Serial pulmonary function tests in the diagnosis of P. carinii pneumonia

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ABSTRACT: The predictive value of serial versus isolated measurements of transfer factor for carbon monoxide (TLCO) in the diagnosis of pneumocystis carinii pneumonia (PCP) in a cohort of 474 HIV-1 seropositive patients, with all stages of HIV disease, was evaluated.

Two groups of patients were studied, one group with serial lung function measurements (Group 1) and another with only a single set of measurements (Group 2). During the study period 118 patients performing serial tests developed a respiratory illness of which 58 were performing monthly and 60 three monthly measurements of lung function (Group 1). In 36 patients from Group 1, where PCP was diagnosed, monthly lung function tests showed a decrease in TLCO from 68% (±5.2) (SEM), (8 weeks prior to illness), to 44% (±2.5) predicted normal at presentation, whereas in 22 patients who did not have PCP, TLCO fell from 71% (±4.5) to 57% (±3.1). TLCO was thus reduced to lower values in those with PCP than in those without PCP (p<0.05). A fall of TLCO of 5% from initial values when used as predictive for presence of PCP had a sensitivity of 75% and a specificity of 28% (positive predictive value 56%; negative predictive value 48%). TLCO was <70% predicted in 72/78 patients with PCP who performed only single lung function tests (Group 2), which gave a sensitivity of 92% and a specificity of 71% as a diagnostic test for PCP when compared with the cohort as a whole. The positive predictive value was 34%, negative predictive value was 98%.

Single or serial measurements of TLCO lack specificity for diagnosis of PCP although it should at least suggest the diagnosis. Serial lung function generally showed lower TLCO in those with PCP than those without. A single TLCO measurement was unable to distinguish PCP from other respiratory disease but has value because of the high negative predictive value making PCP highly unlikely with a normal TLCO.

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Of the pulmonary complications of human immunodeficiency virus (HIV) infection, Pneumocystis carinii pneumonia (PCP) remains the most common major opportunistic infection in Europe and the USA, despite the widespread use of effective prophylaxis [1]. PCP causes diagnostic difficulties because the symptoms are nonspecific [2-4], and physical examination is usually non-contributory. A chest radiograph in PCP may be normal or may show atypical features, and radiographic features of PCP may be seen in other acquired immune deficiency syndrome (AIDS) related pulmonary infections or tumours. A definite diagnosis of PCP, therefore, requires examination of induced sputum, bronchoalveolar lavage, or transbronchial biopsies [5]. Much recent effort has been devoted to the application of indirect tests, including measurement of pulmonary function, in the evaluation of patients with HIV infection, who present with respiratory symptoms [6]. Low values for carbon monoxide transfer factor (TLCO) and vital capacity (VC) have been shown to occur in PCP [7-9]. Documentation of an isolated reduction in TLCO lacks specificity as a diagnostic tool for PCP, as in previous studies [10] we observed a reduction in TLCO in patients with a wide range of HIV-related lung disease. In a subsequent study, utilizing serial measurements of pulmonary function, we found that although often reduced, the value of the TLCO was essentially stable in patients who did not experience a clinical deterioration [11]. Conversely, we observed that there was a decline in TLCO in many patients during a clinical deterioration.

In this study we first looked at the diagnostic value of a single measurement of TLCO at the time of presentation with respiratory disease; and, secondly, we asked whether the magnitude of the decline of TLCO, as identified by serial measurements of pulmonary function, was able to discriminate PCP from other acute respiratory illnesses in HIV-infected patients.
Methods

These studies were performed on a cohort of male homosexual or bisexual HIV seropositive patients. Consecutive patients who attended the sexually-transmitted disease clinic were enrolled. It is policy to include pulmonary function testing in the initial work-up of these patients. The criteria for inclusion in the study were: 1) positive HIV serology; 2) no history of intravenous drug abuse; and 3) informed consent. Exclusion criteria were: 1) respiratory failure; and 2) refusal of the patient to participate.

The patients were classified according to clinical status: 1) 126 asymptomatic HIV seropositive (HIV+) (CDC group II) [12]; 2) 95 with persistent generalized lymphadenopathy (PGL) (CDC group III); 3) 92 with AIDS-related complex (ARC) (CDC group IV, subgroups A, B, C2, E); 4) 35 with non-pulmonary Kaposi’s sarcoma (KS) (mainly skin Kaposi’s sarcoma) (CDC group IV, subgroup D); 5) 19 with non-pulmonary, non-KS AIDS (i.e. opportunistic infection involving other organs) (CDC group IV, subgroup C1); and 6) 107 AIDS patients with pulmonary complications (pulm AIDS), 78 with acute PCP (CDC group IV, subgroup C1), and 42 of these patients 3 months following recovery from PCP (post-PCP), 11 with lung mycobacterial infection (lung myco), 11 with lung Kaposi’s sarcoma (lung KS), and 7 AIDS patients with pulmonary pyogenic bacterial infection.

