BMC Pulmonary Medicine

Research article

Pulmonary function testing in HTLV-I and HTLV-II infected humans: a cohort study

Edward L Murphy*[1,2], Helen E Ownby[3], James W Smith[4], George Garratty[5], Sheila T Hutching[5], Ying Wu[6,7] and Dannie I Ameti[6]

Address: [1]University of California San Francisco, San Francisco, CA, USA, [2]Blood Centers of the Pacific, San Francisco, CA, USA, [3]American Red Cross Blood Services, Southeastern Michigan Region, Detroit, MI, USA, [4]Oklahoma Blood Institute, Oklahoma City, OK, USA, [5]American Red Cross Blood Services, Southern California Region, Los Angeles, CA, USA, [6]Westat, Rockville, MD, USA and [7]Current address: Bristol-Myers Squibb, Wallingford, CT, USA

Email: Edward L Murphy* - murphy@itsa.ucsf.edu; Helen E Ownby - heownby@mindspring.com; James W Smith - jsmith@obi.org; George Garratty - garratty@usa.redcross.org; Sheila T Hutching - hutchins@usa.redcross.org; Ying Wu - ying.wu@bms.com; Dannie I Ameti - ametid1@westat.com

* Corresponding author

Published: 28 July 2003

BMC Pulmonary Medicine 2003, **3**:1

Received: 14 May 2003
Accepted: 28 July 2003

This article is available from: http://www.biomedcentral.com/1471-2466/3/1

Abstract

Background: HTLV-I infection has been linked to lung pathology and HTLV-II has been associated with an increased incidence of pneumonia and acute bronchitis. However it is unknown whether HTLV-I or -II infection alters pulmonary function.

Methods: We performed pulmonary function testing on HTLV-I, HTLV-II and HTLV seronegative subjects from the HTLV outcomes study (HOST), including vital capacity (VC), forced expiratory volume in one second (FEV_1), and diffusing lung capacity for carbon monoxide (DLCO) corrected for hemoglobin and lung volume. Multivariable analysis adjusted for differences in age, gender, race/ethnicity, height and smoking history.

Results: Mean (standard deviation) pulmonary function values among the 257 subjects were as follows: FVC = 3.74 (0.89) L, FEV_1 = 2.93 (0.67) L, $DLCO_{corr}$ = 23.82 (5.89) ml/min/mmHg, alveolar ventilation (VA) = 5.25 (1.20) L and $DLCO_{corr}$/VA = 4.54 (0.87) ml/min/mmHg/L. There were no differences in FVC, FEV1 and $DLCO_{corr}$/VA by HTLV status. For $DLCO_{corr}$, HTLV-I and HTLV-II subjects had slightly lower values than seronegatives, but neither difference was statistically significant after adjustment for confounding.

Conclusions: There was no difference in measured pulmonary function and diffusing capacity in generally healthy HTLV-I and HTLV-II subjects compared to seronegatives. These results suggest that previously described HTLV-associated abnormalities in bronchoalveolar cells and fluid may not affect pulmonary function.

Background

Human T-lymphotropic virus type I (HTLV-I) has been associated with sporadic cases of chronic bronchiolitis and alveolitis, especially in patients with concurrent HTLV associated myelopathy (HAM) [1,2]. HTLV type II (HTLV-II) has been epidemiologically associated with increased incidences of bronchitis and pneumonia among HTLV-II infected persons [3,4].

Biological studies have demonstrated increased levels of CD3+/CD25+ lymphocytes [5], HTLV-I proviral load and HTLV-I tax/rex mRNA expression [6,7], HTLV-I specific IgA [8], soluble interleukin-2 receptors [9], beta-chemokines [7] and soluble intracellular adhesion molecule-1 (ICAM-1) [10], in bronchoalveolar lavage fluid from HTLV-I infected humans. In addition, mice transgenic for HTLV-I p40 tax had lymphocytic infiltration of peribronchial and perivascular lung tissues associated with intrapulmonary expression of tax mRNA [11]. In general, patients with HTLV myelopathy or uveitis had more pronounced biological changes, but some of these studies also found biological changes in the lungs of asymptomatic HTLV-I carriers.

However, whether HTLV-I or HTLV-II alters pulmonary function is unknown. Such information is important because the pathologic spectrum of these chronic human retroviral infections has not been completely described. In addition, such information would be useful to physicians who must counsel or treat persons found to be HTLV-I or -II seropositive by serologic screening at the time of blood donation, military service, or as part of clinical care associated with injection drug use.

We therefore performed standardized pulmonary function testing (PFT) on HTLV-I and HTLV-II infected persons participating in the HTLV Outcomes Study (HOST), a prospective multicenter cohort study of the health outcomes of HTLV infection that was initiated as part of the National Heart Lung and Blood Institute Retrovirus Epidemiology Donor Study.

