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Alveolus-Capillary Permeability on Both Normal and HIV Seroreactive Individuals

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ABSTRACT

The aim of this study was to evaluate the alveolus-capillary permeability by the lung clearance rate of ^{99m}Tc-DTPA(Technetium99m-diethylene triamine penta-acetate), (LCR-DTPA), both in normal and in asymptomatic HIV seroreactive patients. Thirty individuals were studied, 21 seronegative normal volunteers and 9 HIV seroreactive patients presenting normal chest radiography and no respiratory infection symptoms. LCR-DTPA was determined by inhaling ^{99m}Tc-DTPA and obtaining images in a gamma camera. The ^{99m}Tc-DTPA clearance rate in normal individuals was 0.99±0.15%.min^{-1} and in patients 2.31±1.25%.min^{-1}. There was a significant statistical difference between the two groups ($p < 0.05$). Two patients who presented LCR-DTPA higher than 4.3 %.min^{-1} presented pneumocystis pneumonia one month later. Seroreactive AIDS patients, previously asymptomatic that presented pneumonia later showed higher LCR-DTPA than the seroreactive who did not develop the illness. These results suggested that LCR-DTPA could be a predictive method for the clinical development of pneumocystis pneumonia in asymptomatic HIV seroreactive patients.

Key Words: HIV seroreactive, alveolus-capillary permeability, ^{99m}Tc-DTPA clearance, pneumocystis pneumonia

INTRODUCTION

The number of AIDS cases has been increasing all over the world in spite of adoption of health programs aimed at information and guidance of preventive measures. According to the Brazilian Health Ministry, between 1980 and 2001 AIDS cases reported in Brazil were 237,588; 35,387 of them located in Rio de Janeiro (Brazil 2001). Since the onset of the acquired immunodeficiency syndrome (AIDS), both in homosexual individuals and addict of injectable drugs, there has been described opportunistic infections and Kaposi sarcoma in these individuals (Gottlieb et al. 1981). In these cases, nuclear medicine offers powerful non invasive techniques for visualization of infections disorders by whole body imaging (Das et al 2002, Wareham et al 2005). In clinical terms, lung is one of the main target organs of illnesses most frequently in seroreactive patients. About 70% of the HIV seroreactive patients underwent an episode of respiratory illness in the course of

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HIV infection (McGuinness 1997). The most common pathogen of pulmonary infection in HIV seroreactive patients is *Pneumocystis jiroveci* (*Pneumocystis carinii)* (Kuhlman 1996). Pneumocystis pneumonia is usually characterized by progressive dyspnea, hypoxemia with pulmonary infiltration. Pneumocystis pneumonia may be difficult to diagnose because the symptoms – fever, cough and shortness of breath – are non-specific (Katz & Hollander 2004). A lymphocytic alveolitis is commonly noticed during the course of HIV disease. Meignan et al. (1990) have found a high incidence of such an alveolitis in HIV seroreactive patients without detectable lung infection or tumor. The functional integrity of the alveolus-capillary barrier may be altered in aseries of pathologic condition, such as chronic lung diseases and smoking cigarettes, leading to an increase on the alveolus-capillary permeability (Jones et al. 1980, Nery et al. 1988).

Recently, great interest has been developed in the method of measuring respiratory epithelial permeability through the use of radioactive aerosols of low molecular weight solutes, particularly Technetium-99m-diethylene triamine penta-acetate (^{99m}Tc-DTPA) complex. The ^{99m}Tc-DTPA complex when deposited on the pulmonary epithelial surface diffuses from the airspace to the vascular space, hence, it equilibrates rapidly with the total-body extra-cellular fluid space and once in blood stream, it is simultaneously filtered by the kidneys. The procedure to assess the integrity of the pulmonary epithelium is based on the clearance rate of aerosolized ^{99m}Tc-DTPA (Mason et al. 1983).

As the epithelium is the most impermeable component of the alveolar-capillary barrier, injury to this membrane can enhance solute diffusion from the alveolar to the vascular compartment (Barrowcliffe & Jones 1987). Mason et al. (1987) have found in 12 patients with pneumocystis pneumonia very high values of ^{99m}Tc-DTPA clearance rate. In 13 HIV seroreactive patients, with respiratory symptoms of pneumocystis pneumonia, studied by Meignan et al. (1990), the ^{99m}Tc-DTPA clearance was significantly elevated, ranging from 2.00% to 11.60%.min^{-1} (normal = 1.1% ±0.34.min^{-1}). Rosso et al. (1992) studied 39 patients with diagnosis of pneumocystis pneumonia have found a ^{99m}Tc-DTPA clearance greater than 4.5%.min^{-1} and suggested that this clearance value was both sensitive and specific for the diagnosis of pneumocystis pneumonia.

