Advanced Lung Disease in Patients with Cystic Fibrosis Is Associated with Low Diffusion capacity

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ABSTRACT **Background:** The single-breath diffusing capacity of the lungs ($DLCO_{SB}$) test measures the extent to which carbon monoxide (CO) passes from the lung air sacs into the blood. The accessible alveolar volume (VA_{SB}) is measured by inert gas during a 10-second period. The single-breath transfer coefficient of the lung for carbon monoxide (KCO_{SB}) is the $DLCO_{SB}$ divided by VA_{SB} Cystic fibrosis (CF) disease comprises progressive airway obstruction with bronchiectasis and parenchyma fibrosis. Yet, the KCO_{SB} appears insignificant in the assessment of pulmonary function in CF.

Objectives: To challenge the precision of normal KCO_{SB} in CF.

Methods: The authors collected pulmonary function tests (PFT) data from 74 confirmed CF patients (mean age 26 ± 10 years) with various levels of pulmonary disease severity. PFTs included spirometry, $DLCO_{SB}$ and lung volumes calculated via body plethysmography (BP). Alveolar volume (VA_{BP}) was calculated by deducting "anatomical dead space" from total lung capacity (TLC_{BP}) and KCO_{BP} was then determined. We also included individual data of arterial pCO_2 blood-gas level.

Results: KCO_{SB} values were normal or higher than normal in most patients, regardless of patient FEV1 value (R^2 = 0.2204; P < 0.02) or their trapped-air levels. In contrast, the measurements of KCO_{BP} were low parallel with low FEV1 values, and negatively correlated with the elevation of trapped air and pCO_2 levels (R^2 = 0.1383; P = 0.0133, P > 0.05, respectively).

Conclusions: The measurement of VA_{SB} using the short, 10-second perfusion time of the inert gas, represent only the communicative alveolar volume in CF patients with moderate to severe airway obstruction. The findings justify the use of VA_{BP} measured with $DLCO_{SB}$ which correlate with the deterioration of FEV_1 and elevation of pCO_2 level.

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The single-breath diffusion capacity of the lung for carbon monoxide ($DLCO_{SB}$) test determines the efficiency of the alveoli to transfer oxygen from inhaled air to the red blood cells in the pulmonary capillaries [1]. Carbon monoxide (CO) shows superior efficacy to red blood cells and therefore replaces oxygen in the test [1]. The test is standard in the pulmonary function laboratory and is an important tool in the diagnosis and follow-up of patients with progressive pulmonary disease [1].

The $DLCO_{SB}$ test includes inhalation of mixed gases from residual volume (RV) to total lung capacity (TLC) pursued by a breath-hold time of 10 seconds followed by full exhalation, where a sample of the exhaled air is analyzed [2]. The inhaled gas mixture includes CO for the diffusion sample and an inert gas (helium/methane) to determine the alveolar volume (VA_{SB}) available for diffusion [3]. The precision of VA_{SB} depends on the maximal perfusion of the inert gas during the 10 seconds of the test.

The KCO_{SB}, which presents the transfer coefficient for diffusion capacity of the lung, is the product of $DLCO_{SB}$ divided by the VA_{SB}. Thus, the accuracy of KCO_{SB} depends on the open communication passages between the mouth and the available alveoli within the 10-second test time. In the presence of obstructive airways, non-communicative zones or trapped air, the 10-second breath-hold time may not allow proper blending of the inert gas and therefore may not represent true alveolar volume [1-4]. This low VA_{SB} may alter KCO_{SB}, which will appear to be normal or even increased above normal [4-6].

