM at FRC because there is less capillary compression in the smaller alveoli (with the opposite being found at TLC) (*upper panels*). The positive effects of a larger DM lead to an exponential increase in DLCO at higher lung volumes though the relatively lower VC precludes even larger increases in DLCO (*panel B*). The relative predominance of VC over DM leads to an exponential increase in KCO as the lung deflates from TLC towards FRC (*panel B*). See the text for further elaboration.

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Figure 4. A simplified algorithm to interpret the meaning of a low (⇓) lung diffusing capacity for carbon monoxide (DL_{CO})(< lower limit of normal) and its impact on the DL_{CO}/VA ratio (diffusing coefficient, K_{CO}). The diagnosis of restriction or obstruction should be based on tests of ventilatory function, such as spirometry and body plethysmography. Auxiliary parameters to indicate the presence of gas exchange

impairment are presented in the box at the bottom of the figure. See text for further elaboration and the **On-Line Supplement** for illustrative cases.

***** Normal VA may coexist with airflow obstruction in a patient with mild airflow limitation in whom the distributive abnormalities are not severe enough to decrease VA/TLC less than 0.8. *Symbols and Abbreviations*: ⇑= increased; ⇔= unaltered; P_A= alveolar partial pressure, Pa= arterial partial pressure, P_{ET}: end-tidal partial pressure, V_D= dead space ventilation, V_T= tidal volume, $\dot{V}_E$= ventilation, $\dot{V}CO_2$= carbon dioxide production.

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Figure 5. Selected ventilatory and sensory responses to symptom limited incremental CPET in subjects under investigation for exertional dyspnea. Subjects were separated according to the combination of preserved or low peak breathing reserve (BR) versus absence (-) or presence (+) of critical inspiratory constraints (CIC). Note that a low BR (*panel A*) was found in subjects who either low or high levels of dyspnea (*panel C*); conversely, a sizeable fraction of subjects with preserved BR reported severe dyspnea. Regardless of the BR, subjects who develop CIC (*panel B*) and/or presented with poor ventilatory efficiency (high ventilation ($\dot{V}_E$)/ carbon dioxide output ($\dot{V}CO_2$) in *panel D*) were consistently more dyspneic. Note the additive effects of these physiological abnormalities. Shaded areas represent the limits for a low BR, CIC, high dyspnea burden and poor ventilatory efficiency, respectively. The arrows in *panels A-C* indicate the exercise intensities associated with an upward inflection in dyspnea ratings in CIC (+) subjects. See the text for further elaboration.