Methods

Study design and patient population

The enrollment and follow-up procedures of the HOST have been described in detail elsewhere [4]. In brief, persons found to be seropositive for HTLV-I and HTLV-II at the time of routine or autologous blood donation in 1990–1992 at five United States blood centers were eligible for enrollment. HTLV-I and HTLV-II infection status was confirmed with type-specific serology and/or polymerase chain reaction testing. Subjects have been followed approximately every two years with health history questionnaires, physical examinations, and blood testing. At the third biennial visit in 1995–1997, we performed PFT on a randomly selected subset of HTLV-I and -II positive subjects at four of the five HOST centers (American Red Cross Blood Services Southeastern Michigan (Detroit, MI), American Red Cross Blood Services Southern California (Los Angeles, CA), Blood Centers of the Pacific (San Francisco, CA), and the Oklahoma Blood Institute (Oklahoma City, OK)). We also selected seronegative subjects at the same four centers by strata based upon the age, sex and racial distribution of the HTLV positive subjects, and asked them to undergo PFT.

PFT Procedures

In performing the PFTs, we followed standards published by the American Thoracic Society [12]. Spirometers were calibrated according to these standards, and subjects performed three forced expirations. We measured forced vital capacity (FVC) in liters, forced expiratory volume at one second (FEV_1), diffusing lung capacity corrected for hemoglobin ($DLCO_{corr}$) and diffusing lung capacity corrected for hemoglobin and alveolar ventilation ($DLCO_{corr}$/VA). Each subject's best effort, as judged by the highest sum of vital capacity and FEV_1 from among three expiratory efforts, was used in the analysis.

Statistical analysis

For each of the pulmonary function measures, means and 95 percent confidence intervals were calculated. The mean of each parameter was compared between the HTLV-I, HTLV-II and seronegative groups using ANOVA tests (PROC GLM). Outcome variables, FVC, FEV1, $DLCO_{corr}$ and $DLCO_{corr}$/VA were all treated as continuous variables in the model. Multivariable analysis was performed using linear regression, adjusting for age (quartiles: ≤ 40, 41–47, 47–53 and 54+), gender (male or female), race/ethnicity (White, Black, Hispanic, Asian/other), smoking history (nonsmokers, ex-smokers, and current smokers) and weight (study population quartiles, ≤ 66 kg, 67–78 kg, 79–88.5 kg and ≥ 88.5 kg). The model evaluated differences in pulmonary function parameters and their statistical significance when all important confounders, such as smoking, and characteristics of the study subjects were taken into consideration. Due to the limited number of subjects, we were unable to stratify the analysis by center. Nonetheless, power calculations revealed that the study was able to detect a 10 percent difference compared to seronegatives in the parameters measured with power (1 – beta) of 0.65 to 0.85 for HTLV-I, and 0.82 to 0.96 for HTLV-II. All analyses were done using SAS (SAS version 6.12, Cary, NC).

For each of the pulmonary function measures, means and 95 percent confidence intervals were calculated. The mean of each parameter was compared between the HTLV-I, HTLV-II and seronegative groups using ANOVA tests. Multivariable analysis, adjusted for age, gender, race/ethnicity, smoking history and weight, was performed using linear regression. Due to the limited number of subjects, we were unable to stratify the analysis by center. Power calculations revealed that, relative to the seronegatives, the study was able to detect a 10 percent decrease in the parameters measured with power (1 – beta) of 0.65 to 0.85 for HTLV-I and 0.82 to 0.96 for HTLV-II. All analyses were done using SAS (SAS version 6.12, Cary, NC). The

Committee on Human Research of the University of California San Francisco, San Francisco, CA, USA, has approved the study.

Results

Among the 258 subjects enrolled in the study, one subject had only one instead of three expiratory efforts recorded. This subject was eliminated from further analysis, leaving a study population of 257; none had adult T-cell leukemia or HTLV associated myelopathy. The HTLV-I and HTLV-II subjects were comparable to seronegative subjects with regard to age, gender and race/ethnicity, except that HTLV-I subjects were somewhat older, and more likely to be of black race/ethnicity and to be former smokers (Table 1). Although the three groups were of similar height, HTLV-I infected subjects had a non-significant trend toward lower body weight. Thirty-one percent of the HTLV-II subjects were current smokers, compared to only 11 percent of the HTLV-I and seronegative groups. Dating from study enrollment in 1990–92, incident cases of medically-diagnosed pneumonia or acute bronchitis were reported by 22 percent of HTLV-I, 33 percent of HTLV-II, and 21 percent of seronegative subjects in the current analysis. Data on $\log_{10}$ proviral load were available from 38 of 46 HTLV-I subjects (mean = -2.97, standard error 0.24 copies per PBMC) and from 67 of 84 HTLV-II subjects (mean = -3.46, standard error 0.21 copies per PBMC).

