

White Paper: PFT Interpretation per Professor Paul Enright, MD

The author of these editorials, Paul Enright, MD retired from the University of Arizona in Tucson, USA and the National Institute of Occupational Safety and Health (NIOSH) in 2012. n d d has indirectly reimbursed him for travel expenses to give talks at international meetings, but no consulting fees or honoraria.

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1 Office-based DLCO tests help pulmonologists to make important clinical decisions.

Until 2012, pulmonary sub-specialists needed to refer patients to a hospital-based PFT lab when DLCO tests were indicated. The n d d EasyOnePro now provides spirometry and DLCO tests in a lunchbox-sized instrument designed for an outpatient office. DLCO and spirometry results can thus be obtained during a patient's outpatient visit.

DLCO tests require very little effort when compared to spirometry tests. The patient breathes quietly for a minute and then inhales the test gas, holds his breath for ten seconds, and then exhales (but not a forced exhalation). After 4 minutes the maneuver is repeated, with the goal of matching DLCOs from two acceptable tests within 2 English units (otherwise a third test is done).

In adult patients with post-bronchodilator airway obstruction, a low DLCO greatly increases the probability of emphysema due to cigarette smoking, while a normal DLCO makes chronic asthma more likely [Paoletti 2005].

PFT results should not be used in isolation to "make" a diagnosis. The results must be added to other information known about the patient, which determine the pre-test probability of each disease under consideration. For example, the PFT results may increase or decrease the pre-test probability of asthma or a COPD phenotype, and in some cases (such as borderline abnormalities) the PFT results may not change the pre-test probability at all.

In patients with spirometric restriction (a low FVC with a normal FEV1/FVC), a low DLCO increases the pre-test probability of an interstitial lung disease (ILD or IPF), while a normal DLCO makes a chest wall type of restriction more likely [Paoletti 2005, Martinez 2006]. A recent study concluded that "DLCO is more sensitive for demonstrating gas exchange abnormality in fibrotic lung disease than resting PaO₂, exercise P(A-a)O₂ peak, or 6MWT SpO₂" [Wallaert 2012]. A normal VA (from the single-breath helium dilution provided by a DLCO test) rules out restriction of lung volumes without the need for a body box measurement of TLC.

In patients with dyspnea of unknown cause, the pattern of a low DLCO with normal spirometry increases the likelihood of a pulmonary vascular disease [Paoletti 2005], but this pattern

also occurs with several other diseases [Dave 2010], and anemia should be ruled out as a cause for the low DLCO.

Once a diagnosis is made, the percent predicted DLCO provides an objective index of disease severity. A DLCO below 40% predicted, or a decline in DLCO, is associated with increased morbidity and mortality [Latsi 2003] and thus often prompts more aggressive treatment, such as lung volume reduction in patients with very severe emphysema [Criner 2008] or lung transplantation for patients with IPF [Orens 2006]. A low DLCO in an adult smoker suggests the emphysema phenotype of COPD [Al-Kassimi 2011] and is an independent predictor of more rapid subsequent decline in lung function [Nishimura 2012].

Long-term reproducibility of the DLCO instrument is verified using weekly testing of a healthy biological control (usually a member of your office staff). When these quality measures are met in your office, a change of 4 DLCO units from one visit to another is usually outside of the noise of measurement and is a clinically importance difference (higher than the MCID) [Horita 2014].

Follow-up DLCO tests for patients diagnosed with an interstitial lung disease, lung involvement with a collagen-vascular disease (such as rheumatoid arthritis, systemic sclerosis, or scleroderma) or with primary pulmonary hypertension provide objective evidence of the efficacy of treatment or disease progression. A review of the topic concluded that “physiologic testing, especially spirometry and DLCO, have demonstrated value in monitoring response to therapy and identifying disease progression.” [Martinez 2006].

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2 Spirometry and DLCO separate asthma from COPD and CHF in adult smokers with dyspnea.

The differential diagnosis of shortness of breath in a middle-aged or older adult who is a current or former smoker is a very common problem for pulmonary specialists and cardiologists. Spirometry, DLCO, a chest X-ray, and a B-naturetic protein (BNP) test greatly help to identify the etiology of the dyspnea.