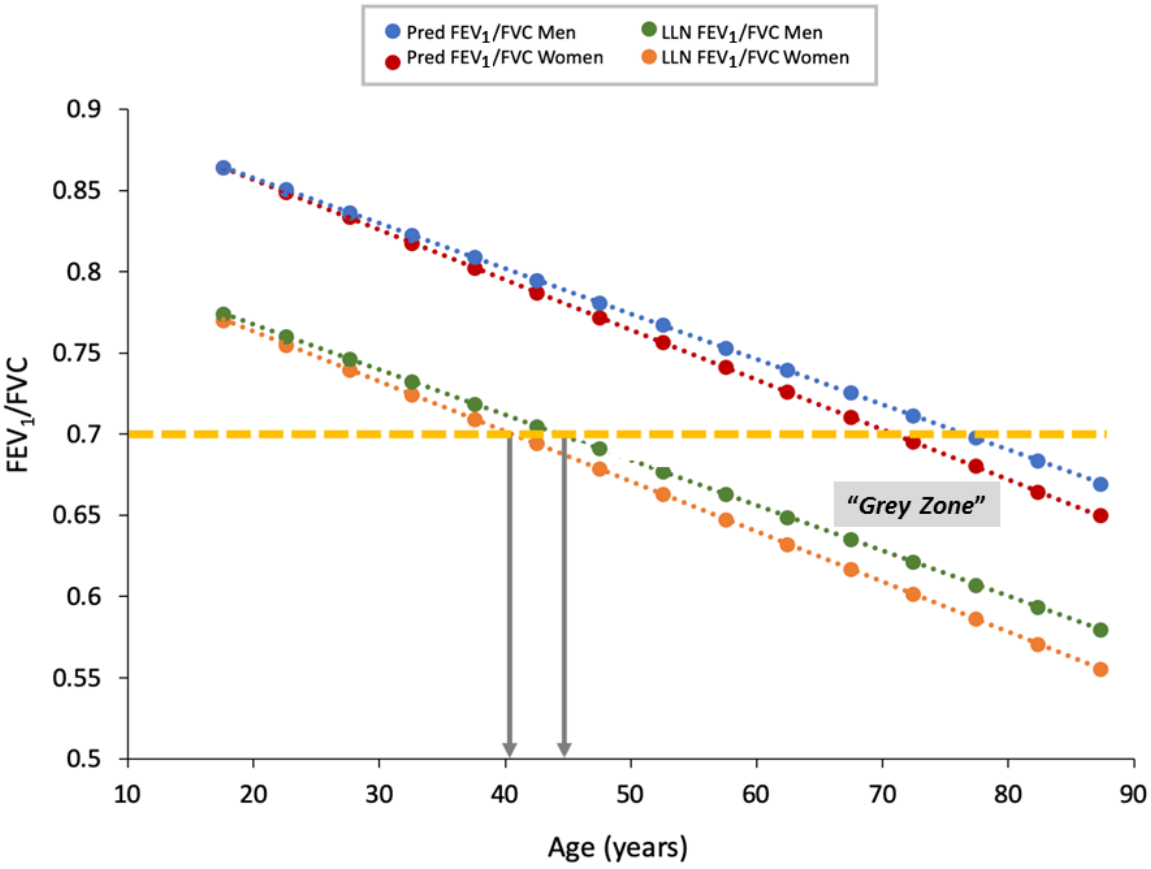
Data are mean±SEM. *p<0.05: versus all groups; † versus low BR, CIC(-) and preserved BR, CIC(+); ‡ versus low BR, CIC(-); **§** versus preserved BR, CIC(-) and preserved BR, CIC (+); **ll** versus low BR, CIC(-) and preserved BR, CIC(-). *Abbreviations:* $\dot{V}_E$= minute ventilation, $\dot{V}CO_2$= carbon dioxide output; V_T= tidal volume; IC_{dyn}: dynamic (i.e., during exercise) inspiratory capacity.