Mean (standard deviation) pulmonary function values among all 257 subjects were as follows: FVC = 3.74 (0.89) L, FEV_1 = 2.93 (0.67) L, $DLCO_{corr}$ = 23.82 (5.89) ml/min/mmHg, alveolar ventilation (VA) = 5.25 (1.20) L and $DLCO_{corr}/VA$ = 4.54 (0.87) ml/min/mmHg/L. These data were comparable to mean values for men and women combined reported by the First National Health and Nutrition Examination (NHANES I) of FVC = 3.82, FEV_1 = 2.94 and $DLCO_{corr}$ = 26.605 [13]. In our study, FVC and FEV_1 were also corrected for height squared (in meters), yielding values of 1.34 (0.24) L/m^2 and 1.05 (0.20) L/m^2, respectively. There was also no significant difference in small airway flow (FEF_{25-75}) between HTLV infected and seronegatives (p = 0.47, data not shown).

Table 1: Demographic characteristics, smoking history, respiratory disease history, height and weight of subjects undergoing PFT, HTLV cohort study.

Variable		HTLV-I n = 46 n(%)	HTLV-II n = 84 n(%)	HTLV Seronegative n = 127 n(%)
Age	21–30	1 (2)	0	7 (6)
	31–40	7 (15)	17 (20)	28 (22)
	41–50	18 (39)	42 (50)	49 (39)
	51–60	8 (17)	15 (18)	24 (19)
	61 plus	12 (26)	10 (12)	19 (15)
Sex	Male	12 (26)	26 (31)	35 (28)
	Female	34 (74)	58 (69)	92 (72)
Race/Ethnicity	Asian/Other	5 (11)	2 (2)	12 (10)
	Black	20 (44)	17 (20)	24 (19)
	Hispanic	4 (9)	28 (33)	34 (26)
	White	17 (37)	37 (44)	57 (45)
Cigarette Smoking	Current Smoker	5 (11)	26 (31)	14 (11)
	Ex-Smoker	19 (41)	30 (36)	32 (25)
	Never Smoked	22 (48)	28 (33)	81 (64)
Pneumonia and/or Bronchitis Diagnosed during study				
	Yes	10 (22)	28 (33)	26 (21)
	No	36 (78)	56 (67)	101 (79)
		mean (SD)	mean (SD)	mean (SD)
Height (Meters)	Males	1.74 (0.07)	1.76 (0.07)	1.77 (0.08)
	Females	1.62 (0.07)	1.63 (0.08)	1.63 (0.07)
Weight	Males	82.0 (11.7)	85.2 (14.4)	89.4 (10.5)
	Females	72.9 (14.5)	77.4 (20.2)	76.2 (18.5)