The aim of this study was to evaluate the permeability of pulmonary epithelium by the determination of the lung clearance rate of ^{99m}Tc-DTPA (LCR-DTPA) both in normal individuals and in non symptomatic HIV seropositive patients.

MATERIALS AND METHODS

Patients

Clearance measurements were made in 21 asymptomatic and healthy volunteers (15 males, 6 females), mean age of 48.9 years old (range from 22 to 69) with no recent history of upper respiratory illness, 7 of them never smoked cigarettes and 14 stopped smoking 1-6 years before the study; in 9 HIV seroreactive patients (4 males and 5 females) mean age 33.2 years old (range from 28 to 40) which presented normal chest radiographs, neither opportunistic infection symptoms nor suggestive signs of pulmonary infection. As smoking increases ^{99m}Tc-DTPA clearance (Jones et al. 1980, Nery et al. 1988) only patients who had refrained from smoking for more than three weeks prior to clearance determinations were included in this study. Patients HIV seroreactive were ordered from DST-AIDS Service at General Hospital of Nova Iguaçu (Rio de Janeiro, Brazil).

This study was approved by the ethic committee of the hospital and patients gave informed consent before undergoing the exam.

Radiopharmaceuticals

The sodium pertechnetate (Na $^{99m}TcO_4$) - obtained from a ^{99}Mo/^{99m}Tc generator - and diethylene triamine penta-acetate (DTPA) was produced by the Institute of Energetic and Nuclear Research (IPEN–CNEN, São Paulo, SP, Brazil). To generate the ^{99m}Tc-DTPA complex, 2.2 MBq (60 mCi) of sodium pertechnetate was introduced into a vial containing 3.3 mg of DTPA. The binding efficiency of $^{99m}TcO_4^-$ to DTPA was over 97% on test preparation seen on chromatography.

Equipment

All images were acquired with a dual-head gamma camera Nucline DH MB 9500 SPECT (Mediso, Budapest, Hungary). The windows were centered over the ^{99m}Tc photo peak with a width of 20%. Parallel holes, low energyu, general purpose collimator was used.

Nebulizer

Aerogama (Gama Medical, Porto Alegre, RS, Brazil), a shielded jet nebulizer that produces an aerosol of 0.86μm MMAD (mass median diameter), with standard geometric deviation of 0.98μm (Droplet and Particle Analyzer, [Malvern, series 2.600], Laboratório de Caracterização Tecnológica – Departamento de Engenharia de Minas, Escola Politécnica, Universidade de São Paulo, São Paulo, Brazil; Report of 06/02/96).

Method

Diagnostic of HIV was done by enzyme-linked immunosorbent assay (ELISA). Absolute CD4 lymphocyte count and the values of serum lactate dehydrogenase were determined. Clearance determination has been described in detail elsewhere (Maliska 1997). A dose of 1.1MBq (30 mCi) of ^{99m}Tc-DTPA preparation was diluted in 2 mL of 0.9% saline solution introduced in the nebulizer and submitted to compressed air at a flow rate of 9L/min to produce the aerosol to be inhaled by mouth through a mouthpiece for 2 min with normal tidal volumes, with a clip in the nose. Immediately after the inhalation, the individual was positioned (in the supine position) with his back facing the detector. Dynamic acquisition of the detected lung field radioactivity was monitored for 15 min, with images of 30 s duration, with a digital gamma camera linked to a computer.Time-activity curves were derived from the activity computed in regions of interest comprising the entire right lung field and fitted by a mono-exponential model according to the equation: $A(t) = Ao.e^{-kt}$, where Ao is the activity contained the lung field immediately after the end of the inhalation. The clearance rate (k) derived from the fit performed on the curves during the first 7 min after the end of the inhalation, was expressed in $\%.min^{-1}$. The half life ($T_{1/2}$) of aerosol permanence in the lung was also determined, as follows: $T_{1/2} = 0.693/k$. Group mean data were expressed as the mean ±standard deviation. Student´s t test was employed for intergroup comparisons. *P* values <0.05 were considered statistically significant.

