Tests of Lung Function: Physiological Principles and Interpretation

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Abstract

Gas exchange between organism and external ambient is the ultimate task of the respiratory system. Its efficiency is critically dependent on the efficiencies of ventilation and gas transport across the airspaces and lung tissues. Therefore, the knowledge of physiological principles underlying tests of lung function at different levels is basic to the understanding of the mechanisms limiting respiratory efficiency under different conditions, such as exercise and disease. The first step of lung function testing in clinical practice is spirometry, but it does not allow distinguishing the causes of airflow obstruction, i.e. airway disease versus emphysema, or establishing a diagnosis of lung restriction. Moreover, the effects of volume history and thoracic gas compressions may complicate its interpretation. Therefore, measurements of lung volumes are often necessary not only to confirm restriction in subjects with restrictive spirometric pattern but also for the assessment of lung hyperinflation. The latter may be due to either static (loss of elastic recoil) or dynamic (airflow limitation) mechanisms. The inhomogeneity of lung mechanics can be assessed by forced oscillations and/or nitrogen washout and may be more sensitive than spirometry to early obstruction of peripheral airways. The final step of lung function testing in clinical practice is the assessment of lung diffusing capacity for carbon monoxide. This test reflects the transport of gases from airspaces to blood across the alveolar-to-capillary barrier. Its interpretation is not always easy because the major resistance to carbon monoxide transfer is in the red cells rather than in the alveolar-to-capillary membrane.

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3.1 Introduction

In any animal species, life requires energy consumption, which is provided by oxygen (O_2) uptake from the external ambient, and carbon dioxide (CO_2) elimination. In mammals, the first step of this process takes place in the lung. During physical activity, metabolic requirements are manifold greater than at rest, thus requiring the respiratory system to increase rapidly its performance. Ventilation is the process of moving the air in and out of the lungs so that gas exchange can occur between the environmental air and the body. The efficiency of ventilation depends on the activity of respiratory muscles and the passive mechanical properties of the respiratory system, mainly stemming from its elastic and resistive structures. Gas exchange is the primary function of the lung and must be able to adapt to different life conditions, such as hypoxia or heavy exercise. The efficiency of gas exchange depends on the efficiency of ventilation, the surface and thickness of air-blood barrier, the magnitude of pulmonary blood flow and haemoglobin concentration ([Hb]).

This chapter will summarize the physiological principles underlying measurements of respiratory mechanics and gas exchange to provide practical keys for their interpretation in health and disease, at rest and on exercise.

3.2 Static Properties of Respiratory System

3.2.1 Subdivisions and Determinants of Lung Volumes

Total lung capacity (TLC) is the volume of air in the lungs at the end of a maximal inspiration and is determined by the static balance between the decreasing force of inspiratory muscles and the increasing inward *recoil of the respiratory system* ($P_{el,rs}$) [1]. In normal subjects at full lung inflation, the inward *recoil pressure of the lung* ($P_{el,L}$) largely exceeds the *recoil pressure of the chest wall* ($P_{el,cw}$), and the pressure–volume (P–V) curve of the lung but not the chest wall exhibits a plateau. Thus, the limit of TLC is represented by the passive characteristics of lung tissue, although elite breath-hold divers can inhale substantial amount of air beyond their normal TLC by *genioglossal insufflation* [2], a phenomenon in part accounted for by gas compression [3] and ability of their lungs to withstand transpulmonary pressure (P_{tp}) values much larger than normal. TLC does not vary substantially with ageing, likely because the decrease in $P_{el,L}$ is balanced by an increase in chest wall stiffness and/or a decrease of inspiratory muscle force [4], and does not change on exercise [5].

An increased TLC can be present in *chronic obstructive pulmonary disease* (COPD), when $P_{el,L}$ is reduced due to emphysema, but it may also occur during severe asthma attacks [6], though the mechanism for this is not clear. A decrease of TLC is the gold standard for the diagnosis of *restrictive disorders*, which can be due to an increase of $P_{el,L}$, or volume shrinkage, or inspiratory muscle weakness [7]. These mechanisms to be distinguished would need measurement of $P_{el,L}$ and maximal inspiratory pressure.

Residual volume (RV) is the volume of air remaining in the lungs after a maximal expiration. In young healthy subjects, its determinant is the static balance between the decreasing force of expiratory muscles and the increasing outward $P_{el,cw}$ [8]. In older subjects and obstructive disorders, this static balance cannot be achieved because airway closure or extreme flow limitation occurs during expiration. The RV/TLC ratio was originally proposed as an index of emphysema, but it may also increase in non-emphysematous air trapping or even in restrictive disorders if RV is proportionally less reduced than TLC.