The GOLD guidelines only recommend spirometry for the diagnosis of COPD, but spirometry alone does not identify the COPD phenotype, which helps to direct optimal therapy. About one-third of adult smokers with airway obstruction following albuterol (salbutamol and/or ipratropium) (post-BD) have “irreversible” asthma which will respond to optimal asthma therapy much better than to anticholinergic COPD inhalers. So it is worthwhile clinically to detect the “hidden asthmatics” (sometimes considered as COPD phenotype A) [Fujimoto 2006] before prescribing a COPD inhaler for smokers with airway obstruction. An “overlap syndrome” of asthma plus COPD requiring treatment for both is highly unlikely [Al-Kassimi 2013].

A DLCO test helps to distinguish asthma from COPD in adult smokers since a low DLCO (after correction for any anemia) greatly increases the pre-test probability of emphysema, while a normal DLCO makes chronic asthma more likely [Paoletti 2005, Goedhart 2006]. Consider measuring the eosinophil count in blood or induced sputum, which are often increased in smokers with hidden asthma [Leigh 2006, Nishimura 2012]. Continued smoking reduces the efficacy of inhaled corticosteroid therapy for patients with asthma, so prolonged pharmaceutical smoking cessation therapy is indicated.

In smokers with airway obstruction, the degree of bronchodilator (BD) responsiveness is usually not helpful for distinguishing asthma from COPD [Tashkin 2008]. Patients with COPD often have a small BD response which fits the traditional ATS/ERS definition of bronchodilator responsiveness (FEV1 or FVC increasing by more than 12% and 0.2 liters). Only when the patient has a large BD response (FEV1 increases more than 25% and more than 0.4 liters), is the post-test probability of asthma greatly increased.

A chest X-ray without infiltrates greatly reduces the likelihood of a chronic lung infection or pulmonary fibrosis causing the dyspnea, while a lung HRCT does so with a very high degree of certainty. A normal DLCO and normal lung volumes (FVC from spirometry and VA from the DLCO test) further reduces the pre-test probability of an interstitial lung disease. Rare pulmonary diseases (and mild cases of interstitial lung disease) which cause dyspnea on exertion and low exercise tolerance (reduced 6 minute walk distance and reduced peak oxygen uptake during maximal exercise tests) may present with normal PFTs (spirometry, lung volumes, and DLCO) [Boros 2012], so an inspiratory and expiratory lung HRCT should be considered in such patients.

Since cigarette smoking is the major cause of both COPD and CHF, it should not be surprising that about 20% of patients with a diagnosis of COPD also have heart failure, which is often not obvious on the physical exam or chest X-ray [Hawkins 2009]. Since dyspnea due to CHF responds very well to therapy (greatly reducing morbidity and mortality) it behooves pulmonologists to look for CHF in patients with dyspnea, even for patients with post-BD airway obstruction [Lejemtel 2007]. It is efficient to start with a simple BNP blood test [Rutten 2007]. A high value greatly increases the pre-test probability of CHF, while a normal value makes CHF much less likely the

etiology of the patient's dyspnea. An intermediate BNP value doesn't help much, so an echocardiogram or cardiac MRI should be obtained for such patients [Hawkins 2009].

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3 Body box tests rarely add diagnostic information to spirometry, DLCO, and a chest X-ray when evaluating patients with spirometric restriction.

Body plethysmographs are used to measure airway resistance, then the shutter closes and FRC is quickly measured, and when the shutter opens again, the subdivisions of the vital capacity are measured. The static lung volumes are then computed (TLC, RV, and ratios such as RV/TLC). The total lung capacity (TLC) is the most important of these because a low TLC has traditionally been the definition of “true restriction” (also described as a restrictive ventilatory defect). On the other hand, “spirometric restriction” is defined as a low vital capacity (FVC and slow VC below the lower limit of the normal range, LLN) but a normal FEV1/FVC (no obstruction). The FVC is the largest component of the TLC.

There are dozens of lung diseases and other conditions which cause a restriction (reduction) of lung volumes. Some of these cause a low FVC but do not cause a low TLC. For example, obesity and malnutrition cause an inability to exhale completely, so the patient does not have an expiratory reserve volume (ERV), which lowers the FVC but not the TLC [Salome 2010]. When a patient cannot inhale as completely (compared to previously when he was healthy), both his FVC and TLC are reduced by an equal amount of volume. When his lung tissue becomes scarred (fibrosis), all of his lung volumes are proportionally reduced. This means that a low FVC (spirometric restriction) is probably as sensitive for detecting mild interstitial lung disease (ILD) as a low TLC (true restriction).