RESULTS

Fig. 1 shows the pulmonary clearance of ^{99m}Tc-DTPA aerosol and its pulmonary distribution in a healthy volunteer. Mean value of pulmonary clearance rate of ^{99m}Tc-DTPA aerosols in normal individuals was 0.99±0.15 $\%.min^{-1}$. Table 1 shows the mean age and the results of LCR-DTPA in $\%.min^{-1}$ and $T_{1/2}$ of LCR-DTPA expressed in min for both groups.

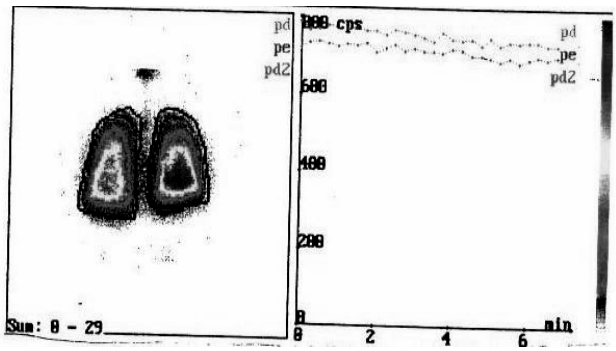

Figure 1 - Curves of radioactive counts versus time, monitored over the lung regions of interest and the image of radioactive aerosol distribution in a healthy volunteer (LCR-DTPA = 0.88 $\%.min^{-1}$)

Table 1 - Lung clearance rate of ^{99m}Tc-DTPA in normal individuals and in HIV serore active patients.

Age in years	**48 ±14,8**	**33,3 ± 5,3**
LCR (%.min^{-1})	0,99± 0,15	2,31 ± 1,15
LCR ($T_{1/2}$.min^{-1})	72,4 ± 10,4	38,6 ± 20,0

(1)mean ± SD

There was a significant statistical difference between the means of normal subjects group and HIV seroreactive group ($p< 0.05$). Mean value of all 9 HIV seroreactive patients was 2.31±1.15%.min^{-1} (Table 2), the value of LCR-DTPA of seroreactive patients nº 7 and 8 was 4.36 ± 0.01%.min^{-1} and the value of the other seven patients seroreactive, that did not develop pneumocystis pneumonia was 1.72 ± 0.60%.min^{-1} ($p<0.01$). The pulmonary clearance of ^{99m}Tc-DTPA in HIV seroreactive patients are shown in Figs. 2 and 3.

Table 2 - Clinical and laboratorial data and LCR values of the HIV seroreactive group.

Patient	**Sex**	**Age(y)**	**Cough**	**Dyspnea**	**SLD unit/L**	***CD_4 cells/mm^3**	****Viral Charge**	**Chest Radiograph**	**LCR (%/min)**
1	F	37	DC	DO	200	150	5,19	Unsp	0,95
2	F	32	DC	DO	…	…	…	Unsp	1,52
3	F	40	CO	DO	…	361	1,32	N	2,64
4	M	37	DC	DP	…	431	2,5	N	1,98
5	M	28	CO	DO	180	300	…	N	1,07
6	F	26	PC	DP	495	107	…	Unsp	1,76
7	M	30	DC	DP	100	100	…	N	4,35
8	M	40	DC	DP	379	155	5,62	N	4,36
9	F	30	DC	DO	…	646	3,86	N	2,14

*CD_4: lymphocyte count; **Viral charge in log of virus/mL

CO: cough out; DC: dry cough; ; PC: productive cough; DO: dyspnea out; DP: dyspnea present; SLD: serum lactate dehydrogenase; N: normal; Unsp = unspecific; LCR: Lung Clearance Rate of ^{99m}Tc-DTPA aerosol;

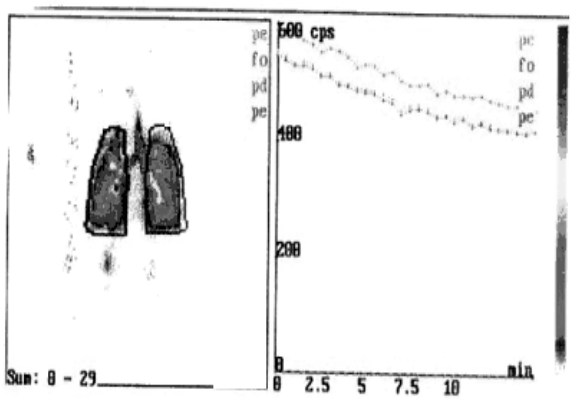

Figure 2 - Curves of radioactive counts versus time, monitored over the lung region of interest and the image of radioactive aerosol distribution in a seroreactive patient - patient No.9 - (LCR-DTPA = 2.14 %.min^{-1})