Vital capacity (VC) is the maximum volume of air that one can mobilize with a single manoeuvre; thus it is the difference between TLC and RV. In young healthy subjects, it is statically determined but in older subjects and obstructive disorders may be limited by the same dynamic mechanism as RV. VC was the first lung volume used clinically [9], and its reduction has been considered as a sign of respiratory disease with prognostic value. A decrease of VC may result from a decrease in TLC or an increase in RV, thus not allowing differentiate between restrictive and obstructive abnormalities [10].

Functional residual capacity (FRC) is the volume of gas remaining in the lungs at the end of a relaxed expiration. In healthy subjects breathing quietly, it is determined by the static balance between the inward $P_{el,L}$ and the outward $P_{el,cw}$ [1], thus corresponding to the *relaxation volume* (V_r) of the respiratory system. In healthy subjects, V_r depends on body position and external pressure acting on chest wall or abdomen. In restrictive disorders, V_r may decrease because of increased $P_{el,L}$ (pulmonary fibrosis, atelectasis, lung resection, alveolar oedema, cardiac diseases) or decreased outward $P_{el,cw}$ (pleural diseases, scoliosis, neuromuscular disorders, obesity) [11]. In obstructive disorders, V_r may increase because of reduced $P_{el,L}$ (emphysema), which defines *static lung hyperinflation*. In normal subjects, FRC is $<V_r$ when expiration is not relaxed but involves expiratory muscle activity, such as during exercise. In obstructive disorders, FRC may be $>V_r$ if expiratory time is reduced [12], or emptying time constant (resistance × compliance) is increased, or expiratory flow is limited during tidal expiration [13, 14]. FRC > V_r defines *dynamic lung hyperinflation*, which is associated with intrinsic positive end-expiratory pressure (PEEPi) [15] and is a major cause of dyspnoea either at rest or on exercise.

Inspiratory capacity (IC) is the maximum volume that can be inspired from the end of a tidal expiration and thus is the difference between FRC and TLC. It has been used as an indirect measure of changes in FRC under conditions where TLC can be assumed to remain constant, e.g. exercise [5] or acute pharmacological interventions [14].

3.2.2 Measurements of Lung Volumes

In vivo, FRC, RV and TLC are measurable by indirect methods only. The classic ones are *multiple-breath nitrogen washout* (MBN_2W), *multiple- or single-breath helium (He) dilution* and *body plethysmography*. Washout and dilution methods are based on the principle of the conservation of mass and measure only the amount of

gas that is present in lung regions communicating with open airways [16], provided corrections for N_2 eliminated from body tissues or He dissolved in blood during the tests are applied. Body plethysmography is based on Boyle's law and measures total thoracic gas volume, including regions possibly not communicating with open airways [17]. Radiographic techniques, either standard chest X-ray [18] or computed tomography (CT) [19], provide measurements of lung volumes close to body plethysmography. In healthy subjects and in restrictive abnormalities, all methods give similar results. In severely obstructed subjects, owing to some regions with time constants indistinguishable from those of tissues, the dilution methods may underestimate FRC and TLC [20, 21], whereas plethysmography tends to overestimate them because changes in mouth and airway pressures may differ substantially during panting [22].

3.3 Dynamic Properties of the Respiratory System

3.3.1 Tidal Breathing

Tidal volume (V_T) is the volume of air inspired and expired per breath. In healthy subjects, the size of V_T is regulated by switching off inspiration before end-tidal inspiratory volume achieves the flat part of P–V curve and terminating expiration when V_r is passively achieved [23]. At rest, normal tidal expiration is slightly longer than inspiration, due to braking effects of glottis narrowing and post-inspiratory activity of inspiratory muscles [23]. In obstructive disorders, the difference between inspiratory and expiratory times increases because of the slow emptying time constant [7]. During exercise, V_T increases mostly by increasing end-inspiratory lung volume but also by decreasing FRC, thus maintaining the operative volume over the linear part of P–V curve and limiting the increased work of breathing [5]. The interest of measuring V_T is restricted to exercise and in ventilated patients.

Work of breathing (WOB) is the product of changes in driving pressure and V_T, which is the energy expenditure to move air in and out of the lungs. In healthy subjects breathing quietly, inspiration requires work by inspiratory muscles to overcome the $P_{el,rs}$ and, to lesser extent, the resistance to airflow $\left(\dot{V}\right)$, whereas expiration is passive, thus requiring no work by expiratory muscles [23]. During exercise, the elastic WOB increases proportionally to V_T and the resistive WOB proportionally to $\dot{V}$ [5]. In restrictive disorders, the elastic WOB increases on inspiration because of the increase of $P_{el,rs}$. In obstructive disorders with dynamic lung hyperinflation, the elastic WOB also increases because the respiratory system operates in the upper part of the P–V curve, where $P_{el,L}$ is large, and additional pressure may be required to overcome PEEPi. In severe airflow obstruction, also resistive WOB may increase, particularly when expiration is completed by the activity of expiratory muscles. Thus, irrespective of the underlying mechanisms, the WOB may increase in both restrictive and obstructive disorders [23].