Cystic fibrosis (CF) disease comprises progressive airway obstruction with bronchiectasis and parenchyma fibrosis [7]. These pathologies may affect both the available capillary blood volume for diffusion as well as the alveoli number available for diffusion. One would therefore expect that KCO_{SB} would decrease with the progression of the disease. Yet studies of KCO_{SB} in CF showed a variable spectrum of decreased to normal to increased values. A slightly elevated KCO_{SB} in the early stages of the disease and reduced values below normal as the disease advances was previously found [8,9]. These studies imply that the elevation is partly due to the maximal inspiration against obstructed airways causing abnormally negative intra-thoracic pressures, thereby increasing the pulmonary capillary blood volume. Furthermore, elevated KCO_{SB}

values were related to dyspnea and high respiratory rate, causing increased pulmonary circulation, which improves non-ventilated regions of the lung [10]. O' Brodovich and colleagues [10] found normal KCO_{SB} and proposed that hypoxic pulmonary vasoconstriction ends to recruit the pulmonary vascular bed at the apexes [11]. A normal or elevated KCO was also found in adult CF patients [12,13]. These findings led to the conclusion that the diffusion capacity at rest is not suitable as an early marker of progressive deterioration of CF lung disease.

Corbet et al. [14] tested the correlation between partial pressure of carbon dioxide (pCO_2) and DLCO in CF. They found a reduction of fractional CO uptake with increasing arterial-alveolar CO_2 pressure differences and suggested that the decrease in diffusing capacity in cystic fibrosis is caused by ventilation-perfusion inequality. Weinreich and co-authors [15] also found a significant association between DLCO and the difference between arterial and end-tidal CO_2 in subjects with chronic obstructive lung disease.

We questioned the normal or elevated diffusion capacity of the lung in CF patients. Our study evaluated whether KCO_{SB} is genuinely normal in CF patients by comparing the alveolar volumes measured via the single-breath technique (VA_{SB}) to the alveolar volume derived from the body plethysmograph (VA_{BP}). Both values of KCO were calculated in relation to other lung function tests and arterial pCO_2 levels.

PATIENTS AND METHODS

STUDY DESIGN

This study was retrospective and cross-sectional.

PATIENT DATA

We obtained lung function data from CF patients who routinely visited the National Center for Cystic Fibrosis, located in the Safra Children's Hospital at Sheba Medical Center, Israel. The lung function tests included spirometry, lung volume measurements by body plethysmography, and $DLCO_{SB}$ measurements via the single-breath CO technique.

INCLUSION CRITERIA

Patient data were included if spirometry, body-plethysmography, single-breath diffusion capacity test, and partial pressure of carbon dioxide (pCO_2) in arterial blood were available from a single visit to the center and tests were technically reliable.

EXCLUSION CRITERIA

Pulmonary lung disease exacerbations within 3 months prior to the tests, technically incorrect pulmonary function tests, or non-availability of blood gases constituted exclusion criteria. The ethics committee of the Sheba Medical Center, Israel, approved the study (Approval no. 5083SMC).

PULMONARY FUNCTION TESTS

Spirometry

Flow/volume measurements were performed according to American Thoracic Society (ATS)/European Respiratory Society recommendations [17] using the nSpire spirometer (nSpire Health, Inc., CO, USA).

$DLCO_{SB}$

We preformed diffusion measurements using the Jeager Master Screen PFT system (CareFusion Corporation, San Diego, CA, USA) according to GOLD guidelines [2]. We used the mixture of CO (0.3%), CH_4 (0.28%), O2 20.6%, and N_2 for balance. Once the mouthpiece and nose clip were in place, the patient performed tidal breathing for a sufficient time to assure comfort with the mouthpiece. The patient was then asked to exhale to residual volume (RV) where he/she switched to the mixed gas while rapidly inhaling it up to TLC. Breath-hold time was aimed for 10 seconds (no evidence of leaks, Valsalva or Mueller maneuver were noticed during the tests) followed by full expiration to allowed proper sample collection analysis. Hemoglobin levels were added to the computer program to allow proper analysis of diffusion.

Body plethysmography

Patients performed static lung volume measurements using the Jeager Master Screen PFT system (CareFusion) according to guidelines [19].

We tested pCO_2 in arterial blood. Arterial blood samples obtained with a heparinized syringe were sent to the laboratory for analysis. Gases were analyzed within less than 15 minutes using the blood gas analysis machine (Gem Premier 3000, model 5700; Instrumentation Laboratory, Lexington, MA, USA) calibrated according to standard quality assurance protocols.