The primary indication for measurement of the TLC is for patients with spirometric restriction (a low FVC), to see if they also have “true restriction” (a low TLC). However, “true restriction” could have been ruled out for some of them (more quickly and less expensively) by measuring slow vital capacity, by noting a normal FEV6 (in cases of submaximal exhalation without a flat volume-time plateau), by considering the post-bronchodilator FVC, or by finding a normal VA from the DLCO test [Odo 2013]. Large studies show that the single-breath VA from the DLCO test is equivalent to the TLC obtained from a body box or multi-breath technique in normal subjects and patients without airway obstruction [Mitchell 1968, Punjabi 1998, Swanney 2004]. A study of over 6000 patients concluded that “VA accurately predicts TLC in patients with mild or no airflow obstruction.” [Punjabi 1999] The VA measured during single-breath DLCO tests has also been called the “effective lung volume” [Homan 2002] and abbreviated as TLC-SB [Milite 2009].

About half of the patients with spirometric restriction (but no airway obstruction) referred to a PFT lab have a “true” restriction -- whether lung volumes are measured using a body box or a gas dilution or washout technique [Aaron 1999, Punjabi 1999]. The others are categorized as having a “non-specific pattern.” The only study ever done to characterize patients with this non-specific pattern found that on average, they have a wide variety of conditions (including obesity) [Hyatt 2009] and those with a normal DLCO generally have a benign clinical course [Iyer 2010].

A low TLC (true restriction) is not sensitive for detecting early or mild interstitial lung disease (ILD) or idiopathic pulmonary fibrosis (IPF). Many patients with infiltrates on chest x-ray and lung HRCT and biopsy proven IPF have a normal TLC [Cortes 2013, Noble 2011, Kondoh 2013, Wallaert 2012]. This is also true for patients with sarcoidosis [Boros 2013]. This means that a normal TLC (regardless of the method used to measure it) should not be used to rule out ILD or IPF. DLCO and lung imaging must also be obtained.

There are 4 commonly available PFTs which measure static lung volumes: body plethysmography, multi-breath nitrogen washout, multi-breath helium dilution, and single-breath helium dilution [Kendrick 1996]. The body box TLC is considered the "gold standard" test and has an efficiency advantage since several TLC measurements can be obtained within a couple of minutes, while the multi-breath tests take up to 20 minutes to obtain a single TLC measurement [Wanger 2005]. Almost every hospital-based PFT lab has a body box, which is used to quickly measure both static lung volumes and airway resistance. Hundreds of thousands of body box tests have been done annually for the last fifty years.

It is revolutionary to suggest that these body box tests add little clinically useful information [Enright 2011]. However, there is a paucity of evidence that when results from spirometry, DLCO, VA from the DLCO test, and a chest X-ray are available to the physician detecting non-malignant, non-infectious lung disease, that addition of either static lung volumes or airway resistance from a body box add anything other than revenue for a pulmonary department. A pulmonary specialist who is not the medical director of a PFT lab and merely wishes to obtain PFTs to detect and manage lung disease in her outpatient office should consider the evidence for taking the time and money to refer patients to a PFT lab for tests in a body box because both spirometry and DLCO tests can now be performed quickly in the office using a lunchbox-sized instrument.

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4 **Body box tests add little or no diagnostic information to spirometry, DLCO, and a chest X-ray when evaluating patients with *airway obstruction*.**

About two-thirds of patients referred for PFTs in a hospital-based lab have airway obstruction (also known as airflow limitation) as defined by a low FEV1/FVC [Punjabi 1999]. There are 3 potential reasons for body plethysmography tests in these patients: 1) to confirm airway disease by demonstrating high airway resistance, 2) to detect hyperinflation or air trapping, and 3) in those with a low FVC to rule out a super-imposed restriction (a mixed pattern with airway obstruction and a low TLC). However, a recent review concluded that “Lung volumes do not provide much additional information for clinical decision making in most patients.” [Ruppel 2012]