Lung function testing was performed at 1 or 3 monthly intervals, as part of routine out-patient follow-up. Compliance was high, as many patients were attending on a regular basis for monitoring of zidovudine therapy, or were involved in other studies relating to their HIV infection.

Patients seropositive for HIV with an abnormal chest radiograph, or TLco of <70% predicted, or prominent respiratory symptoms (i.e. persistent cough, or moderate to severe exertion, or dyspnoea) underwent fiberoptic bronchoscopy with bronchoalveolar lavage, with or without transbronchial biopsy [13]. All patients had the following lung function tests: forced expiratory volume in one second (FEV1), peak expiratory flow (PEF), forced vital capacity (FVC), alveolar volume (VA), and diffusing capacity of the lung for CO (TLco). The diffusion coefficient (Kco) was derived from TLco and VA. Measurements were made using a dry bellow spirometer, and the single breath helium dilution method (PK Morgan transfer test model C machine, PK Morgan, Gillingham, Kent, UK). Corrections for temperature and haemoglobin [14] were included when calculating values of TLco. All measurements were made after a period of rest. Tests were repeated at approximately 3 monthly intervals, depending on stage of disease and clinical indications. If a decline in TLco was noted in consecutive tests, then lung function measurements were repeated 4 weeks later.

To reduce the risk of cross-infection between patients, modifications were made to the equipment. Lung function testing apparatus designated for HIV seropositive patients was used throughout. One way valve safety mouthpieces (Vitalograph Ltd, Buckingham, UK) were used for spirometry, to avoid the risk of inhaling pathogens from the spirometer. A Pall Ultipor breathing system filter (Pall Biomedical, Havant, Portsmouth) was placed distal to the mouthpiece during the CO transfer test. The increased tidal volume of 150 ml due to the presence of the filter was incorporated in the calculation. Plastic mouthpieces and noseclips were sterilized in 2% glutaraldehyde for 1 h between patients, and the remainder of the apparatus dismantled and sterilized weekly for >3 h in 2% glutaraldehyde.

Values were compared with those predicted for age, sex and height [14], and statistical comparisons were made using the Mann-Whitney U test. This study was approved by the hospital Ethics Committee.

Results

Of the 118 patients who had an acute respiratory illness and were performing serial lung function tests patients (Group 1), PCP was confirmed in 65 patients. The other 53 patients with acute non-PCP respiratory disease were initially thought to have PCP on the basis of symptoms and chest radiograph appearance, but following bronchoalveolar lavage these patients were found not to have PCP but pyogenic bacterial chest infection, mycobacterial infection, or no established aetiological diagnosis. None of these patients required or received treatment for PCP. Data from respiratory function tests performed at monthly intervals were available from 36 patients with PCP and from 22 patients with acute non-PCP respiratory disease. Data from tests performed at 3 monthly intervals were available in the remainder. In the larger group of 474 patients with all categories of HIV disease, comparison was made between the results of an isolated measurement of lung function and the clinical stage of HIV-related disease at that time.

Serial measurement of TLco (Group 1)

When the TLco values 8 weeks prior to the respiratory illness were compared, the TLco was found to have been reduced both in those with PCP and in those with acute non-PCP respiratory disease. The TLco in those with PCP was 68±3.2% predicted (means±SEM), and in those with acute non-PCP respiratory disease was 71±4.5% predicted.

In patients who developed PCP, there was a small fall in TLco by 1 month prior to the diagnosis of PCP, when compared to TLco measurements 8 weeks prior to the respiratory illness (fig. 1). During the 4 weeks leading up to the diagnosis of PCP, there was a further more marked decline in TLco. One month after the diagnosis of PCP and the initiation of therapy, the TLco values were similar to those 1 month prior to diagnosis. There was a further slow improvement in TLco when measurements were taken 8 weeks after PCP, the TLco values being only slightly below those recorded 2 months prior to PCP.

The pattern of changes in TLco in patients with acute non-PCP respiratory disease was similar, but the magnitude of the changes was less marked. Thus, the reduction of TLco during the acute illness was from 71 to 57%,
when compared to 68 to 44% for the PCP group. The nadir values of Tlco were significantly lower in the PCP patients than in the acute non-PCP respiratory disease patients (p<0.05).

Fig. 1. - Serial measurements of Tlco, FVC and Kco in HIV seropositive patients with PCP (△), and with acute respiratory disease other than PCP (○). 0 week: onset respiratory illness. **: p<0.05. Tlco: transfer factor of the lung for carbon monoxide; FVC: forced vital capacity; Kco: carbon monoxide diffusion coefficient; PCP: Pneumocystis carinii pneumonia. Data are presented as means±sEM.

Fig. 2. - Frequency distribution of Tlco (as percentages of predicted normal values) in the different categories of HIV-related disease, showing numbers of patients with values of ≤70% and of ≥70% (delineated by dotted line). HIV: human immunodeficiency virus; PGL: persistent generalized lymphadenopathy; ARC: acquired immune deficiency syndrome (AIDS)-related complex; KS: Kaposi's Sarcoma; PCP: Pneumocystis carinii pneumonia; myco: mycobacterial infection; pyog: pyogenic bacterial infection.
The changes in TLco were also reflected in changes in the FVC. There was a marked decline in FVC in the 1 month prior to the diagnosis of PCP, which was less marked in patients found to have non-PCP respiratory disease. Similarly, the nadir FVC value was significantly lower in the PCP group, when compared with the acute non-PCP respiratory disease group (p<0.05). There was a slight reduction in Kco, which was similar in both patient groups.