DATA ANALYSIS

Spirometry

We chose the best FEV1+FVC from the session for further analysis. Spirometry values (FEV1, FVC, and FEF25-75) were related to GLI reference values.

Diffusion test

We reported the higher of two acceptable tests. DLCO, VA, and KCO_{SB} were calculated by the program [2]. The DLCO program deducted automatically the anatomic dead space (the volume of the conducting airways from the nose or mouth to the level of the terminal bronchioles). VA_{SB} was derived from dilution of the inspired tracer gas (methane). The KCO_{SB} was calculated automatically during the test.

Lung volume measurements

We reported the following parameters: TLC, RV, functional re-

sidual capacity, and RV/TLC ratio. We used predicted values from the ATS [21]. For calculating VA_{BP} we deducted the anatomical dead space from the TLC for each patient.

STATISTICS

We tested lung functions for normal distribution. We used paired *t*-tests to compare the differences between measurements of the same subject. Pearson correlation tests determined associations between spirometry and/or static lung volume indices and VA_{SB} or VAbp. Findings were reported as mean ± standard deviation when normally distributed or as median with 95% confidence limit if non-normally distributed. Statistical significance was set at $P < 0.05$.

RESULTS

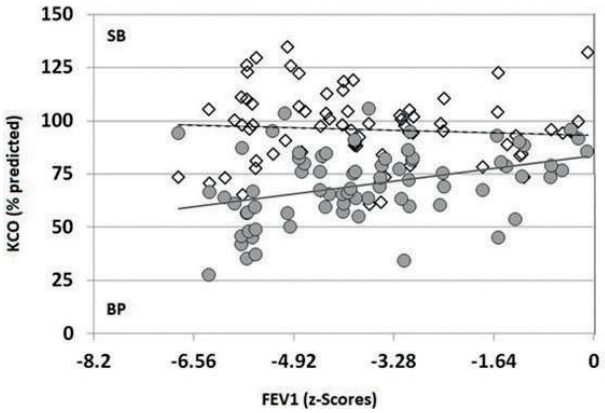
Data were available from 74 CF patients (40 males): mean age 26 ±10 years (range 12–59 years), mean BMI 20 ± 3 kg/m^2, pCO_2 level was 46 ± 6 mmHg. Data for arterial was available from 52 patients. There was no significant difference between males and females. Of the 74 patients, 56 (75.6%) had at least one severe mutation (class I or class II). Spirometry (percentage predicted) showed a forced vital capacity (FVC) of 65 ± 20%, forced expiratory volume in the first second of expiration (FEV1) of 53 ± 23%, and mid expiratory flows (FEF25–75) of 80 ± 18%.

Table 1 presents the cohorts' lung volumes results measured by both plethysmography and the $DLCO_{SB}$ test. The results demonstrate that VA_{SB} values were significantly lower than VA_{BP} values, resulting in normal KCO_{SB} but lower than normal KCObp.

Figure 1. KCO level in relation to FEV1

KCO_{BP} (% predicted values) decrease alongside the decline in FEV1 (z-scores) (R2 = 0.2204, $P < 0.02$). KCO_{SB} remains normal or higher than normal with no correlation with FEV1 severity (R2 = 0.0055, $P > 0.05$)

DLCO = diffusing capacity of the lungs, KCO = DLCO divided by accessible alveolar volume, BP = body plethysmography, SB = single breath



The distribution of levels of KCO (low, normal, or high) in the patients related to the method of measurement are shown in Table 1. Using the single-breath method, 92% of the patients showed lower than normal VA_{SB} compared to only 19% as measured by the plethysmography. Furthermore, 70% of the patients had normal KCO_{SB} while the KCO_{BP} method exhibited 70% had

