# Pulmonary microvascular permeability and gas exchange in patients with syndrome X

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**Abstract**
**Aim:** This clinical study was planned to assess pulmonary microvascular permeability in patients with Syndrome X (SX) by using a functional imaging tool, technetium-99m-diethyltriaminepentaaceticacid ($^{99m}$Tc-DTPA) lung clearance scintigraphy, and the pulmonary functions test, which includes diffusion capacity of the lung for carbon monoxide ($DL_{CO}$).
**Methods:** The study population consisted of 22 non-smoker subjects divided into two groups. First group comprised 12 patients (4 male, 8 female, mean age: 48±4 years, range 36 to 65) with SX. Ten healthy subject (4 men, 6 female, mean age: 45±3 years, range 34 to 58) were served as control group. Volumetric pulmonary functions, including $DL_{CO}$ were also performed before lung scintigraphy. Alveolar epithelial permeability was assessed by measuring the pulmonary clearance of an inhaled $^{99m}$Tc-DTPA using a gamma camera.
**Results:** Spirometric data was comparable in both groups. Although volumetric pulmonary measurements were similar, $DL_{CO}$ values of SX patients were lower than those in control (20.9±1.7 ml/min/mmHg vs. 27.8±1.3 ml/min/mmHg, p=0.002). The mean clearance rate of $^{99m}$Tc-DTPA in control subjects was 106±6 min, and this value was lower than patients with SX (179±19 min; p=0.0001).
**Conclusion:** We conclude that lung is a target organ for SX. The pulmonary gas exchange and microvascular permeability, which is measured by 99mTc-DTPA scintigraphy, are restricted without change of volumetric pulmonary functions in patients with SX. Hippokratia 2012; 16 (2): 113-117

**Key words:** $^{99m}$Tc-DTPA, syndrome X, lung, carbon monoxide diffusing capacity, microvascular

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Kemp[1] introduced the term Syndrome X (SX) to describe a group of patients with angina pectoris and positive exercise electrocardigraphic test with normal coronary angiograms. Some of these patients had regional myocardial perfusion defect and/or wall motion abnormalities[2-4]. The exact pathophysiological mechanisms underlying this condition are not well understood, and many mechanisms for the chest pain have been suggested. Since the epicardial coronary arteries are defined angiographically normal, attention has been focused on dysfunction of the coronary microcirculation[5]. In some studies, microvascular dysfunction has been accused to cause angina[6-8]. In addition to exertional chest pain, all these patients had complain of breathlessness, with no evidence of airway obstruction or resting left ventricular dysfunction[9]. Cannon et al[10] reported that airway hyper responsiveness is frequently demonstrable in patients with microvascular angina; moreover they hypothesized that this syndrome may represent a more generalized abnormality of vascular and nonvascular smooth muscle function. Recent studies reported that patients with SX

had endothelial dysfunction[11] and generalized arterial distensibility[12]. There are a few studies about the microvascular angiopathy of SX on the other organ system[13-15]. As the other microangiopathic disease, the best known is diabetes mellitus[16]. Besides the others, the most familler microangiopathic disease is DM in which the lung could be a target organ for microvascular pathologies in patients with SX. Thereby, this clinical study was planned to assess pulmonary microvascular permeability in patients with SX by using a functional imaging tool, technetium-99m-diethyltriaminepentaaceticacid ($^{99m}$Tc-DTPA) lung clearance scintigraphy, and the pulmonary functions test, which includes diffusion capacity of the lung for carbon monoxide ($DL_{CO}$).

## Material and Methods

The study population consisted of 22 non-smoker subjects divided into two groups. First group comprised 12 patients (4 men, mean age: 48±4 years, range 36 to 65) with SX, which was defined as a combination of chest pain, positive treadmill exercise test, negative ergonovine

and hyperventilation test, and angiographically proven normal coronary arteries, and no existence of diabetes mellitus, hypertension and left ventricular hypertrophy. Left ventricular hypertrophy was defined echocardiographically as a left ventricular mass index greater than 134 g/m$^2$ in men and greater than 110 g/m$^2$ in women. Ten healthy subject (4 men, mean age: 45±3 years, range 34 to 58) without coronary artery disease, pulmonary disease and diabetes mellitus served as control group.