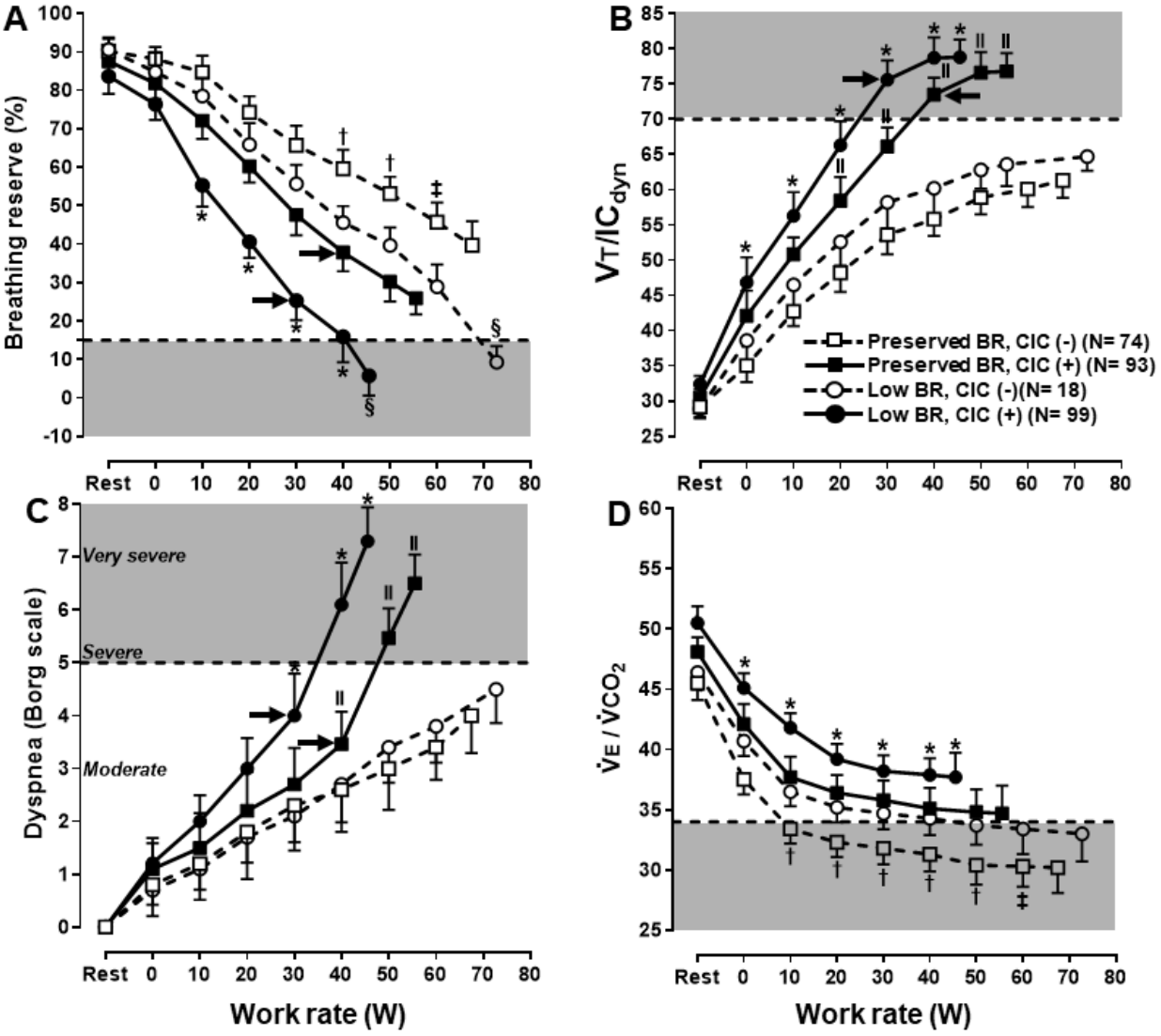
Reproduced, with the permission of the publisher, from: *Neder JA, Berton DC, Marillier M, Bernard A-C, O Donnell DE, Canadian Respiratory Research Network. The role of evaluating inspiratory constraints and ventilatory inefficiency in the investigation of dyspnea of unclear etiology. Respir Med 2019;158:6–13.*