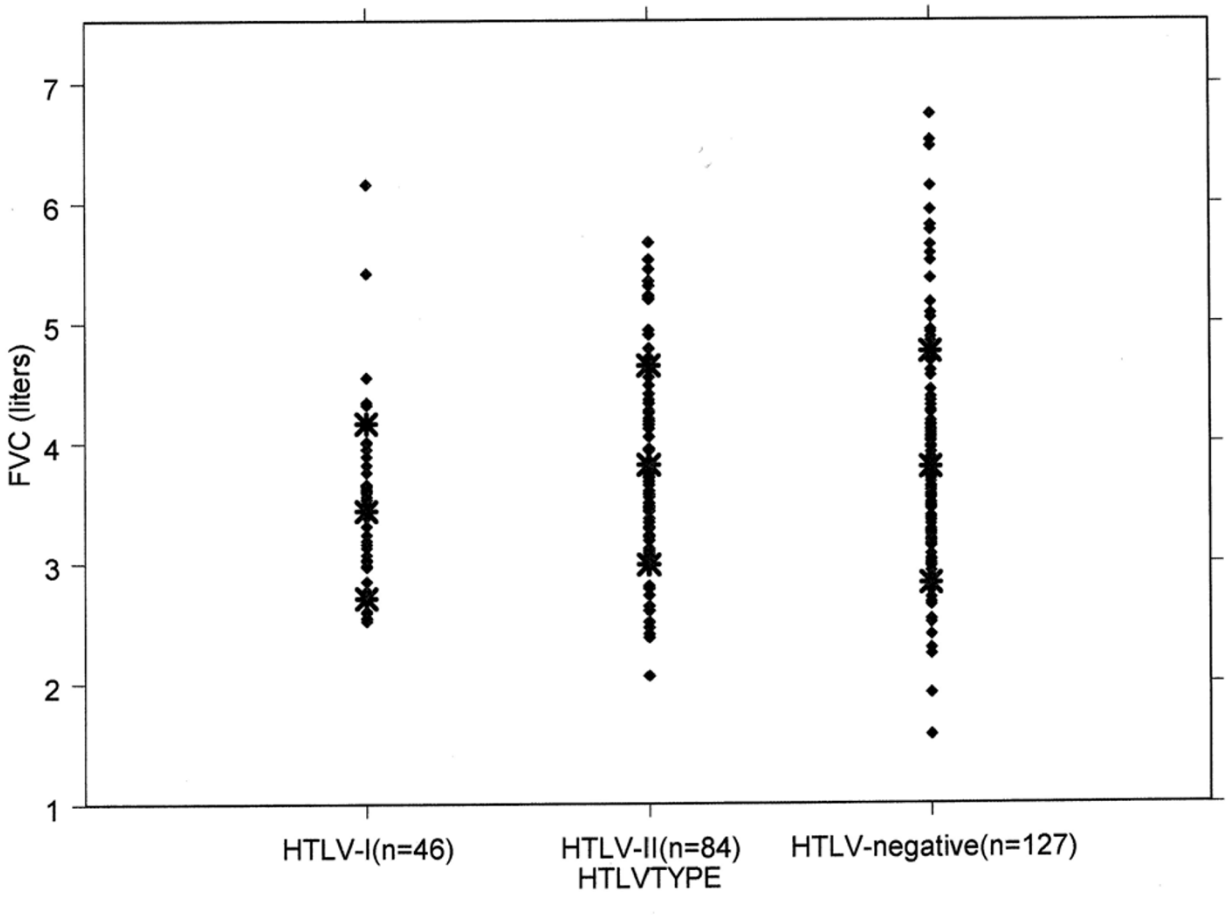

Figure 1
Scatter plot showing values of forced vital capacity (FVC) for each subject, with bars indicating mean, and mean plus and minus standard deviation, by HTLV status.

Figures 1 through 4 show the raw pulmonary function values, stratified by HTLV status. The HTLV-I group had slightly lower mean FVC, FEV_1 and $DLCO_{corr}$ than did the seronegative group, but no such difference was apparent for the HTLV-II group.

The results of the multivariable linear regression analysis are presented in Table 2. For both FVC and FEV1 adjusted for height squared, mean values were only minimally smaller for the HTLV-I group, and no different at all for the HTLV-II group, both compared to HTLV seronegatives. For $DLCO_{corr}$, the HTLV-I group had mean values that were about ten percent lower, and the HTLV-II group about five percent lower, compared to seronegatives. However these differences narrowed after adjustment for potential confounding variables and neither was statistically significant, although there was a trend toward lower adjusted DLCOcorr for the HTLV-I group. DLCO corrected for alveolar ventilation ($DLCO_{corr}$/VA) showed no differences between both HTLV groups and seronegatives in either the unadjusted or the multivariable analysis. Finally, there was no association between DLCO and the level of HTLV-I or HTLV-II proviral load among the HTLV seropositives (data not shown).

Discussion

This study did not reveal significant differences between HTLV-I or -II infected and uninfected persons in pulmo-