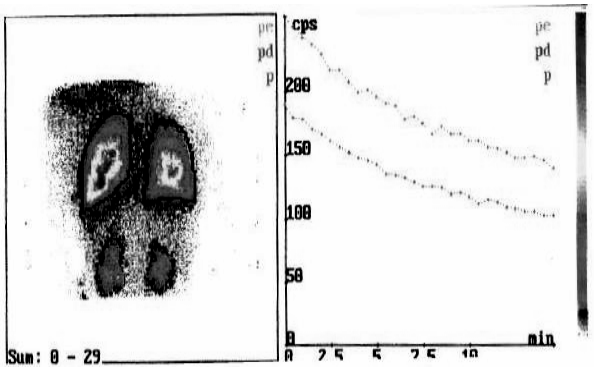

Figure 3 - Curves of radio active counts versus time Monitored over the lung regions of interest and the image of radioactive aerosol distribution in a sero-reactive patient - No.7 -, who had late developed pneumocystis pneumonia (LCR-DTPA = 4.35 %.min^{-1}). Note the accentuated decline in the curves of radioactivity counts as compared to the curves in Fig. 1 and 2, and also the image of intense ^{99m}Tc-DTPA elimination through the kidneys

DISCUSSION

The HIV seroreactive patients are subject to opportunistic infections, due to the loss of inflammatory response and during their short life intervals they can present pneumocystis pneumonia episodes (Mills 1986).

In contrast to gases, which are able to diffuse through the whole of the alveolar-capillary area, the diffusion of hydrophilic solutes, such as ^{99m}Tc-DTPA, is thought to be restricted to the much smaller surface area occupied by the intercellular junctions. Some studies have shown that solute permeation of epithelial junctions is about 10 times less than that of the endothelium. The equivalent pore radii calculated from physiological studies are around 0.6 – 1.0 nm for the epithelium and around 4.0 – 5.8 nm or more for the endothelium (Taylor & Gaar 1970). As the epithelium is the most impermeable component of the alveolar-capillary barrier, injury to this membrane can enhance solute diffusion from the alveolar to the vascular compartment (Barrowcliffe & Jones 1987).

Measurement of lung clearance of aerosolized ^{99m}Tc-DTPA is currently used to assess the integrity of the alveolus-capillary barrier. The clearances rate of ^{99m}Tc-DTPA (LCR-DTPA) is increased in a wide variety of both acute and chronic diseases that result in morphologic injury to the pulmonary epithelium. Elevated ^{99m}Tc-DTPA clearances have been documented among patients with neonatal and adult respiratory distress syndromes, idiopathic pulmonary fibrosis, progressive systemic sclerosis, pneumoconiosis, silicosis and otherwise normal smokers (Jeffries et al. 1984, Rinderknecht et al. 1980, Pinheiro et al. 2000; Pinheiro et al. 2003; Jones et al.1980, Nery at al.1988, Clark et al.1988). Loss of type I cell is characteristic of these conditions, except in normal smokers. Increases in epithelial permeability presumably reflect epithelial injury in patients with pneumocystis infections and those with adult respiratory distress syndrome. Both of these disorders are associated with pathologically diffuse alveolar damage (Mason et al. 1985).

In 12 patients with pneumocystis pneumonia, Mason et al. (1987) have found values of LCR-DTPA greater than 4.7 %.min^{-1}, Rosso et al. (1992) have found in 39 patients with pneumocystis pneumonia values of ^{99m}Tc-DTPA clearance greater than 4.5%.min^{-1} and proposed the method for diagnosing pneumocystis pneumonia. Mason et al. (1987) found that LCR-DTPA returned toward normal values during a period of several weeks to several months in patients who were successfully treated for their pneumocystis pneumonia. In three patients clearance failed to improve in a consistent manner with trimethoprim-sulfamethoxazole. Two of these patients subsequently died because of respiratory failure and the third eventually did well with an experimental drug (Mason at al.1987).

In the present study, lung epithelial permeability measured by the ^{99m}Tc-DTPA clearance rate was elevated (LCR-DTPA of 1.72 ± 0.60%.min^{-1}) in seven non symptomatic HIV seroreactive patients that did not develop pneumocystis pneumonia later. The two other patients showed a clearance rate of 4.35 and 4.36 %.min^{-1}. One month later, they developed pneumocystis pneumonia, one of them died in consequence of his refusal to undergo a specific treatment. The other underwent the proposed treatment (trimethoprim sulfamethoxazole) and had an excellent therapeutic response. Such facts were in agreement with the low count of CD_4 leucocytes of these two patients (100 and 155 cells/mm^3), but not with the other group of patients HIV seroreactive that did not develop the illness. In those patients, there was a disagreement between the CD_4 leucocytes count and the LCR-DTPA values.