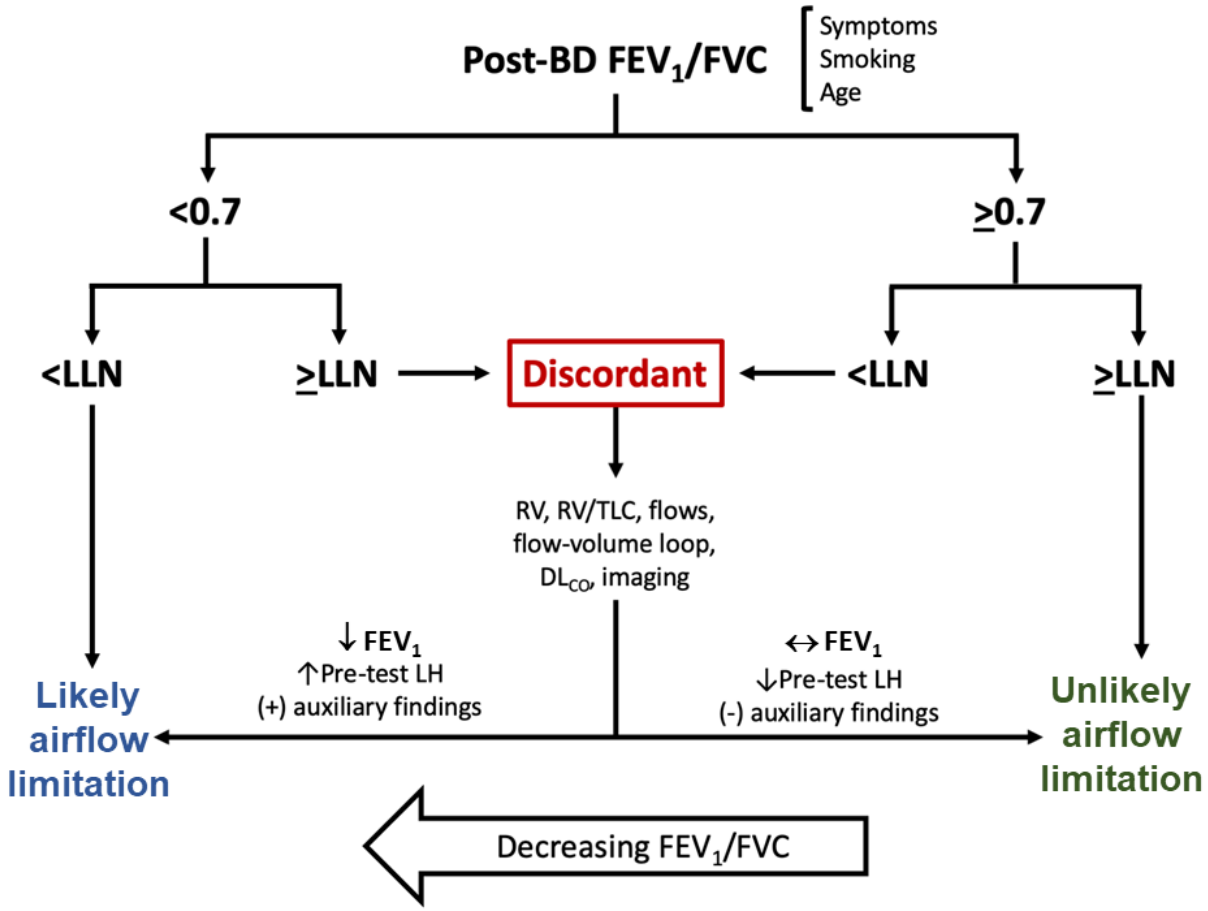
Figure 6. A pragmatic protocol for the investigation of undetermined dyspnea feasible to be performed in most PFT labs from tertiary centers. Note that the sequence of testing might change according to the readiness with which a given test can be performed and the individual pre-test likelihood (LH) of abnormality. See the text for further elaboration.