1) It is relatively easy to dismiss the value of airway resistance since no professional pulmonary society has published guidelines for these tests. The ATS/ERS 2005 PFT standards do not include them. CPT codes used in the United States for reimbursement do not allow for additional payment for airway resistance when lung volumes are measured by body plethysmography [Flesch 2012]. The primary advantage of airway resistance tests done in a body box is that they require very little patient effort when compared to forced spirometry tests, and they can be corrected for the static lung volume at which they were measured (specific resistance or specific conductance). Measurement of specific resistance can be useful in pre-school children, but routine biological controls are necessary to ensure accuracy [Poorisrisak 2009]. In adults, it is reassuring when spirometry and airway resistance tests both suggest airway obstruction, but when they disagree, the spirometry results are almost always considered more reliable. Reference values for airway resistance tests are also poorly established when compared to spirometry reference values.

2) Body plethysmography also enables relatively rapid measurements of static lung volumes (when compared to helium dilution and nitrogen washout techniques). The hyperinflation which usually accompanies airflow limitation can be detected by a high residual volume (RV) or high RV/TLC [Ruppel 2012]. On the other hand, the degree of hyperinflation is directly associated with the degree of airway obstruction (as measured by percent predicted FEV1), in both asthma and COPD [Dykstra 1999]. Studies have not yet been done to demonstrate that knowledge of the presence, severity, or change in RV adds any clinically useful information to spirometric measurements of FVC, slow VC, or inspiratory capacity (IC). The FVC or IC are much more easily measured as an index of physiologic improvement when the airflow limitation and thus the hyperinflation of severe COPD or asthma are successfully treated. The ATS/ERS 2005 PFT guidelines did not even attempt to define hyperinflation (perhaps a high RV/TLC), over-distention (perhaps a high TLC), trapped air volume (TAV, perhaps TLCbox minus VA), or “pendelluft” [Wanger 2005]. In addition, the upper limit of the normal range for RV/TLC and TAV are poorly established, since only one or two studies have ever measured spirometry, lung volumes, and DLCO from the healthy subset of a population-based sample of adults or children.

3) About 10% of patients referred to a large PFT lab have a true mixed pattern of airway obstruction and true restriction [Punjabi 1999]. Only about ten percent of patients with a “mixed pattern” on spirometry (obstruction and restriction) have a low TLC when measured by body plethysmography [Dykstra 1999]. These patients commonly have a restrictive disorder superimposed on asthma or COPD. In the other 9 of 10 cases, the low FVC was due to hyperinflation

(a high residual volume), caused either by asthma or COPD. The chest x-ray will also show hyperinflation, but not infiltrates in these cases.

In patients with moderate to very severe airway obstruction, the VA (single-breath TLC) indeed under-estimates the TLC as measured by body box or multi-breath washout or multi-breath dilution techniques [Punjabi 1999, Milite 2009]. The difference is called the trapped air volume (TAV) and is primarily due to emphysema (as determined by lung HRCT) [van der Lee 2006]. The more severe the obstruction, the larger is the TAV. Based on the severity of the obstruction (FEV1/FVC or FEV1 %predicted), a “correction” can be made to the VA which allows the TLC to be estimated [Punjabi 1999, Swanney 2004, Khalid 2011]. However, I fail to see the clinical value of using a calculation in an attempt to rule out true restriction (a mixed pattern). There are much better tests which will help with the differential diagnosis in such cases.

A mixed pattern can be categorized as restriction due to 1) a chest wall condition (kyphosis, scoliosis, pleural thickening or effusion, etc), or diaphragm weakness (neuromuscular disease or malnutrition), or severe obesity; or due to 2) interstitial lung disease, heart failure, or pneumonia. DLCO, MIP, and BNP tests should be used to differentiate between restriction due to these major categories. A normal DLCO makes a chest wall condition more likely to be the cause of the restriction. A low MIP (maximal inspiratory pressure) makes diaphragm weakness the more likely cause. A high B-naturetic protein (BNP) level makes heart failure the more likely cause of the superimposed restriction [Le Jemtel 2007, Guder 2012]. Diaphragm weakness due to malnutrition and mechanical disadvantage is common in very severe COPD and in heart failure due to sarcopenia. Lung HRCT, DLCO, MIP, and BNP tests will thus be more helpful for the differential diagnosis of patients with the pattern of airway obstruction, low FVC, and low VA (a mixed pattern) than will body box measurement of the TLC. When a lung HRCT is done, the TLC can be measured from the scans.