Respiratory system resistance (R_{rs}) is the sum of all pressures dissipated across airway, lung parenchyma and chest wall divided by $\dot{V}$. R_{rs} can be measured by

superimposing high-frequency forced oscillations to tidal breathing [24]. In healthy subjects, R_{rs} is independent of oscillation frequency, whereas in subjects with obstructive disorders is increased at low frequencies and decreases at high frequencies. Modelling studies have suggested that such a frequency dependence is due to central airway resistance dominating at high frequencies with inhomogeneity and peripheral resistance dominating at low frequencies. This method also provides the reactance of the respiratory system (X_{rs}), which reflects gas compliance at low frequency and gas inertance at high frequencies. X_{rs} is negative at low frequencies and more so in the presence of reduced lung volume (e.g. restrictive disorders) or ventilation inhomogeneity (e.g. obstructive disorders). Moreover, a more negative X_{rs} on expiration than inspiration is suggestive of EFL [25, 26].

Airway resistance (R_{aw}) is the ratio of alveolar-to-mouth pressure difference and $\dot{V}$. During tidal breathing, most of R_{aw} is in the upper airways [27] with large intra- and interindividual variability, likely due to anatomical differences. The contribution of larynx to R_{aw} is greater on expiration than inspiration, because its calibre increases during the latter. R_{aw} can be measured by body plethysmography [17] or interruptor technique [28]. With the former, changes of alveolar pressure (PA) are assumed to be equal to changes in box volume or pressure, and laryngeal resistance can be minimized by panting, during which vocal cords are maximally abducted. With the latter, PA is assumed to be equal to the mouth pressure drop following a rapid airway occlusion, which may not be fully true because of damping in lung and chest wall tissues. In healthy subjects, R_{aw} is virtually independent of breathing frequency but highly dependent on lung volume, because the calibre of intraparenchymal airways varies approximately with the cube root of volume and the resistance to laminar $\dot{V}$ is inversely related to the fourth power of airway radius [29]. The inverse of R_{aw}, i.e. airway conductance (G_{aw}), increases linearly with lung volume; thus specific airway conductance ($sG_{aw} = sG_{aw}/FRC$) is a reasonable correction for lung volume.

Pulmonary resistance (R_L) is the ratio of P_{tp} to $\dot{V}$ and includes R_{aw} and tissue resistance (R_{ti}). P_{tp} can be measured by an oesophageal balloon and R_L derived from the classic equation of motion [23]. R_L decreases with breathing frequency, due to the frequency dependence of R_{ti}, and lung volume, due to the volume dependence of R_{aw} [29]. The contribution of peripheral R_{aw} to total R_L is 25–30% in healthy subjects and 50–60% in COPD [30]. The use of R_L for clinical purposes is limited.

3.3.2 Forced Manoeuvres

Forced expiration was introduced in 1947 by Tiffeneau and Pinelli [31] and has become the mainstay of pulmonary function testing. Studies on the relationships between flow, volume and pressure showed that most of forced expiratory manoeuvre is effort independent [32], thus confirming its validity as a test of lung function.

Expiratory flow limitation (*EFL)* is a phenomenon occurring during forced expiration in all mammals' lungs, either healthy or diseased. Its evidence stems from the

observation that, at lung volumes <75% of VC, forced expiratory $\dot{V}$ increases with pressure up to a point above which it cannot further increase with increasing effort [32, 33]. EFL, initially explained with waterfall analogy [34] and equal-pressure point theory [35], was subsequently enlightened by the *wave-speed theory* [36]. Briefly, because airways are collapsible tubes, the maximum expiratory $\dot{V}$ $\left(\dot{V}_{\mathrm{E}}\ \max\right)$, at a given point of each airway, is determined by cross-sectional area (A), wall elastance ($E = \Delta P/\Delta A$) and gas density (ρ):

$$\dot{V}_{\mathrm{E}}\ \max/\ A = \left(\frac{A}{\rho}\cdot\frac{\Delta P}{\Delta A}\right)^{1/2}$$