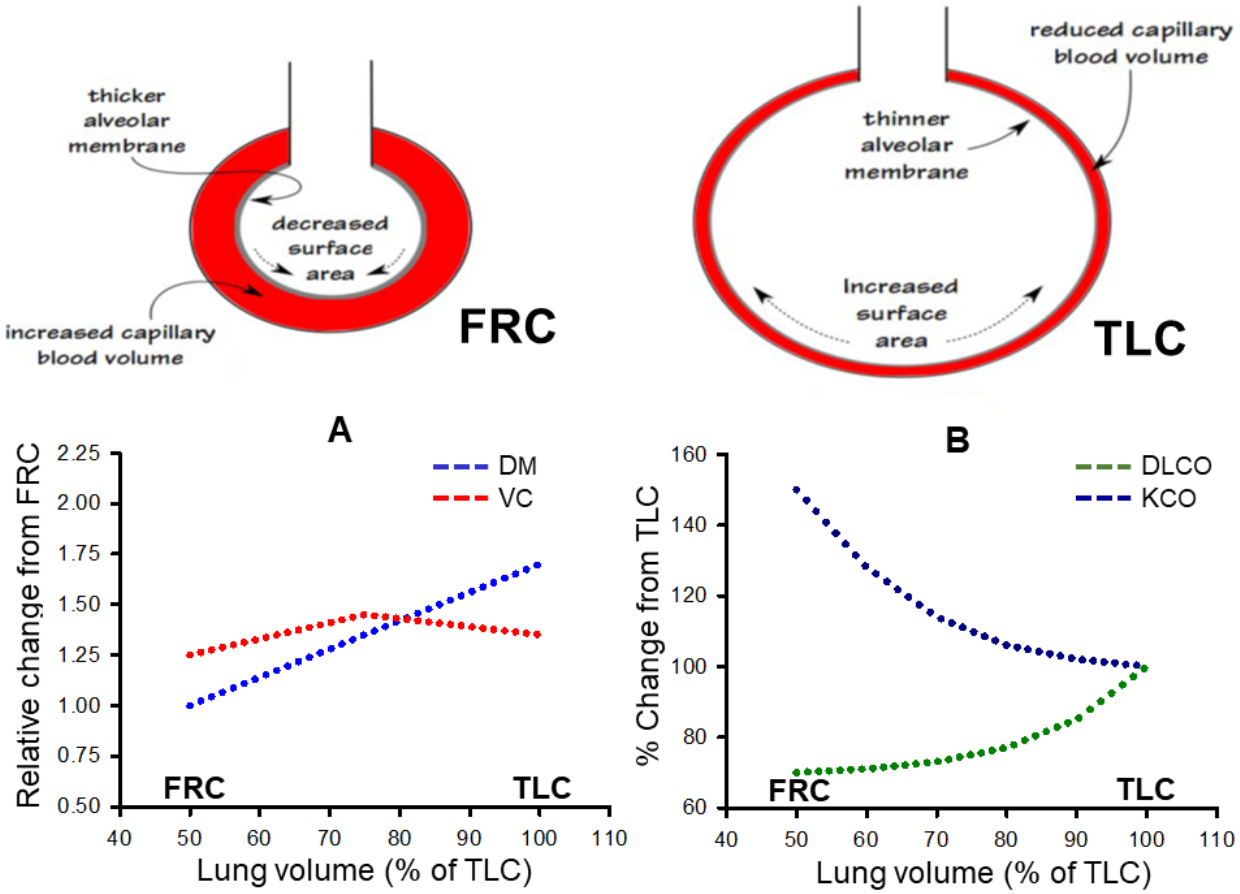
[a] Maximal static pressures, sniff inspiratory pressure (advisable), Δ forced vital capacity seated-to-supine.