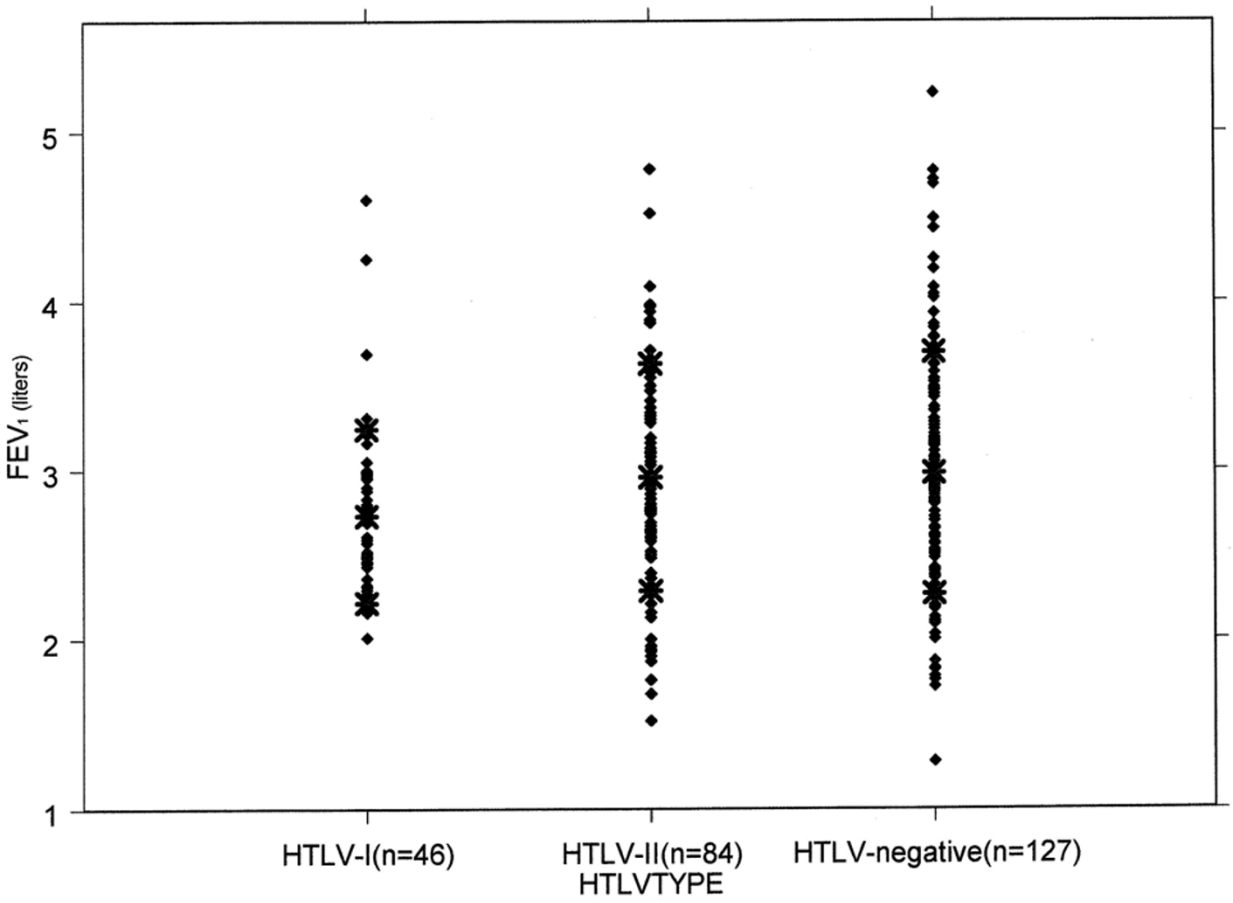

Figure 2
Scatter plot showing values of forced expiratory volume in one second (FEV1) for each subject, with bars indicating mean, and mean plus and minus standard deviation, by HTLV status.

nary function or diffusing capacity, after adjustment for confounding variables. This normal pulmonary function data are in contrast to previous reports of bronchio-alveolitis and differences in biological measurements in broncho-alveolar lavage fluid among persons with HTLV-I infection [1,7].

Most previous reports of HTLV-I bronchio-alveolitis reported more frequent and severe pathological and biological abnormalities of bronchoalveolar lavage fluid in patients with HTLV myelopathy or uveitis compared to HTLV-I carriers without apparent disease [6,8,14]. Since our patients were without overt inflammatory disease, we cannot comment on potential pulmonary function abnormalities in patients with clinical inflammation. Likewise a rare case of bronchio-alveolitis among our study group could have had pulmonary function abnormalities that were masked by our comparison of mean values among the HTLV-I, HTLV-II and seronegative groups. Finally, our subjects could have had clinical or subclinical pulmonary inflammation due to HTLV-I or HTLV-II infection, but this inflammation was not of sufficient severity or duration to manifest measurable decrements in overt pulmonary function.

Data from the cohort study from which these subjects were drawn has revealed an increased incidence of pneumonia and acute bronchitis among HTLV-II, and to a