The small elevation in LCR-DTPA in patients that did not develop pneumocystis pneumonia perhaps could be explained by the observation of Meignan et al. (1990) that lymphocytic alveolitis was observed in 70% of HIV seroreactive patients without detectable lung opportunistic infection. Alveolar HIV- specific cytolytic T-lymphocytes were found in patients at early stage of HIV disease and gradually disappeared during the course of HIV infection. Meignan et al. (1990) observed lymphocytic alveolitis in patients with normal LCR-DTPA and without alveolar lytic activity and suggested that the alteration of pulmonary epithelial permeability as measured by LCR-DTPA could be induced by the presence of CD8+D44+ lymphocytes reacting *in vivo* with HIV-infected alveolar macrophages.

Documentation of *Pneumocystis jiroveci* infections usually requires invasive diagnostic procedures. Bronchoscopy is generally conducted in patients with a predisposing factor, such as AIDS, who present with cough, fever and dyspnea with hypoxemia and pulmonary infiltrate. Galium-67 scans are sometimes used to help to determine which patients require bronchoscopy (Coleman et al.1984), but the main disadvantage of this method is the minimum 48h delay to have the results (Mason et al. 1987). It is important to note that mean value of LCR-DTPA of seroreactive patients nº 7 and 8 (4.36 %.min^{-1}) was more than four times higher the mean value of normal volunteers, in contrast with mean value (1.72%.min^{-1}) for the other seven patients that did not develop pneumocystis pneumonia, which was too close to mean normal value. This observation suggested that the procedure was very sensitive, however, to detect specific pathogenic organism bronchoscopy must be performed.

Three points should be emphasized. One is that irradiation exposure to ^{99m}Tc-DTPA clearance studies is minimal. The doses can be compared with the annual natural irradiation dose and to the radiation dose delivered by one chest radiography. In a larger sense, the irradiation dose due to scintigraphic examination is between the natural environmental dose and radiological dose (Baulieu 1993). The other one is that LCR-DTPA studies appears to be useful as a screening test because it is non-invasive, physiologic, easy to perform, well tolerated and permits quantification of data. Third is that the method can be used to test efficacy of medication because clearance rates normalize after treatment (Mason et al. in 1987).

Than, it could be concluded that the present study was in agreement with literature and suggested that LCR-DTPA could be a good predictive method for the clinical development of pneumocystis pneumonia in non symptomatic HIV seroreactive patients.

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RESUMO

A integridade funcional da barreira alvéolo-capilar pode ser alterada por diversas condições patológicas e por outros fatores como a irritação do epitélio alveolar, provocada pelo fumo etc, levando a um aumento da permeabilidade alvéolo-capilar. O objetivo deste trabalho foi verificar a permeabilidade do epitélio pulmonar através da determinação da taxa de depuração pulmonar do aerossol de ^{99m}Tc-DTPA (LCR-DTPA) em indivíduos normais e em pacientes assintomáticos

HIV sororreativos. Foram estudados 30 indivíduos, sendo 21 voluntários normais e 9 HIV sororreativos sem sintomas de infecção oportunista, com radiografias de tórax normais ou sem sinais sugestivos de infecção pulmonar. A LCR-DTPA foi determinada após inalação de ^{99m}Tc-DTPA sob a forma de aerossóis e contagem externa da radiação, em função do tempo, em gama câmara. A LCR-DTPA dos controles foi de 0.99±0.15 %.min^{-1} e nos pacientes sororreativos,de 2.31±1.15%.min^{-1} houve diferença significativa entre os dois grupos ($p< 0.05$). Dois pacientes tiveram LCR-DTPA acima de 4,3%.min^{-1}, estes desenvolveram um mês após o exame. Observou-se que os pacientes sororreativos por Imunodeficiência Adquirida (SIDA), sem sintomas específicos para pneumocistose que posteriormente desenvolveram a doença, a LCR-DTPA foi significativamente maior que a dos outros HIV pneumocistose clínica sororreativos que não desenvolveram a doença ($p<0.01$). Estes resultados sugerem que a LCR-DTPA pode ser um método preditivo do desenvolvimento clínico da pneumocistose, não invasivo, de fácil realização e cômodo, para o paciente HIV sororreativo assintomático.

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