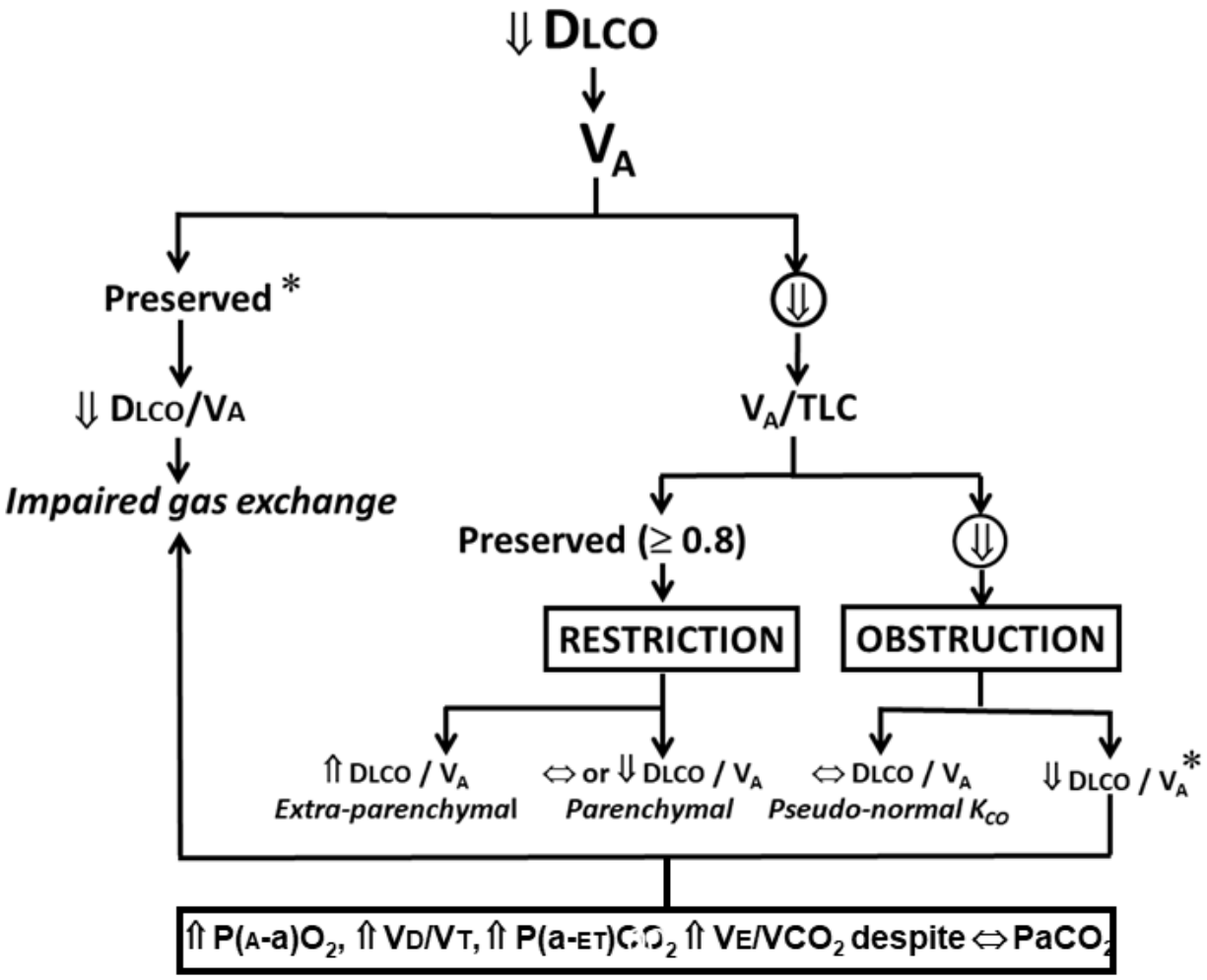
Symbols and Abbreviations: ⊗: impaired, ECG: electrocardiogram, TT: transthoracic, CBC: cell blood count, BD: bronchodilator, ABGs: arterial blood gases, V_D: dead space, V_T= tidal volume, CPET: cardiopulmonary exercise testing, MRI: magnetic resonance imaging, DEL: delivery, UTIL: utilization, DISF BREATH: dysfunctional breathing, HV: hyperventilation.