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5 How to optimize the quality and clinical value of DLCO tests.

The results of DLCO tests can be used for three types of medical decisions: 1) Helping to detect and diagnose a lung disease in patients with respiratory symptoms or an increased risk (and helping with the differential diagnosis), 2) Helping to determine the severity of a lung disease (degree of impairment and risk of morbidity and mortality), and 3) During follow-up, helping to determine if the previously diagnosed disease has progressed or has responded to treatment. The *quality* of the DLCO test is most important for the third clinical question (and for multi-center clinical trials), when the DLCO results from the follow-up exam (often months later) are compared to the results from the baseline exam.

When the patient is tested for the first time, the DLCO and VA results are compared to reference equations obtained from groups of healthy people. The predicted values and the lower limits of the normal range (LLN) are computed from the selected reference equations. The primary goal of this comparison is to minimize misclassification, that is to minimize the risk of a false positive or false negative interpretation of the results, since this could harm the patient.

An incorrect interpretation of PFT results can either cause unnecessary diagnostic procedures or treatment (due to a false positive diagnosis), or cause a delay in beneficial treatment (due to a false negative interpretation or incorrect differential diagnosis). For example, if the DLCO is falsely low, an expensive lung HRCT or cardiopulmonary exercise test may be ordered. Another example: if asthma is missed in an adult former smoker, the benefits of avoiding asthma triggers and inhaled corticosteroid therapy are delayed until the correct diagnosis is made later.

Start by selecting the best available DLCO and spirometry reference equations. In most cases, the GLI spirometry equations are the best since they included healthy people from many countries and ethnic/racial backgrounds and they cover the widest range of ages. The ATS and ERS only provided a list of DLCO studies, but did not suggest which one was the best. The GLI group is working on new and improved reference equations for DLCO and VA, but they will not be available for a couple of years. Meanwhile, for adults, I recommend the old DLCO and static lung volume reference equations from the study of Albert Miller and colleagues from a population sample of people in the state of Michigan [Miller 1983].

Configure your DLCO instrument to display and print the repeatability of FEV1, FVC, DLCO, and VA and print the test session quality grades (A-F). Tell your staff to perform additional test maneuvers when the repeatability is not good or when the quality grade is D or F. Use caution when interpreting results without an A or B quality grade.

Use the LLNs (not 80% predicted) when determining if results are abnormally low. This is a problem in many PFT labs [Manish 2012]. Do not use the KCO (DLCO/VA) when trying to detect interstitial lung disease (ILD) since half of the patients in large studies with an ILD confirmed by lung HRCT and biopsy have a normal KCO (but low DLCO) [van der Lee 2006, Fitting 2004, Wallaert 2012].

Individual DLCO instruments have been shown to drift over time. These studies included large hospital-based PFT labs with highly popular, expensive PFT systems [Jensen 2007]. While the ndd EasyOnePro was designed to be very accurate when compared to the Hans Rudolph DLCO

validation system, studies of the long-term accuracy of this relatively new instrument "in the field" (outpatient clinics) have not been published. For this reason, I recommend weekly biological control tests to determine if the instrument has drifted "out of control." The first 10-20 tests are used to establish a baseline and normal range for the biological control subject. Each week thereafter, the current result is compared to the baseline range. Such a quality assurance program is essential when using DLCO results to make baseline to follow-up comparisons (both in routine clinical practice and for clinical trials). The confidence interval of DLCO from the healthy biological control also informs the clinician how large of a change in DLCO is outside of the normal month to month variation (noise of measurement).

A DLCO validation system has been commercially available (from Hans Rudolph) for many years [Jensen 2003, Jensen 2007, Jensen 2009], but very few PFT labs use it routinely, so it is not practical for me to suggest that every outpatient clinic with an ndd EasyOnePro purchase and use one of these systems. However, large clinical trials using change in DLCO as a primary outcome measure do invest in a DLCO validator for each study site. This improves the statistical power to show small mean changes (treatment efficacy) between study groups [Wise 2007, Jensen 2009].

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