**Pulmonary function tests:** Spirometric parameters, forced expiratory volume in 1 s (FEV$_1$), forced vital capacity (FVC), total lung capacity (TLC), diffusing capacity of the lung for carbon monoxide (DL$_{CO}$) and alveolar volume (V$_A$) were measured with a water-sealed spirometer (Sensor Medics 2400, Bilthoven, The Netherlands). Values were expressed as percentages of the predicted values calculated according to sex, weight, height and age [17]. Spirometry was performed in the standard sitting position at least three times in accordance with American Thoracic Society recommendations [18]. The best values of FVC and FEV$_1$ were selected for analysis. TLC was estimated with the helium dilution method. DL$_{CO}$ was measured in the sitting position with the single-breath method [19]. DL$_{CO}$ values were corrected for the hemoglobin concentration of the patient. For this correction, we used the following equation: Corrected DL$_{CO}$ = Measured DL$_{CO}$* [1.00 + (%COHb/100)]. Transfer coefficient (K$_{CO}$) was calculated from DL$_{CO}$ /V$_A$.

**$^{99m}$Tc-DTPA aerosol inhalation scintigraphy:** Tc-99m DTPA (CIS, France) was chelated by introducing 1480MBq of sodium $^{99m}$TcO$_4^-$ into 5 ml of normal saline. Tc-99m DTPA was placed in the nebulizer reservoir of a commercially available system (Venticis II, CIS, France). Aerosols with a mass median diameter of 0.8 µ were produced with oxygen in flow of 10-12 L/min. Patients inhaled for 3 min in the sited position. Approximately 10% total activity was administered to patients during the 3-min inhalation. The subjects were placed over a gamma camera (Orbiter; Siemens Corp., Iselin, NJ, USA) with low- energy; all-purpose collimator and lung fields were imaged in posterior projection. One-minute frames were acquired in a 64x64 matrix for 30 min. Regions of interest (ROIs) were drawn around the periphery of the lungs and on the major airways on the first-minute image (Figure 1). To obtain a pure alveolar ROI and to exclude the entire bronchial activity, the outer third of each lung was used as the peripheral lung region. The inner two-thirds of the lung was defined as the central lung region. The brightness of the image was increased to visualize body background and the lung periphery, thereby permitting correct definition of the peripheral ROIs. Time-activity curves were generated and curves were corrected for $^{99m}$Tc decay. $T_{1/2}$ was calculated by placing a mono-exponential fit on the curves. $T_{1/2}$ of whole lung was calculated as the mean of the $T_{1/2}$ of the left lung and the right lung. Penetration index (PI) was also calculated by dividing the peripheral total counts by the sum of the peripheral and central total counts on the first-minute image, in order
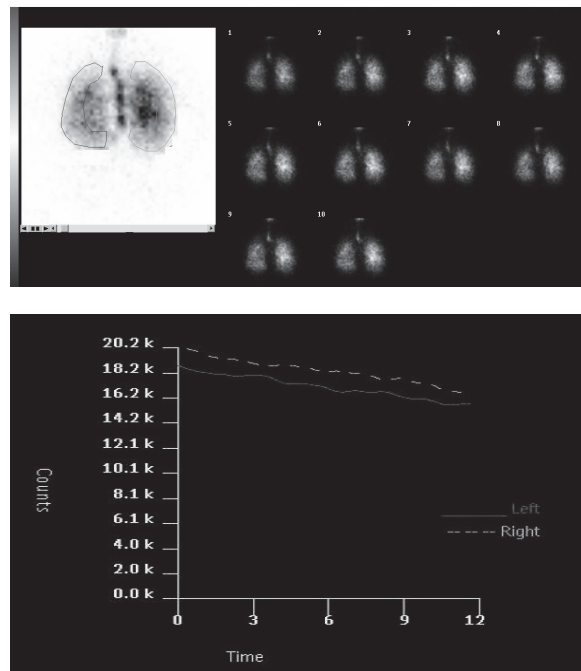