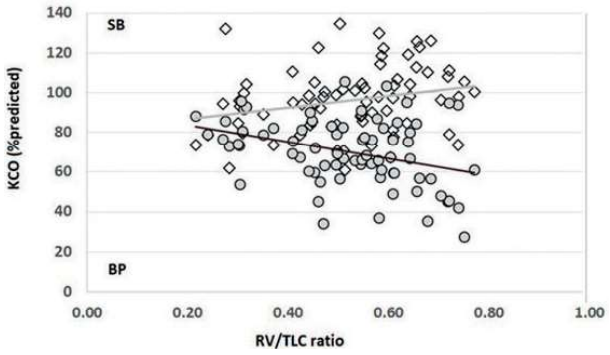
Table 1. Lung volume results (% predicted) measured either by plethysmography or by the DLCO test and plethysmography and the relative KCO_{SB} or KCO_{BP}

	DLCO test % predicted	Plethysmography %predicted	*P* value
Lung volumes results (measured either by plethysmography or by the DLCO test)			
VA	73 ± 21	99 ± 18	0.0001
RV	81 (42–255)	193 (78–394)	0.0001
Number of patients with low, normal, or high KCO in relation to the methods of measuring*			
VA	102 ± 18	68 ± 17	0.0001
Below 80% predicted	48 (92)	10 (19)	0.0001
Normal	4 (8)	38 (73)	0.0001
Above 120% predicted	0 (0)	4 (8)	0.0281
KCO			
Below 80% predicted	10 (19)	36 (70)	0.0001
Normal	36 (70)	16 (30)	0.0001
Above 120% predicted	6 (11)	0 (0)	0.0064

*Number of patients with disturbed KCO in relation to the method of measurements
DLCO = diffusing capacity of the lungs, KCO = DLCO divided by accessible alveolar volume, RV = residual volume, VA = alveolar volume, BP = body plethysmography, SB = single breath

Figure 2. The correlation between KCO and residual volume to total lung capacity ratio (RV/TLC ratio) measured by the plethysmograph

DLCO = diffusing capacity of the lungs, KCO = DLCO divided by accessible alveolar volume, RV = residual volume, TLC = total lung capacity, VA = alveolar volume, BP = body plethysmography, SB = single breath



lower than normal values.

The relationship between FEV1 and KCO is presented in Figure 1. The figure shows that KCO_{BP} (% predicted values) is decreased alongside the decrease in FEV1 ($R_2 = 0.2204$, $P < 0.02$). KCO_{SB} remains normal or higher than normal with no correlation with FEV1 severity ($R_2 = 0.0055$, $P > 0.05$).

The correlation between KCO and residual volume to total lung capacity ratio (RV/TLC ratio) measured by the plethysmograph is shown in Figure 2. KCO_{BP} values are lower in patients with high ratios of RV/TLC (Sx.y = 16.11, $P = 0.003$) while KCO_{SB} values are significantly increased alongside the trapped air (Sx,y = 0.16.78; $P = 0.0416$).

The correlation between KCO and pCO_2 level is presented in Figure 3. The figure demonstrates that KCO_{SB} fluctuates within the normal range with a positive trend correlated with pCO_2 levels. KCO_{BP} negatively correlates with pCO_2 levels.

DISCUSSION

In this study, we questioned the reliability of KCO_{SB} as measured by the single-breath diffusion capacity method in CF patients. The alveolar volume measured in patients with CF with advanced lung disease is lower than the true volume due to airway obstruction and trapped air. As in former studies [14], we found that KCO_{SB} values were normal or higher than normal in most subjects, regardless of their lung disease severity. These findings did not relate to the patient's FEV1 or to their trapped-air levels. In contrast, the measurement of KCO_{BP} was lower than normal in parallel with decreased levels of FEV1, which negatively correlated with the elevation of trapped air and pCO_2 levels. Our findings may therefore reflect a decrease in accessible alveolar volume rather than impaired gas transfer.