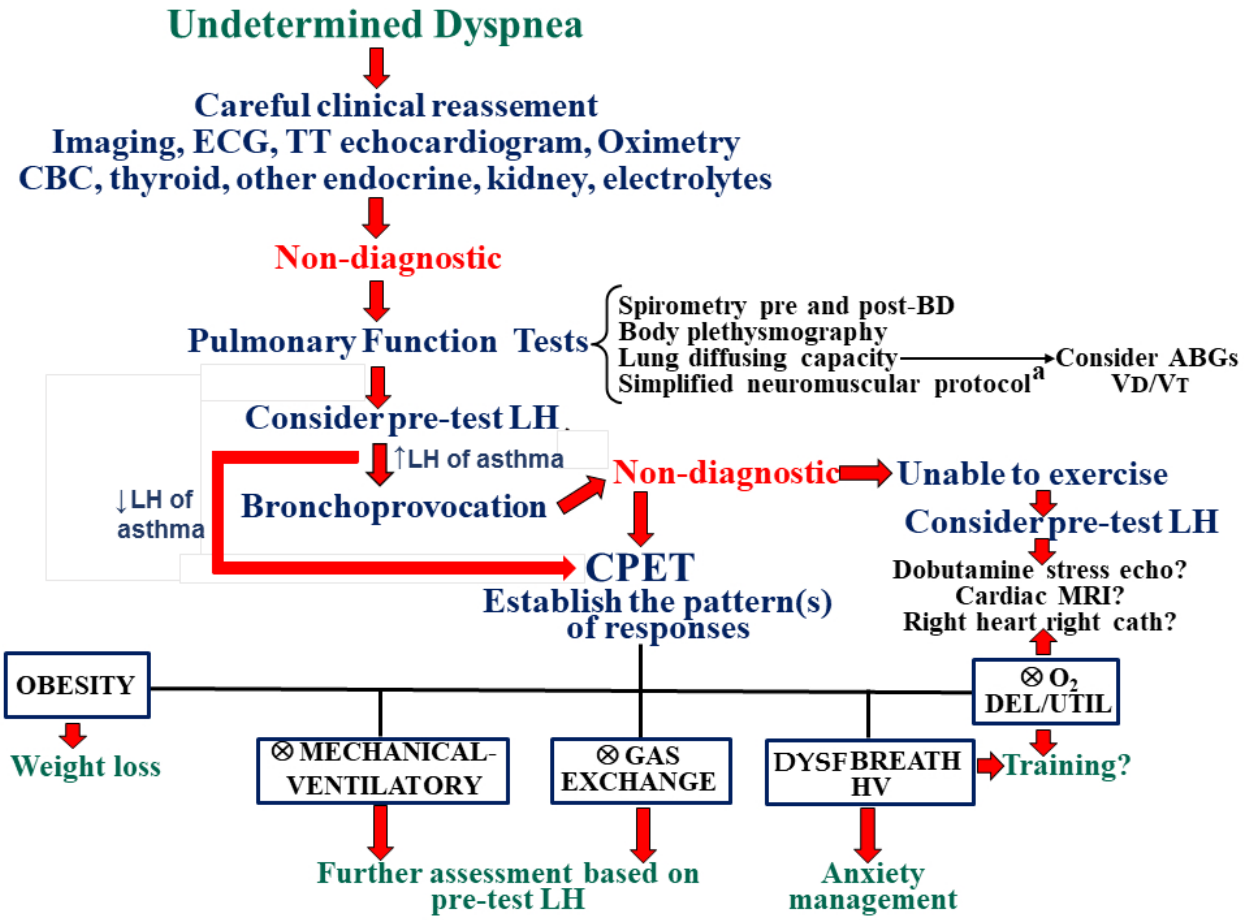

Pred FEV1/FVC Men
Pred FEV1/FVC Women
LLN FEV1/FVC Men
LLN FEV1/FVC Women
FEV1/FVC
0.9
0.85
0.8
0.75
0.7
0.65
0.6
0.55
0.5
10
20
30
40
50
60
70
80
90
Age (years)
"Grey Zone"


A
Breathing reserve (%)
B
V_T/IC_{dyn}
Preserved BR, CIC (-) (N= 74)
Preserved BR, CIC (+) (N= 93)
Low BR, CIC (-)(N= 18)
Low BR, CIC (+) (N= 99)
C
Dyspnea (Borg scale)
Very severe
Severe
Moderate
D
$\dot{V}_E / \dot{V}CO_2$
Rest 0 10 20 30 40 50 60 70 80
Work rate (W)