**Figure 1: A:** Serial images of $^{99m}$Tc-DTPA aerosol inhalation scintigraphy and ROI selection on the first-minute image. **B:**$^{99m}$Tc-DTPA clearance curve.
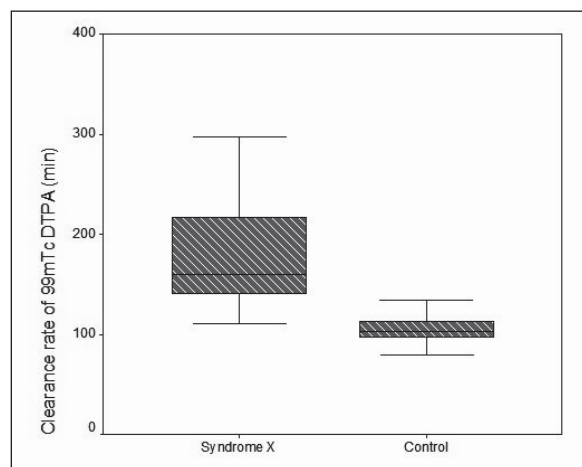


**Figure 2:** The mean t1/2 values of study groups. There are significant differences between syndrome X and control subjects (p=0001).

to quantify the distribution of the inhaled aerosol [PI = peripheral total counts/(peripheral total counts + central total counts)].

**Statistical analysis:** Values are expressed as mean ± SEM. Statistical comparisons of the data between the groups were carried out using Mann Whitney U tests. Relation between scintigraphic data and pulmonary function test variables were assessed with Pearson correlation an r coefficient. A p value < 0.05 was set as statistical significance.

**Table 1:** Comparison of demographic variables and hemoglobin values in patients with syndrome X and control subjects.

|  | Syndrome X | Control | P |
|---|---|---|---|
| **Age, years** | 49.0±2.6 | 46.5±3.1 | NS |
| **Weight, kg** | 77.0±3.17 | 87.2±2.2 | NS |
| **Height, cm** | 161.3±3.0 | 171.7±5.5 | NS |
| **Hemoglobin, g/100 ml** | 13.35±0.3 | 13.85±0.23 | NS |

**NS:** Non-significant. Values are expressed as mean±SE.

**Table 2:** Volumetric lung function values in patients with syndrome X and control subjects.

|  | Syndrome X | Control | P |
|---|---|---|---|
| **$FEV_1$ liters** | 2.6±0.2 | 3.2±0.2 | NS |
| **$FEV_1$ (%)*** | 100±4 | 98±4 | NS |
| **FVC liters** | 3.0±0.2 | 3.8±0.3 | NS |
| **FVC (%)*** | 97±3 | 103±5 | NS |
| **FEV1/FVC(%)*** | 86±1.7 | 84±1.9 | NS |
| **VC liters** | 2.9±0.3 | 3.6±0.4 | NS |
| **VC (%)*** | 99±5 | 100±5 | NS |
| **TLC liters** | 4.9±0.5 | 5.8±0.4 | NS |
| **TLC (%)*** | 92±3 | 99±7 | NS |

**$FEV_1$:** Forced expiratory volume in 1 s, **FVC:** Forced vital capacity, **TLC:** Total lung capacity, **VC:** Vital capacity, **NS:** Non-significant. *****: Values are expressed as percent predicted. Values are expressed as mean±SE.

**Table 3:** DLCO, $DL_{COc}$, $K_{CO}$ values and scintigraphic index in patients with syndrome X and control subjects.

|  | Syndrome X | Control | P |
|---|---|---|---|
| **$DL_{CO}$ ml/min/mmHg** | 20.9±1.7 | 27.8±1.3 | 0.002 |
| **$DL_{CO}$ (%)*** | 79±4 | 99±2 | 0.003 |
| **$DL_{COc}$ ml/min/mmHg** | 20.9±1.7 | 27.9±1.3 | 0.006 |
| **$K_{CO}$ ml/min/mmHg** | 4.3±0.2 | 4.7±0.2 | NS |
| **$K_{CO}$ (%)*** | 68.8±3.9 | 79.0±3.5 | NS |
| **PI (%)** | 52±2 | 59±3 | NS |
| **[99m]Tc-DTPA CR (min)** | 179±19 | 106±6 | 0.0001 |

**$DL_{CO}$:** Diffusing capacity of the lung for carbon monoxide, **$DL_{COc}$** Corrected diffusing capacity of the lung for carbon monoxide, **$K_{CO}$:** Transfer coefficient, **PI:** Penetration index, **CR:** ^{99m}Tc-DTPA clearance rate (t ½ values), **NS:** Non-significant. *****: Values are expressed as percent predicted. Values are expressed as mean±SE.