The point at which this phenomenon occurs along the airways is called *choke point*. Because P is a function of lung volume and P_{L}, the choke point moves from the trachea at high lung volume down the bronchial tree as the lung empties during forced expiration and progressively to the more compliant peripheral airways. For this reason, $\dot{V}_{\mathrm{E}}\ \max$ at mid-to-low lung volumes was proposed as more sensitive than the usual spirometric indices for early detection of *small airway disease*. However, their clinical usefulness is not demonstrated [37]. Moreover, $\dot{V}_{E}\ \max$ can be equally reduced whether P is decreased due to frictional losses upstream from the limiting segment (small-airway obstruction) or loss of $P_{\mathrm{el,L}}$ (emphysema), which makes it impossible to separate the mechanisms of EFL by simple spirometry. Because of the inverse relationship between $\dot{V}_{\mathrm{E}}\ \max$ and ρ, breathing a low-density mixture, e.g. 80% He and 20% O_2, can increase $\dot{V}_{\mathrm{E}}\ \max$ at high-to-mid lung volumes, when the flow-limiting segment is in the large airways where P drops due to convective acceleration and turbulent flow. A reduction of density dependence was thus proposed as a sign of obstruction of peripheral airways, where $\dot{V}$ is laminar and viscosity-dependent [38]. However, unaltered density dependence was observed in severe COPD [39], possibly because it reflects more the ratio of lung volume to central airway calibre rather than the latter by itself [40].

Effects of volume history and thoracic gas compression occur during forced expiration manoeuvre and may profoundly influence spirometric measurements (Fig. 3.1). *First*, full lung inflation to TLC may cause transient changes of airway calibre, namely, *bronchodilation during induced bronchoconstriction* [41] and *bronchoconstriction during spontaneous asthma* [42] or *COPD* [43]. *Second*, because of EFL and gas compression, changes in expired volume lag true changes in lung volume. This effect, which can be shown by plotting $\dot{V}_{\mathrm{E}}\ \max$ measured at the mouth against expired or plethysmographic volume, is small in healthy subjects but may be large when R_{aw} and lung volume are increased [44] and may amplify changes in airway calibre [45]. Because of these effects, the forced expiratory

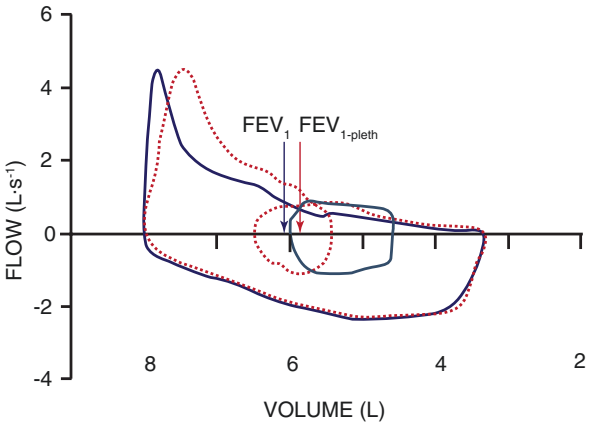

Fig. 3.1 Representative tidal and maximal flow-volume curves in emphysema. Flow is plotted against expired volume (*continuous line*) or thoracic volume measured by plethysmography (*dotted line*). Forced expiratory volume in 1 s measured by plethysmography ($FEV_{1\text{-pleth}}$) is larger than at the mouth (FEV_1). Note that tidal expiratory flow exceeds forced expiratory flow when plotted against expired but not against thoracic volume

volume in 1 s (FEV_1) may either overestimate or underestimate the degree of airway narrowing and drug-induced changes.

EFL and tidal breathing. Normally, tidal breathing requires a $\dot{V}$ much less than $\dot{V}\,\max$, even on exercise. Only in extremely fit athletes and in subjects affected by respiratory diseases, tidal $\dot{V}_E$ may impinge on $\dot{V}_E\,\max$, suggesting breathing under EFL conditions, though this finding may be in part due to volume history and gas compression. Thus, the gold standard for identifying EFL during tidal breathing is by showing no increase in tidal $\dot{V}_E$ with increasing intrapleural pressure (P_{pl}). Alternative non-invasive methods proposed for identification of EFL during tidal breathing void of volume history and gas compression effects include the comparison of tidal and submaximal $\dot{V}_E$ obtained voluntarily [46] or by manual compression of the abdominal wall [47], application of expiratory negative pressure at mouth [48], interrupt or technique [49] and reduction of X_{rs} during expiration [25, 26]. For practical purposes, owing to the association between EFL and dynamic lung hyperinflation [46], changes in FRC or IC following bronchodynamic interventions (e.g. bronchial challenge or reversibility test) or during exercise may be taken as suggestive of tidal EFL.