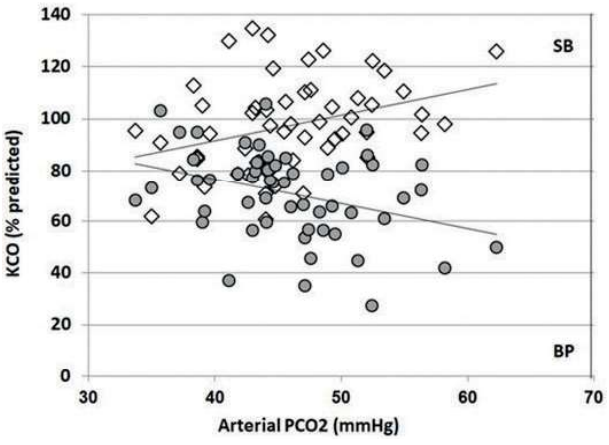
The major cause of morbidity and mortality in subjects with cystic fibrosis (CF) is lung disease [22]. Both inflammation and ineffective airway clearance lead to the appearance of bronchiectasis and permanent structural damage to the airways. Progressively impaired lung function eventually results in respiratory failure and death [23]. Thus, the former finding of increased or normal KCO in CF should have raised the doubt of the accuracy of single-breath methodology and the conclusion that $DLCO_{SB}$ plays no role in CF lung function follow-up. [10-15]. Further, the conclusion that increased KCO_{SB} is caused by failure to expand the lung, increased capillary volume and flow [13] is not very likely since these pathologies are not common in CF disease.

Lung volume measurements during the VA^{SB} rely on the patient efforts of reaching true RV and TLC and on the relatively short (10-seconds) period allowing the inert gas to perfuse within the lung space. In the precision of lung volumes by the helium dilution technique, it takes several minutes to establish equilibrium of the gas, while the patient is mixing the air within the lung [19]. Indeed, the accuracy of the helium dilution technique is debated in the presence of airway obstruction [25]. Conversely, the accuracy of TLC measurements via plethysmography depends on the pressure/volume changes between box pressure during inspiration and expiration against mouth occlusion in a closed box. In healthy patients, VA_{BP} and VA_{SB} are similar [2]. During severe obstruction and significant air trapping, the volume/pressure ratio may not represent true alveolar pressure or change in volume, resulting in incorrectly higher than normal alveolar volume [25]. Yet, our finding of a correlation between

Figure 3. The correlation between KCO and pCO_2 level

The graph shows that KCO_{SB} fluctuates within the normal range and correlated negatively with pCO_2 levels ($P = 0.0129$). KCO_{BP} positively correlated with pCO_2 levels ($P = 0.0112$)

DLCO = diffusing capacity of the lungs, KCO = DLCO divided by accessible alveolar volume, BP = body plethysmography, SB = single breath



KCO_{BP} and decreased FEV1 (%predicted) and the rise in trapped air and arterial pCO_2, hints that KCO_{BP} may describe true diffusion capacity better than KCO_{SB} in CF patients. Similar findings were presented in chronic obstructive pulmonary disease (COPD) [3], where significant discrepancy between the TLC and VA_{SB} measurements during the methacho line challenge test were found.

It is crucial to acknowledge the importance of VA measured via plethysmography as the true alveolar lung volume available for lung diffusion in CF patients. We also believe that the use of VA_{BP} instead of VA_{SB} (measured by DLCO) may reflect the diffusion capacity pathophysiology more properly.

LIMITATIONS

The study was retrospective, and data were derived from CF patients at a single center. Yet, this limitation might actually be of an advantage since the same laboratory technicians performed all the tests. Moreover, as only the volume to where the inert gas penetrates comprises the true diffusion, but this ignores the trapped air and the pathophysiology of advancing lung disease in CF.

CONCLUSIONS

KCO_{BP} values are decreased in severe CF lung disease along with low FEV1 and high trapped air levels and the elevation of arterial pCO_2 levels. Deterioration in KCO_{BP} probably begins when FEV1 is only mildly reduced. Conversely, KCO_{SB} remains mostly within the normal range and poorly corresponds with either FEV1 decline, trapped air, or elevation of pCO_2 levels. These findings may justify the measurements of alveolar volume via the body plethysmography to establish KCO in subjects with cystic fibrosis.

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Achievement is largely the product of steadily raising one's level of aspiration and expectation.
Jack Nicklaus (Born 1940), American golfer