### Results

Demographic variables and hemoglobin values were similar in SX and control group (Table1). Spirometric data was comparable in both groups. When comparison to volumetric lung function parameters no difference was found in SX and control groups (Table 2). Hovewer, $DL_{CO}$ and $DL_{COc}$ values of SX patients were lower than those in control (Table 3). ^{99m}Tc-DTPA aerosol was distributed uniformly throughout the lungs of all subjects without central deposition. SX patients had lower PI values than control subjects, but did not reach significant level. The mean PI values of SX and control groups were 52±2% and 59±3%,

respectively. The mean clearance rate of ^{99m}Tc-DTPA in control subjects was 106±6 min. The highest T ½ value was noted in SX patients (179±19 min; p=0.0001) (Figure 2). Scintigraphic index were summarized in Table 3.

### Discussion

The most important contribution of presented study is to show pulmonary gas exchanges including $DL_{CO}$ (transfer factor) for carbon monoxide and microvascular permeability measuring 99mTc-DTPA scintigraphy, which are restricted without change of volumetric pulmonary function in patients with SX.

$DL_{CO}$ as a lung function test can provide information about the transport of gas from alveolar air to haemoglobin. Decreased $DL_{CO}$ in patients with SX can explain microvascular angiopathy of lung alveolar capillaries. Cannon et al[10] are hypothesized that this syndrome may represent a more generalized abnormality of vascular and nonvascular smooth muscle function. Recently, Pai et al[13] findings were supported this systemic microvascular abnormalities in patients with SX, and reported that SX was a systemic vascular disorder with a high incidence of hypoperfusion lesions of the brain using 99m Tc-ECD brain SPECT. Our previous two scintigraphic studies, including brain[15] and myocardial perfusion[4], have also been suggested the systemic microvascular abnormalities in patients with SX. Besides Bund et al[14] also showed that there were morphological abnormalities in small arteries obtained from biopsies of skin and subcutaneous fat.

[99m]Tc- DTPA radioaerosol scintigraphy has been used to detect functional defects of the alveolo-capillary barrier in different interstitial lung disease or lung toxicity[20-27]. The ^{99m}Tc-DTPA complex has a molecular weight of 490 Dalton[21]. When it is deposited on the pulmonary epithelial surface, it diffuses from the air space to the vascular space and is finally filtered by the kidneys. The overall change in alveolar clearance of the solute is dependents on several factors: the surface area for transfer, the concentration gradient across the alveolar-capillary membrane, and the diffusion distance or epithelial wall thickness[10,27]. In contrast to gases, which are able to diffuse throughout the whole of the alveolar-capillary surface area, the diffusion of hydrophilic solutes is thought to be restricted to the much more smaller surface area occupied by the intercellular junction. In both diffusion of gas and solute, capillary endothelium is rate limiting part of alveolar-capillary membrane. The finding of present study suggested that lung is a target organ in patients with SX, and microvascular angiopathy of lung capillaries is restricting diffusion, without change of volumetric pulmonary function.

Montorsi et al[28] reported a circadian variation of coronary vascular response to exercise in patients with SX by using cardiopulmonary exercise test. Some other studies have suggested a potential etiological role of excessive sympathetic activation[29-32]. The lungs, capillary endothelium are a major organ for removal of circulating monoamines and play a significant role in the inactivation of circulating norepinephrine[33]. It might be speculated that if microvascular pathology effects capillary endothelium of lung, this impact also may be responsible for the circadian variation, altering monoamine degradation.

Low $DL_{CO}$ and $K_{CO}$ is a well known pathology of some microvascular damage, e.g. chronic heart failure, primary pulmonary hypertension[34]. To our best knowledge, there is no data in English literature to assess gas exchange and microvascular permeability by using ^{99m}Tc-DTPA lung radioaerosol scintigraphy in patients with SX.

The major study limitation was the small size of the study group. When comparison to SX and control groups we found differences in both $DL_{CO}$ and the mean clearance rate of ^{99m}Tc-DTPA measurements in the present study. However futher studies in larger groups could be intensified reability of the results. The present study Additionally, diffusion capacity of the membranes and microvascular blood volume could be calculated separately by Roughton and Forster method[19]. It should be noted , as a limitation of our study is that the diffusing capacity of the alveolar-capillary membrane and capillary blood volume for available gas exchange were not separately determined; this might be helpful during the clarifying the findings.

We conclude that lung is a target organ for SX. The pulmonary gas exchanges and microvascular permeability, measured by ^{99m}Tc-DTPA scintigraphy, are restricted without change of volumetric pulmonary function in patients with SX.

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