Forced inspiration is mostly dependent on the force of inspiratory muscles and their shortening velocity. At 50% of FVC, inspiratory $\dot{V}\,\max$ slightly exceeds $\dot{V}_E\,\max$ in normal subjects; it is reduced more than $\dot{V}_E\,\max$ in case of variable extrathoracic obstruction and similarly decreased in fixed obstruction [50].

3.4 Distribution of Ventilation and Pulmonary Gas Exchange

In healthy lungs, each tidal inspiration (~500 mL) at rest brings a column of fresh air by convection into the acinus and by convection plus diffusion up to the entrance of alveolar ducts [51]. Airflow velocity falls from ~1 m· s^{-1} in the trachea to <1 cm· s^{-1} in the first order respiratory bronchioles because the airway total cross-sectional area increases with every generation. In exercise, flow velocities are up to ten times greater, in proportion to the increased ventilation ($\dot{V}$).

At FRC, there is a gradient of lung expansion from gravity-dependent to nondependent lung regions. On expiration to RV, the former reach their minimum volume before the latter. This phenomenon is due to regional gravity-dependent *small-airway closure* and is more prominent in the elderly [52] and in the early phase of COPD due to the decline of $P_{el,L}$ [53]. Non-uniform alveolar $\dot{V}$ ($\dot{V}_A$) has physiological and clinical significance, both intrinsically (gas mixing inefficiency) and because the distribution of $\dot{V}_A$ is a determinant of ventilation-to-perfusion ratio ($\dot{V}_A / \dot{Q}$).

3.4.1 Measurements of Ventilation Heterogeneity

Single-breath N_2 washout (SBN$_2$W) is a simple test requiring an inspiration of 100% O_2 from RV to TLC followed by a slow expiration to RV [53, 54]. The resulting percentage change in N_2 concentration versus expired volume curve ([ΔN_2]%·L^{-1}) has four phases with *phase I* representing the N_2-free anatomic dead space, *phase II* the fast rising [N_2] from the transition zone between airways and alveolar space, *phase III* the slowly rising [N_2] from alveolar space and *phase IV* a sharp increase of [N_2] from apical zones. The slope of phase III (S_{III}) is in large part gravity-independent [55] and considered to reflect uneven emptying of adjacent lung regions, possibly at small-airway level [56]. By contrast, phase IV represents the closing volume (CV) of gravity-dependent lung regions. The CV is of physiological interest but not particularly useful for clinical practice [57], and the transition from phase III to IV is often not detectable in obstructed patients.

Multiple-breath N_2 washout (MBN$_2$W) was first introduced in 1940 to measure FRC [58]. However, more information than just FRC can be derived from the analysis of N_2 exponential decay curve. In particular, the volume of pure O_2 that must be breathed in order to lower expired [N_2] to 1/40th of initial value is a simple parameter describing gas mixing efficiency [59]. Correcting for lung size using FRC allows derivation of the *lung clearance index* (LCI) [60], which, despite its wide biological variability [61], has been shown to be more sensitive than spirometry or airflow resistance measurements in detecting lung function abnormalities in children with cystic fibrosis [62]. A major advance in the field was the introduction of the analysis of S_{III} of the first 20 breaths of MBN$_2$W [63]. This approach has the advantages over the SBN$_2$W of distinguishing convective-dependent inhomogeneity at airway branching points proximal to the entrance to the acinus from diffusive-convective-dependent inhomogeneity located within or between acini [64].

3.4.2 Alveolar-to-Capillary Gas Exchange

The sandwich of tissues separating the alveolar spaces from blood in the lung must be crossed bidirectionally by O_2 and CO_2 passive molecular diffusion. The diffusive resistance offered by alveolar-capillary membrane is very small, largely because this is exceedingly thin, i.e. a fraction of μm on average, and extremely large, i.e. ~50–150 m^2 [65]. However, the diffusive resistance to O_2 uptake may become measurable under various conditions leading to *diffusion limitation* of alveolar gas exchange and arterial hypoxemia. In clinical practice, carbon monoxide (CO) instead of O_2 is used for measurements of lung diffusing capacity (DL_{CO}) owing to its very high capacitance coefficient (β) and low (<3) $D/\left(\dot{Q}\beta\right)$ ratio [66]. A value of alveolar-capillary O_2 transfer can be, therefore, calculated based on a DL_{O_2}/DL_{CO} ratio of ~1.61 [67]. Basically, DL_{CO} measures surface area and thickness of the air-blood barrier available for gas exchange. In health, it represents the *upper bound* value for alveolar-capillary gas exchange. CO entering pulmonary capillary blood binds to the haem group of circulating Hb as COHb at an extremely low and unmeasurable capillary partial pressure. Hence, CO uptake is independent of pulmonary $\dot{Q}$ but critically dependent on capillary blood volume and [Hb] [68].