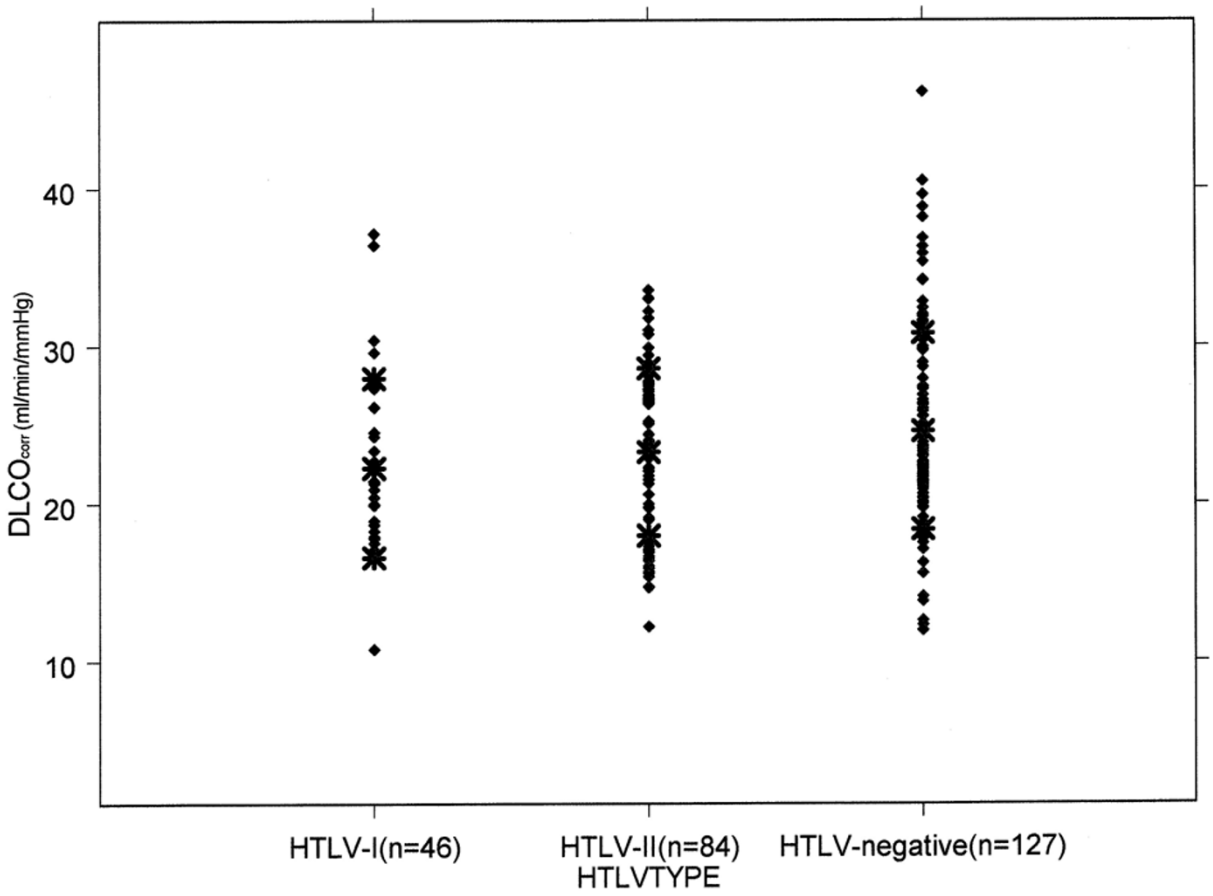

Figure 3
Scatter plot showing values of diffusing capacity of carbon monoxide corrected for hemoglobin (DLCOcorr) for each subject, with bars indicating mean, and mean plus and minus standard deviation, by HTLV status.

lesser degree HTLV-I, infected humans [3,4]. Those results were based upon analyses of reported physician diagnoses of these illnesses, and were adjusted statistically to account for differences in socioeconomic status, cigarette smoking and alcohol intake between HTLV infected and uninfected subjects. Although we initially attributed these illnesses to an increased susceptibility to bacterial infection, we now propose the hypothesis that these diagnoses may have been due to immunological mechanisms as in cases of HTLV-I bronchio-alveolitis. The negative results of current study, although reassuring to persons with HTLV-I or HTLV-II infection, cannot exclude either of these hypotheses.

Strengths of the current study include its setting in a well characterized cohort study of humans with laboratory confirmed HTLV-I and HTLV-II infection, and the inclusion of an appropriate control group. Due to information gathered in the cohort study, we were also able to control for other potential confounding variables such as cigarette smoking and alcohol intake. Weaknesses include moderate size of the study, which made us unable to detect PFT differences that were less than about ten percent. PFT's were done at four different sites, which could have resulted in increased variability of the results. The PFTs that we used may be insensitive to minor degrees of pulmonary damage, and with this cross-sectional data we may have missed a progressive loss of pulmonary function over time in the HTLV groups.