Relationship between magnitude of decline in TLco and presence of PCP

In the study Group 1 of 118 patients, the magnitude of the decline in TLco over a 3 month period was not related to the underlying diagnosis. The TLco declined by a mean of 14.7±1.7% in those with PCP, and 10.5±1.3% in those with acute non-PCP respiratory disease. The median decline in the two groups was 11.0 and 9.0%, respectively. Although the greatest declines occurred in those with PCP, there was considerable overlap between the groups. A cut-off value of decline in TLco of 5% predicted was taken. When used as a diagnostic test for PCP, this had a sensitivity and specificity of 75% and 28%, respectively. This test had a positive predictive value of 56%, and a negative predictive value of 48%.

Isolated measurement of TLco (Group 2)

Seventy eight of the 474 patients in the overall study had acute PCP either at presentation or during the follow-up period. During acute PCP in this group, the TLco was 49±1.8% of predicted normal, the FVC was 74±2.6%, and the Kco 72±2.3%. Only 6 out of 78 patients with PCP had a TLco of >70% predicted, whereas 52 and 38 patients had values for FVC and Kco of >70%. Although the TLco was the most sensitive index for the presence of PCP, a reduced TLco was not specific for PCP, as marked reductions in TLco were also seen in other categories of pulmonary disease (fig. 2). When a TLco value of <70% predicted was used to diagnose PCP, the sensitivity of the test was 92%. The specificity of the test, when compared to all other patient groups, i.e., the cohort of 474 patients was 71%. The specificity was further reduced to 62% when patients with PCP were compared only with the patients from the cohort with other respiratory complications of HIV infection, namely pulmonary Kaposi's sarcoma, mycobacterial infection, and pyogenic bacterial infection. When compared to the cohort as a whole the positive predictive value was 34%, and the negative predictive value was 98%. The negative predictive value was lower at 33%, when acute PCP was compared to pulmonary Kaposi's sarcoma, mycobacterial infection, and pyogenic bacterial infection.

Discussion

In this study we have assessed the ability of serial lung function tests to identify HIV seropositive patients with respiratory complications, and the ability of these tests to distinguish between patients with PCP and patients with other acute respiratory illness. This study confirms previous findings [10] that a low TLco is a sensitive index for pulmonary disease in AIDS, in that it was reduced to below 70% of predicted normal in 92% of patients with PCP. However, a low value for TLco was not specific for PCP, with a specificity of 71% when compared to the cohort as a whole, and of 62% when compared to those groups of patients with respiratory complications of HIV infections other than PCP. On the other hand, in view of the high negative predictive value (98%) of a low TLco measurement, a single measurement of TLco can be of clinical and diagnostic value since, if the TLco is normal, PCP is virtually excluded.

Low values for TLco could not be attributed to intravenous drug abuse, as none of the patients in this study were intravenous drug abusers [15]. Serial measurements of lung function in HIV seropositive patients, initiated prior to the onset of an acute respiratory illness, have the theoretical advantage that changes in TLco can be related to the individual's own baseline value, although in practice it may be difficult to obtain measurements prior to respiratory illness. The present study found that there was a decrease from baseline in TLco in patients with PCP and acute non-PCP respiratory disease. This decline, at least in the PCP patients, commenced prior to 1 month before the diagnosis was made. However, the greater part of the decline in TLco in both groups occurred in the 4 weeks prior to clinical presentation and diagnosis by bronchoscopy. When the groups were considered as a whole, the PCP patients had TLco values lower than the patients with acute non-PCP respiratory disease. When each individual was considered, there was considerable overlap between the magnitude of the decline in TLco between the two patient groups. Thus, if a further decrease in TLco of 5%, when compared to the individual's initial value, was used as a diagnostic test for PCP, it had a sensitivity of 75% and a specificity of 28%. It would be difficult in practice to offer serial lung function testing to all HIV positive patients, and this study suggests that such a policy would not help identify those with PCP.

The exact pathogenic mechanism underlying the decline in TLco and HIV-infected patients is unclear. We have not been able to document a consistent defect in the lungs of asymptomatic HIV seropositive patients with reduced TLco using exercise tests, diethylenetriamine penta-acetic acid (DTPA) clearance, or high resolution computed tomography (CT) scanning [16].

In a previous study [11], the TLco remained essentially unchanged in the absence of a clinical deterioration, and we argued that HIV infection alone did not result in progressive lung damage. The present study extends these observations by finding that both PCP and acute non-PCP respiratory disease caused an acute deterioration in lung function over a few weeks. The data suggest that a decline in TLco exceeding 5% may indicate an acute respiratory illness, but cannot identify those with acute PCP.

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References


