Transfer factor of the lung for carbon monoxide: what is the significance of an abnormal result?

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An abnormal T_{LCO} value is predictive of survival https://bit.ly/2RmgCXF

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Introduction

In respiratory publications, there is a distinction between articles focusing on pathogenesis, which is linked to diagnosis, and those dealing with function, which is important for treatment. In the COVID-19 pandemic, an understanding of viral structure and replication underpinned the development of vaccines; on the other hand, the monitoring of pulmonary function was essential for deciding oxygen requirements and the need for ventilatory assistance. The study published in this issue of the *European Respiratory Journal* by Miller and Cooper [1] deals with pulmonary function testing, and with one test in particular, one of the most important, namely the carbon monoxide transfer factor (T_{LCO}). The authors address an apparently simple problem: how to grade an abnormal T_{LCO} in terms of severity, with its implications for survival.

What is a normal value for T_{LCO}?

The T_{LCO}, measured by the single breath and breath holding method, was introduced as a clinical measurement more than 60 years ago [2] but, surprisingly, no comprehensive reference equations emerged until 2017 [3]. Earlier regression equations were based on relatively small studies from single laboratories, some of which included smokers. T_{LCO} guidelines and technical reports from 1993–2017 [4–7] always acknowledged that a definitive study needed to be done. The definitive study, part of the Global Lung Function Initiative (GLI) [3], was based on 12 660 asymptomatic lifetime non-smokers from 19 centres in 14 countries. Regression equations were developed from age 5 to 85 years to predict T_{LCO} and its components, K_{CO} and alveolar volume (V_A). Though not perfect (see later), this study was a significant step forward in clinical T_{LCO} assessment. Miller and Cooper [1] found that the GLI study [3] was the most suitable for their purpose, that of grading T_{LCO} values in relation to survival, although they did try other authors' equations. Amazingly, their analysis [1] turned up impossibly low T_{LCO} z-scores (z is the number of standard deviations the measured T_{LCO} differs from the predicted T_{LCO}) in many older women. The authors of the GLI study [3] admitted an error in sex assignment in one of their 19 sources, and their revised predictions can be accessed [8]. The 2017 GLI predictions for T_{LCO} [3] were about 15% lower than earlier reference equations (from 1969 to 1993), but the difference was less (about −8%) *versus* more recent studies (from 2008 to 2015).

T_{LCO} variables: age, sex and stature

The single breath measurement of T_{LCO} is the product of two measurements [9]: the rate of uptake of CO from alveolar gas, expressed as a slope *versus* time, *i.e.* a rate constant, k_{CO}, with units time^{-1}, and the volume of alveolar gas (V_A) accessed by the inhaled CO. Since the measurement is made during breath holding at full inflation, V_A in healthy subjects approximates to total lung capacity (TLC). $T_{LCO}=V_A \times K_{CO}$, where K_{CO} is k_{CO} per unit barometric pressure (minus water vapour pressure at 37°C). The between-subject coefficient of variance (COV), as standard deviation of the estimate/predicted mean, is 13–15% over the whole age range [3]. The major influences on the T_{LCO} measurement in healthy populations, as reflected in regression equations, are age, sex and height; only age is an important predictor for K_{CO}, and only sex and height for V_A. Minor influences are body weight, physical activity (related to fitness), living at altitude and a history of smoking. Modern regression equations exclude those with a history of smoking.