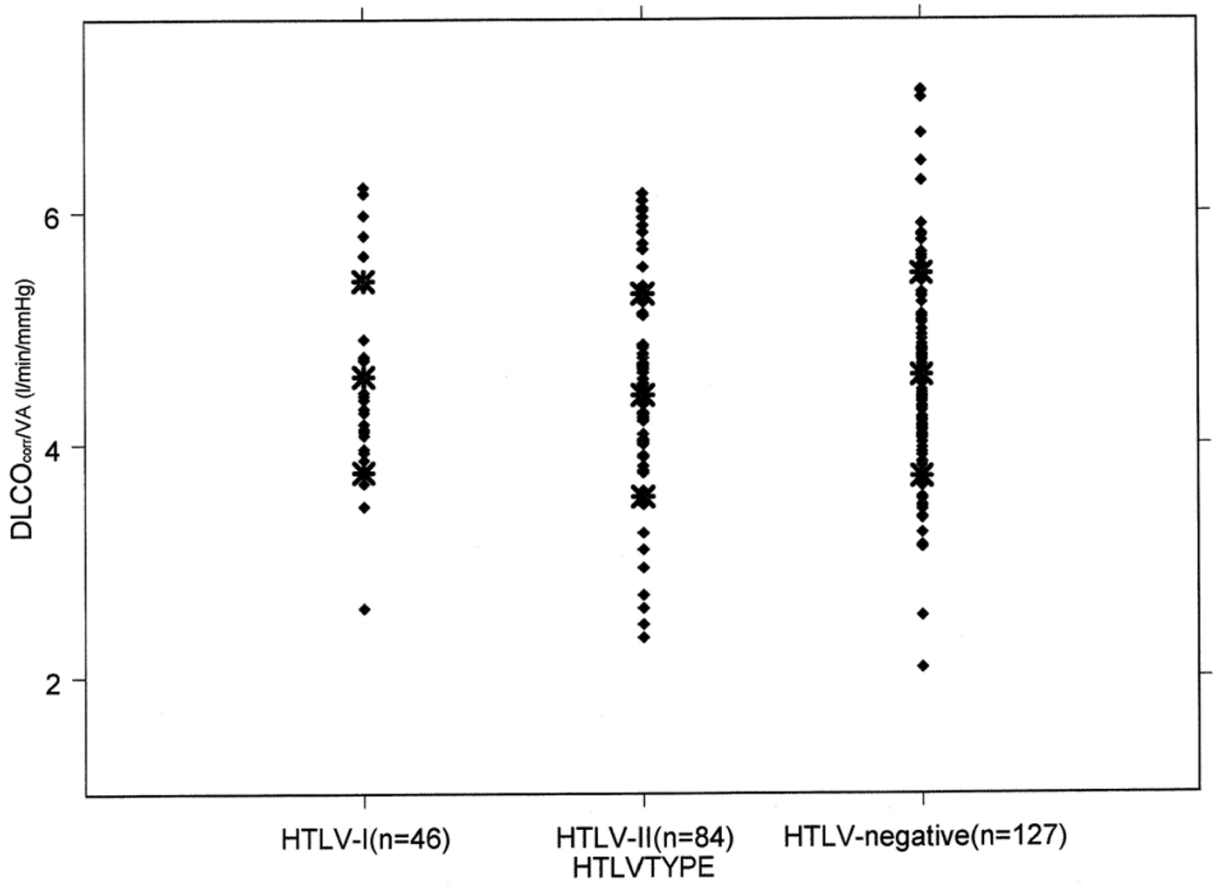

Figure 4
Scatter plot showing values of diffusing capacity of carbon monoxide corrected for hemoglobin and alveolar ventilation (DLCOcorr/VA) for each subject, with bars indicating mean, and mean plus and minus standard deviation, by HTLV status.

Table 2: Unadjusted and adjusted (for age, sex, race, smoking history and body weight) comparison of pulmonary function values between the HTLV-I or HTLV-II groups, versus the HTLV seronegatives.

Variable	Seronegative mean	HTLV-I vs. Seronegatives		HTLV-II vs. Seronegatives	
		Unadj Diff in Means	Adjusted Diff (95%CI)	Unadj Diff in Means	Adjusted Diff (95%CI)
FVC/height^2 (liters/m^2)	1.35	-0.09	-0.02 (-0.09, 0.05)	0.02	0.01 (-0.04, 0.07)
FEV_1/height^2 (liters/m^2)	1.06	-0.05	-0.01 (-0.07, 0.05)	0.00	0.00 (-0.04, 0.05)
$DLCO_{corr}$ (ml/minute/mmHG)	24.58	-2.31	-1.23 (-3.20, 0.74)	-1.31	-0.34 (-1.77, 1.09)
$DLCO_{corr/VA}$ (ml/minute/mmHg)	4.6	-0.02	0.05 (-0.28, 0.38)	-0.18	0.03 (-0.21, 0.27)

Conclusions

In conclusion, this moderate size study did not reveal any statistically significant differences in pulmonary function between generally healthy HTLV-I or -II infected persons and comparable HTLV seronegatives. However it could not rule out subtle differences in lung inflammation that might lead to functional impairment over a longer follow-up period. Further studies of the immunologic characteristics of bronchoalveolar lavage cells from HTLV-I or -II infected humans are needed, especially in persons with a history of recurrent pneumonia or acute bronchitis but without myelopathy or uveitis.

Competing interests

None declared.

Author's contributions

Study Design: Murphy, Ameti

Patient Accrual: Ownby, Smith, Garratty, Hutching

Data Analysis: Murphy, Wu

Manuscript Writing: Murphy

Manuscript Comments & Reviews: all authors

Acknowledgments

We are indebted to the study nurses (Janis Campbell, Peggy Richie, Alberta Rodney, Kate Sclimenti, Diana Wilke, Rebecca Ruedy, Elane Moore), to the staff of the PFT units at Detroit Receiving Hospital, Pomona Valley Hospital Medical Center, Long Beach Memorial Medical Center, San Francisco General Hospital and Presbyterian Hospital of Oklahoma City, and to the subjects who agreed to undergo PFT.