Single-breath DL_{CO} is used in clinical laboratories, with a breath-hold time of 9–11 s at maximal inspiration (~TLC). This technique was originally described by Marie Krogh in 1915 [69] and subsequently modified with the addition of He as marker inert gas [70]. Its technical standards [71] and reference values [72] have been recently updated. In brief, both CO and the relevant marker gas (He or CH_4) mix immediately after inhalation with the gas resident in the lung at ~RV. During the subsequent breath-hold at TLC, CO is taken up from the alveoli, but He and CH_4 are not. Therefore, the [He] or [CH_4] in alveolar gas on expiration can be back-extrapolated to the effective time zero and to the initial alveolar [CO] before uptake has occurred. DL_{CO} is, then, obtained as follows:

$$DL_{CO} = k_{CO} \cdot V_A$$

where k_{CO} is the rate constant of CO alveolar uptake during the breath-hold and V_A the alveolar volume, i.e. the maximal lung volume available for dilution to inhaled CO and He or CH_4 [73]. Because the measurement is made at full lung inflation, V_A is in the presence of low gas phase resistance within 5–10% of TLC measured by plethysmography. K_{CO} is the transfer factor per unit alveolar volume and mathematically equal to DL_{CO}/V_A but is not DL_{CO} corrected for lung volume because K_{CO} is actually the rate constant k_{CO} normalized to barometric pressure. Thus, K_{CO} is better regarded as the transfer factor per alveolus or per acinus, representing the efficiency of the CO alveolar uptake [73]. Single-breath DL_{CO} is measured during an unphysiological manoeuvre (breath-holding at ~TLC), but this has the advantages of (*a)* a "reproducible" lung volume and (*b)* optimization of the test gas distribution. However, the latter condition is hardly ever achieved in the presence of airflow

obstruction where the distribution of test gases to peripheral gas-exchange units is variably compromised. Thus, in COPD patients V_A is often severely underestimated, and DL_{CO} may be considered the *lower bound* value of effective pulmonary gas exchange [73].

3.4.3 Subcomponents of Lung Diffusing Capacity

Anatomically, the blood-gas barrier encompasses the surfactant lining layer, alveolar epithelium, interstitium, capillary endothelium, plasma, erythrocyte plasmalemma and the Hb molecule within erythrocytes [65].

Two-step PA_{O_2} method. In 1957, Roughton and Forster [74] found that, owing to competitive binding between CO and O_2 for Hb-accessible sites, DL_{CO} fell systematically when O_2 alveolar partial pressure (PA_{O_2}) was increased. According to their method, the DL_{CO} measured at PA_{O_2} of 100 and 500 mmHg, respectively, may be graphically partitioned into two resistances arranged in series as follows:

$$\frac{1}{DL_{CO}} = \frac{1}{DM_{CO}} + \frac{1}{\vartheta_{CO} \cdot Vc}$$

where DM_{CO} represents the membrane diffusive conductance for CO, ϑ_{CO} is the rate of reaction of CO with deoxy-Hb in the red blood cell and Vc is the pulmonary capillary blood volume. The latter two subcomponents constitute the *erythrocyte conductance* (De_{CO}) which is the *reactive* or O_2-dependent part of the transfer resistance. Following this approach, both $DM_{CO}$and De_{CO} are estimated to be ~50% each at rest and ~80% and ~122%, respectively, on exercise [75]. However, nonlinearity of the $1/\vartheta_{CO}$- PA_{O_2} relationship could lead to an overestimation of the zero PA_{O_2} *y*-intercept and underestimation of DM_{CO} suggesting that 75–80% of the transfer resistance is due to $1/De_{CO}$, which is in accordance with calculations based on morphometric data [65].

Simultaneous uptake of nitric oxide (NO) and CO. This method takes advantage of the extremely rapid and greater than CO chemical combination of NO with Hb [76] to solve the Roughton-Forster equation with a single manoeuvre [77, 78]. DL_{NO} approximates the morphometric value of DL_{O_2} [65], whereas the DL_{NO}/DL_{CO} ratio is ranging from 4.3 to 5.3 [77, 78]. Although it was demonstrated that there is a *significant* $1/De_{NO}$ [79], peri- and intraerythrocyte resistance to NO uptake is negligible as compared to CO, and DL_{NO} can be regarded operationally as a surrogate for DM_{NO} [80].