Post-BD FEV1/FVC
Symptoms
Smoking
Age
<0.7
≥0.7
<LLN
≥LLN
Discordant
<LLN
≥LLN
RV, RV/TLC, flows,
flow-volume loop,
DLCO, imaging
↓ FEV1
↑Pre-test LH
(+) auxiliary findings
↔ FEV1
↓Pre-test LH
(-) auxiliary findings
Likely airflow limitation
Unlikely airflow limitation
Decreasing FEV1/FVC


thicker alveolar membrane
decreased surface area
increased capillary blood volume
FRC
reduced capillary blood volume
thinner alveolar membrane
Increased surface area
TLC
A
Relative change from FRC
DM
VC
FRC
TLC
Lung volume (% of TLC)
B
% Change from TLC
DLCO
KCO
FRC
TLC
Lung volume (% of TLC)


⇓ DLCO
VA
Preserved *
⇓ DLCO/VA
Impaired gas exchange
⇓
VA/TLC
Preserved (≥ 0.8)
⇓
RESTRICTION
OBSTRUCTION
⇑ DLCO / VA
Extra-parenchymal
⇔ or ⇓ DLCO / VA
Parenchymal
⇔ DLCO / VA
Pseudo-normal KCO
⇓ DLCO / VA*
⇑ P(A-a)O2, ⇑ VD/VT, ⇑ P(a-ET)CO2 ⇑ VE/VCO2 despite ⇔ PaCO2


Undetermined Dyspnea
Careful clinical reassement
Imaging, ECG, TT echocardiogram, Oximetry
CBC, thyroid, other endocrine, kidney, electrolytes
Non-diagnostic
Pulmonary Function Tests
Spirometry pre and post-BD
Body plethysmography
Lung diffusing capacity
Simplified neuromuscular protocol
a
Consider ABGs
VD/VT
Consider pre-test LH
↑LH of asthma
↓LH of asthma
Bronchoprovocation
Non-diagnostic
Unable to exercise
Consider pre-test LH
Dobutamine stress echo?
Cardiac MRI?
Right heart right cath?
CPET
Establish the pattern(s) of responses
OBESITY
Weight loss
⊗ MECHANICAL-VENTILATORY
⊗ GAS EXCHANGE
DYSF BREATH HV
⊗ O2 DEL/UTIL
Training?
Further assessment based on pre-test LH
Anxiety management

List of Abbreviations

ACO: asthma-COPD overlap
BD: bronchodilator
BMI: body mass index
CC: closing capacity
COPD: chronic obstructive pulmonary disease
CPET: cardiopulmonary exercise test
D_{LCO}: lung diffusing capacity for carbon monoxide
D_M: membrane diffusing capacity
EELV: end-expiratory lung volume
ERV: expiratory reserve volume
$FEF_{25-75\%}$: forced expiratory flow between 25% and 75% of FVC
FEV_1: forced expiratory volume in one second
FRC: functional residual capacity
FVC: forced vital capacity
Hb: hemoglobin
IC: inspiratory capacity
ILD: interstitial lung disease
K_{CO}: diffusing coefficient for carbon monoxide (D_{LCO}/V_A ratio)
LLN: lower limit of normal
Pa: arterial partial pressure
P_{ET}: end-tidal partial pressure
PFTs: pulmonary function tests
PRISm: preserved ratio- impaired spirometry
RV: residual volume
*s*Raw: specific airway resistance
SVC: "slow" vital capacity
TLC: total lung capacity
V_A: alveolar volume
Vc: capillary volume
$\dot{V}CO_2$: carbon dioxide output
V_D: dead space
$\dot{V}_E$: minute ventilation
$\dot{V}O_2$: oxygen uptake
V_T: tidal volume