References

1. Sugimoto M, Kitaichi M, Ikeda A, Nagai S and Izumi T: **Chronic bronchioloalveolitis associated with human T-cell lymphotrophic virus type I infection** *Curr Opin Pulm Med* 1998, **4:**98-102.
2. Matsuse T, Fukuchi Y, Hsu CY, Nagase T, Higashimoto N, Teramoto S, Matsui H, Sudo E, Kida K, Morinari H, Fukayama M, Ouchi Y and Orimo H: **Detection of human T lymphotropic virus type I proviral DNA in patients with diffuse panbronchiolitis** *Respirology* 1996, **1:**139-144.
3. Murphy EL, Glynn SA, Fridey J, Sacher RA, Smith JW, Wright DJ, Newman B, Gibble JW, Ameti DI, Nass CC, Schreiber GB and Nemo GJ: **Increased prevalence of infectious diseases and other adverse outcomes in human T lymphotropic virus types I- and II-infected blood donors. Retrovirus Epidemiology Donor Study (REDS) Study Group** *J Infect Dis* 1997, **176:**1468-1475.
4. Murphy EL, Glynn SA, Fridey J, Smith JW, Sacher RA, Nass CC, Ownby HE, Wright DJ and Nemo GJ: **Increased incidence of infectious diseases during prospective follow-up of human T-lymphotropic virus type II- and I-infected blood donors. Retrovirus Epidemiology Donor Study** *Arch Intern Med* 1999, **159:**1485-1491.
5. Mukae H, Kohno S, Morikawa N, Kadota J, Matsukura S and Hara K: **Increase in T-cells bearing CD25 in bronchoalveolar lavage fluid from HAM/TSP patients and HTLV-I carriers** *Microbiol Immunol* 1994, **38:**55-62.
6. Mita S, Sugimoto M, Nakamura M, Murakami T, Tokunaga M, Uyama E and Araki S: **Increased human T lymphotropic virus type-1 (HTLV-1) proviral DNA in peripheral blood mononuclear cells and bronchoalveolar lavage cells from Japanese patients with HTLV-1-associated myelopathy** *Am J Trop Med Hyg* 1993, **48:**170-177.
7. Seki M, Higashiyama Y, Mizokami A, Kadota J, Moriuchi R, Kohno S, Suzuki Y, Takahashi K, Gojobori T and Katamine S: **Up-regulation of human T lymphotropic virus type I (HTLV-1) tax/rex mRNA in infected lung tissues** *Clin Exp Immunol* 2000, **120:**488-498.
8. Sugimoto M, Imamura F, Matsumoto M, Sonoda E, Cho I and Ando M: **Pulmonary involvement in patients with human T lymphotropic virus type I-associated myelopathy: the presence of specific IgA antibody in bronchoalveolar lavage fluid** *Am J Trop Med Hyg* 1993, **48:**803-811.
9. Sugimoto M, Nakashima H, Matsumoto M, Uyama E, Ando M and Araki S: **Pulmonary involvement in patients with HTLV-I-associated myelopathy: increased soluble IL-2 receptors in bronchoalveolar lavage fluid** *Am Rev Respir Dis* 1989, **139:**1329-1335.
10. Seki M, Higashiyama Y, Kadota J, Mukae H, Yanagihara K, Tomono K and Kohno S: **Elevated levels of soluble adhesion molecules in sera and BAL fluid of individuals infected with human T-cell lymphotropic virus type I** *Chest* 2000, **118:**1754-1761.
11. Kawakami K, Miyazato A, Iwakura Y and Saito A: **Induction of lymphocytic inflammatory changes in lung interstitium by human T lymphotropic virus type I** *Am J Respir Crit Care Med* 1999, **160:**995-1000.
12. **Lung function testing: selection of reference values and interpretative strategies. American Thoracic Society** *Am Rev Respir Dis* 1991, **144:**1202-1218.
13. Neas LM and Schwartz J: **Pulmonary function levels as predictors of mortality in a national sample of US adults** *Am J Epidemiol* 1998, **147:**1011-1018.
14. Sugimoto M, Mita S, Tokunaga M, Yamaguchi K, Cho I, Matsumoto M, Mochizuki M, Araki S, Takatsuki K and Ando M: **Pulmonary involvement in human T-cell lymphotropic virus type-I uveitis: T-lymphocytosis and high proviral DNA load in bronchoalveolar lavage fluid** *Eur Respir J* 1993, **6:**938-943.

Pre-publication history

The pre-publication history for this paper can be accessed here:

http://www.biomedcentral.com/1471-2466/3/1/prepub