3.5 Interpretative Strategies

Clinical practice recommendations jointly published by the American Thoracic Society and the European Respiratory Society provide a flowchart to assess spirometry, lung volumes and DL_{CO} results [81]. The interpretation of pulmonary function

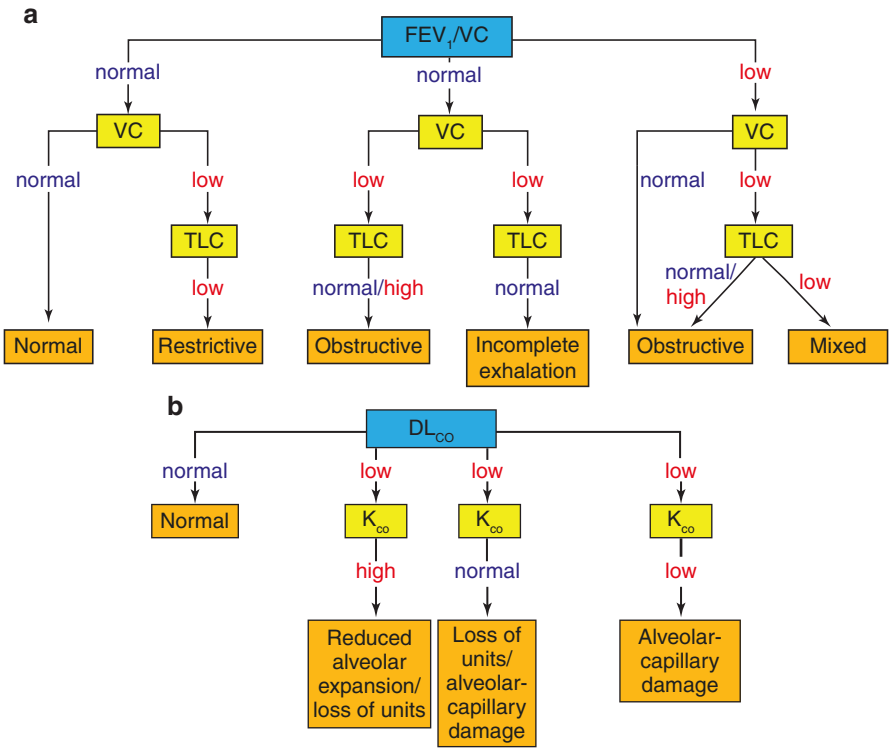

Fig. 3.2 Simplified interpretative algorithms for spirometry and lung volumes (Panel a), and lung diffusing capacity (Panel b) in clinical practice. FEV_1, forced expiratory volume in 1 s; VC, vital capacity, TLC, total lung capacity, DL_{CO}, lung diffusing capacity for carbon monoxide adjusted for effective [Hb], K_{CO}, carbon monoxide transfer factor per unit alveolar volume (DL_{CO}/V_A)

tests is based on the comparison of measurements with the reference values of healthy people of the same sex, age and height.

Spirometry and lung volumes are the first step in the interpretation of pulmonary function tests (Fig. 3.2, panel a), starting from the *FEV_1/VC ratio*. If this is normal and VC is below the fifth percentile of the normal distribution (LLN), then *restriction* may be suspected, but it requires to be confirmed by a reduction of TLC. Otherwise, the reduction of VC may be the result of an increase in RV, due to either *air trapping* (early obstruction) or *reduced force of expiratory muscles*. If FEV_1/VC is <LLN, then *airflow obstruction* is present but may be associated with either normal or reduced VC. When the latter is the case, measurement of TLC is required to say whether the reduced VC is due to air trapping or a *mixed obstructive-restrictive* abnormality. A reversibility test with an inhaled bronchodilator may help distinguish between *fully reversible* (generally present in asthma) and *fixed* (generally present in COPD) airflow obstruction. However, a partial response does not allow to differentiate between asthma and COPD or predict the efficacy of long-term bronchodilator treatment [81].

DL_{CO} is the final step in the interpretation of pulmonary function tests (Fig. 3.2, panel b). Because the DL_{CO} is the product of the K_{CO} and V_A, its final value can result from a number of combinations of both K_{CO} and V_A, each pattern being associated with a different pathological process. With *normal or increased* DL_{CO}, the *increment of* K_{CO} observed on exercise may be due to the pulmonary $\dot{Q}$-driven increase of Vc and Vc/V_A [82]. On the other hand, a *reduced* DL_{CO} with a K_{CO} *substantially increased* may be seen with a low (e.g. <0.85) V_A/TLC ratio and results from *reduced alveolar expansion* with decreased DM_{CO}, unchanged Vc and increased Vc/V_A. Alternatively, a *low* DL_{CO} *with normal or moderately increased* K_{CO} may be due to localized loss of alveolar units in both lungs or after lung resection, i.e. *loss of lung units* with all subcomponents increased. Because K_{CO} is a measure of alveolar-capillary integrity, a mutual *decrement of both* DL_{CO} *and* K_{CO} is observed in emphysema, pulmonary fibrosis and microvascular damage [73]. The relevant interrelationships between V_A and K_{CO} and with the different diffusion components and subcomponents are shown in Fig. 3.3.