T_{LCO} variables: ethnic origin

Although 15% of the GLI subjects were of non-European ancestry, the GLI study [3] unaccountably did not provide any equations for ethnicity other than European ancestry. Since 10.4% of MILLER and COOPER [1]'s subjects were of non-European ancestry origin, ensuring these patients had appropriate reference values was a matter that these authors had to address. T_{LCO} has been measured in 32 sub-Saharan Africans and 32 European Caucasians, matched for age, sex and height [10]. T_{LCO} was, on average, 13% lower in those of African descent, caused by a lower V_A per unit standing height, related to a lower sitting to standing height ratio in Africans. There was no significant ethnic difference in K_{CO}, which is consistent with the minimal effect of height on K_{CO} in the GLI study [3]. In a GLI study of multi-ethnic reference values for spirometry, QUANJER *et al.* [11] found that height-adjusted forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were 14.4–15.7% less for Afro-American and South-East Asian females (12.3–15.5% less in males). On the basis that T_{LCO} ethnic differences are related to V_A and not K_{CO} differences, and that V_A differences will mirror FVC differences, MILLER and COOPER [1] quite reasonably applied the appropriate ethnicity-specific GLI [11] coefficients for FVC to the T_{LCO} of their non-European subjects. These "ethnically appropriate" reference values largely eliminated the under-representation of non-Europeans among those with T_{LCO} values above normal (z-scores 0 to +10.0); MILLER and COOPER [1] argued that the distribution of high-normal T_{LCO} values should not *a priori* differ between Europeans and those of non-European ancestry who were living in the same vicinity.

Quantifying a low T_{LCO} measurement

Traditionally, pulmonary function test results have been reported as a percentage of the predicted value (PP) for a given age, sex and height. The lower limit of normal is set arbitrarily at 80 PP. Even when related to age, sex and height, PP is not scientifically valid as it takes no account of the COV in the regression equation for predicting T_{LCO} [4, 12]. The lower limit of normal (LLN) in statistical terms is 1.645 RSDs below the predicted value, where RSD is the residual standard deviation around the population mean for a particular age, sex, height and ethnic origin. 95% of a healthy population will have a T_{LCO} value greater than the LLN, and 5% will have a value >ULN. RSDs are now referred to as z-scores. The LLN is usually less than a PP of 80%, and is age dependent, as is the COV or RSD (table 1). PP is also less sensitive than z-scores. In table 1, a three-fold deterioration in T_{LCO} z-scores (from −1.645 to −4.62) leads to a less than two-fold reduction in PP at age 40 years (from 79 PP to 41 PP). For T_{LCO}, PP tracks the z-score fairly closely (tables 1 and 2), but there are important discrepancies. For example, in table 2, a 70 year old with T_{LCO} 26 PP has a better predicted survival (moderate severity) than a 40 year old with *T*LCO 33 PP (in the severe category). The use of PP (% predicted) cannot be recommended.

Grading a low T_{LCO} measurement

Obviously, the greater the deficit in pulmonary function, whether as FEV_1 or T_{LCO}, in terms of z-scores or PP, the greater will be the impairment in the ability to perform physical work or to lead a normal active life. Ultimately, it is survival which is critical; many studies have shown that impairment of ventilatory function (for which FEV_1 is usually chosen [13]) or gas exchange potential (T_{LCO} being the marker [14]) correlates with an increased risk of early death compared to those with normal pulmonary function. Thus, MILLER and COOPER [1] chose survival as a yardstick for establishing severity categories for a low T_{LCO} value. Pulmonary results from 13 829 patients seen at Queen Elizabeth University Hospital, Birmingham, UK over the period 1996–2016 were examined. Survival up to the end date (2016) and the clinical reason for referral were noted. Neither the cause of death nor a specific respiratory diagnosis was known.

TABLE 1 Global Lung Function Initiative (GLI) predictions [3, 8] in a representative female (F), height 165 cm, at age 40 and 70 years

	A: T_{LCO} pred mmol·min^{-1}·kPa^{-1}	B: T_{LCO} RSD mmol·min^{-1}·kPa^{-1}	C: T_{LCO} (z=−1.645) mmol·min^{-1}·kPa^{-1}	D: T_{LCO} (z=−1.645) PP	E: T_{LCO} (z=−4.62) mmol·min^{-1}·kPa^{-1}	F: T_{LCO} (z=−4.62) PP
F: 40 years, 165 cm	7.37	0.94	5.83	79	3.03	41
F: 70 years, 165 cm	6.51	0.98	4.9	75	1.98	30

Predicted values shown for carbon monoxide transfer factor (T_{LCO}) (column A), 1 residual standard deviation (1 RSD) of the prediction (column B), a measurement of T_{LCO} and its % of predicted normal (PP) at z-scores −1.645, equivalent to lower limit of normal (LLN) (columns C and D), and −4.62, equivalent to LLN x 3 (columns E and F). All columns show an age dependency.