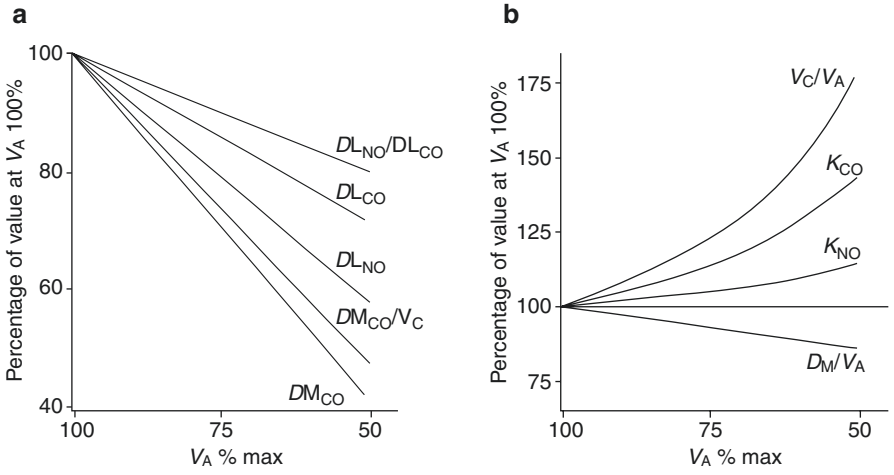

Fig. 3.3 Plots of (**a**) lung diffusing capacity for nitric oxide (DL_{NO}) and carbon monoxide (DL_{CO}), their ratio (DL_{NO}/DL_{CO}), alveolar-capillary membrane diffusing capacity for CO (DM_{CO}) and the DM_{CO} to pulmonary capillary blood volume (Vc) ratio (DM_{CO}/Vc), as they relate to the percentage of maximal alveolar volume (V_A) (*x*-axis) compared to their percentage value at maximal V_A (*y*-axis) and (**b**) rates of alveolar uptake for NO and CO per unit time and pressure, K_{NO} and K_{CO} (mathematically equivalent to DL_{NO}/V_A and DL_{CO}/V_A,respectively) and DM and Vc, both per unit V_A (DM/V_A and Vc/V_A), as the expansion of the lung is changed voluntarily in normal subjects (100% of maximal V_A, which is approximately TLC, and 50% of maximal V_A, which is approximately FRC). Note in (**a**) that with diminishing lung expansion (ΔV_A), ΔDL_{NO} is better related to DM_{CO} (ΔDM_{CO}) and $\Delta DM_{CO}/Vc$ change than the DL_{CO} change. In (**b**), ΔK_{CO} is a better reflection of changes in the pulmonary microcirculation (Vc/V_A) than the K_{NO}; decrease of DM/V_A with ΔV_A suggests *isotropic change* as alveolar dimensions reduce with concomitant thickening of the alveolar-capillary membrane. Reproduced with permission of the © ERS 2018: *European Respiratory Journal Feb 2017, 49 (2) 1600962; DOI:* https://doi.org/10.1183/13993003.00962-2016

General recommendations. For each parameter, the 90% confidence interval represents the normal range. Fixed ratios, such as FEV_1/VC of 0.70 and 80% of predicted, should not be assumed as lower limits of normal, because they are age- and sex-biased, thus causing underdiagnosis in young and female subjects but overdiagnosis in old and male subjects.

Key Points

- Static lung volumes are regulated by the elastic properties of the lung and chest wall.
- Static lung hyperinflation is defined as an increase in relaxation volume of the respiratory system, generally due to loss of lung elastic recoil (emphysema).
- Dynamic lung hyperinflation is defined as an end-tidal expiratory volume above the relaxation volume and is generally due to expiratory flow limitation.
- Expiratory flow limitation occurs during forced expiration in both healthy and diseased subjects, though at different levels.
- Spirometry generally allows detecting obstructive disorders, whereas measurements of lung volumes are necessary to confirm lung restriction.
- Forced inspiratory flow can help identify extrathoracic or fixed airflow obstruction.
- No parameter from forced expiratory manoeuvre is specific for small airway function.
- Ventilation inhomogeneity is present in normal lungs but is much greater in lung disease.
- The uptake of carbon monoxide is largely dependent on pulmonary microcirculation.
- Lung diffusing capacity is the result of various combinations of carbon monoxide uptake, and alveolar volume; thus correction for lung volume is not reliable.

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