TABLE 2 Global Lung Function Initiative (GLI) predictions for carbon monoxide transfer factor (T_{LCO}) [3, 8] in a representative male, height 175 cm, at age 40 and 70 years

Age 40 years (T_{LCO} predicted 10.11 mmol·min^{-1}·kPa^{-1})		Age 70 years (T_{LCO} predicted 8.4 mmol·min^{-1}·kPa^{-1})		Age 40 or 70 years			
T_{LCO} mmol·min^{-1}·kPa^{-1}	T_{LCO} PP	T_{LCO} mmol·min^{-1}·kPa^{-1}	T_{LCO} PP	T_{LCO} z-scores	Hazard ratio	Severity category [1]	Chance of death *versus* control %
8.75	87	7.05	84	−1.0	1.0	Normal	50
6.7	66	5.03	60	−2.5	2.0	Mild	67
4.67	46	2.63	26	−4.0	3.4	Moderate	77
3.31	33	0.98	12	−5.5	6.6	Severe	87

Predicted values shown for z-scores from −1.0 to −5.5 (arbitrarily chosen to fall within each of the four severity categories) with % predicted (PP), hazard ratios, severity category according to Miller and Cooper [1] and chance of death *versus* a control population.

Previous studies [7] had proposed six categories of airflow obstruction in terms of PP FEV_1 or FEV_1/FVC, from no obstruction (PP >80) to mild (PP >70) through moderately severe (PP 50–59) to very severe (PP <35). Quanjer *et al.* [15] substituted z-scores for each of the above PP categories, z-score >−1.645 (no obstruction), ⩾−2.0 (mild), <−3.0 and ⩾−2.5 (moderately severe), to <−4.0 (very severe), respectively to remove the age bias (table 1). Miller and Cooper [1] linked T_{LCO} z-scores and T_{LCO} PP to survival on the basis of hazard ratios, where a hazard ratio of 2.0 means that a T_{LCO}-impaired group will die at twice the rate of a healthy control group, without specifying the length of any individual's survival. For the control (presumed healthy) group, the hazard ratio is 1.0, so $(HR_{actual}/(1+HR_{actual}))\times100$ gives the percentage chance of death occurring in relation to the control group (table 2). In terms of the three mildest categories [15] (for FEV_1 a PP >50 or z-scores ⩾−3.0), the hazard ratios were sufficiently similar to be described by a single category. Thus, Miller and Cooper [1] proposed a four-category classification for T_{LCO}: normal, z-score ⩾−1.645, mild ⩾−3.0, moderate ⩾−5.0 and severe <−5.0, as summarised in table 2. For the same z-score, note the large effect of age on PP in table 2.

An alternative approach to pulmonary function prediction of survival was suggested by Miller and Pedersen [16]. They expressed FEV_1 as multiples of the minimum level compatible with life, using the 1st centile values (0.4 L for females and 0.5 L for males) found from patients with abnormal lung function. For a 75 year old healthy male of height 175 cm, an FEV_1 of 0.4 L has a T_{LCO} z–score of −4.17 and PP 17.0 (−6.51 and PP 11.5 for a 30 year old). This approach might be difficult in practice because a subject with a T_{LCO} <20% predicted could have an FVC too low (<1.0 L) for an adequate expiratory sample to be obtained with the single breath test.

Conclusion

The FEV_1 and FVC (and their ratio), together with the T_{LCO} (and its components, K_{CO} and V_A), are the cornerstone of routine pulmonary function test assessment. This combination of pulmonary function tests has descriptive information, useful in suggesting, supporting or refuting a clinical diagnosis [9]. In addition, the study reported by Miller and Cooper [1] in this issue of the *European Respiratory Journal* shows that quantitative information on T_{LCO} reduction is predictive of survival, and that the T_{LCO} may be better than the FEV_1 or FVC in this regard.

Conflict of interest: M. Hughes has nothing to disclose.

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