Eur Respir J 1999; 13: 133–136
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European Respiratory Journal
ISSN 0903-1936

Clearance of inhaled technetium-99m-DTPA as a clinical index of pulmonary vascular disease in systemic sclerosis

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Clearance of inhaled technetium-99m-DTPA as a clinical index of pulmonary vascular disease in systemic sclerosis. O.M. Kon, Z. Daniil, C.M. Black, R.M. du Bois. ©ERS Journals Ltd 1999.

ABSTRACT: This study evaluated the utility of the clearance time of inhaled diethylenetriamine pentaacetate (DTPA) to distinguish pulmonary vascular disease from early fibrosing alveolitis (FA) in patients with systemic sclerosis (SSc). It was hypothesized that this would be preserved in patients with vascular disease compared with FA, despite similar gas-transfer deficits and matching lung volumes, because of the preservation of alveolar epithelial integrity.

All patients had SSc and were categorized into a control group (C; n=9), pulmonary vascular group (VAS; n=14) or FA group (n=14) dependent on the appearance on a computed tomography (CT) scan and the transfer factor of the lung for carbon monoxide ($T_{L,CO}$) (VAS and FA ≤70%, C ≥80%). All patients had a forced vital capacity (FVC) of >80%.

The $T_{L,CO}$ (median) was similar in the VAS (57.5%) and FA (60%) groups. There was a significant difference in median DTPA clearance half-times between FA (21.25 min) and VAS (46.5 min) (p=0.014) and between FA and C (84.5 min) (p=0.0004). No difference was found between VAS and C (p=0.0778). Follow-up data from the VAS group showed no subsequent development of FA on the CT scan and no decrease in FVC (n=13, mean 42 months).

These results suggest that clearance of diethylenetriamine pentaacetate is preserved in patients likely to have pulmonary vascular disease and may be useful in distinguishing fibrosing alveolitis from vascular disease in systemic sclerosis.

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Keywords: Fibrosing alveolitis
pulmonary vascular disease
systemic sclerosis
technetium-99m-diethylenetriamine pentaacetate

Received: August 31 1998
Accepted after revision February 26 1998

Pulmonary involvement in systemic sclerosis (SSc) is present in 70% of patients at *post mortem* examination [1]. The most common pulmonary complication is fibrosing alveolitis (FA) [2], but isolated pulmonary vascular disease is also well recognized in SSc [3–6] and has also been speculated to be the cause of isolated decreases in the total diffusing capacity of the lung for carbon monoxide ($T_{L,CO}$) [7]. Isolated vascular disease has been noted in particular to be common in patients with limited disease calcinosis, Raynaud's phenomenon, oesophageal involvement sclerodactyly and telangiectasia (CREST) syndrome [8, 9]. Current therapy for predominant vascular disease in this group of patients comprises vasodilator treatment, in contrast to the immunosuppressant regimens used for FA in SSc. Differentiating these two pulmonary complications of SSc is, therefore, of practical significance.

An isolated decrease in $T_{L,CO}$ with preserved lung volumes and a normal chest radiograph is suggestive of the presence of pure pulmonary vasculopathy and has been described previously [10]. High-resolution computed tomography (HRCT) can increase the sensitivity of identification of FA, but absolute confirmation to differentiate vasculopathy from early FA has required invasive biopsy procedures.

Inhaled technetium-labelled diethylenetriamine pentaacetate (^{99m}Tc-DTPA) clearance times have previously been shown to be abnormal in SSc patients with FA [11, 12] and to be useful in predicting the clinical course of their parenchymal disease [13]. There is also evidence that ^{99m}Tc-DTPA clearance times may also be abnormal before plain chest radiograph [14] and computed tomography (CT) [11] changes in FA. Therefore, it was predicted that DTPA clearance times would be slower in predominant vascular disease in SSc than in patients with FA and SSc. This is because preservation of alveolar epithelial integrity, together with obliteration of the vascular bed (the normal route of clearance of isotope from the lung), would prevent removal of the isotope from the airspace. Therefore, ^{99m}Tc-DTPA clearance times were evaluated retrospectively in two groups of nonsmoking patients with SSc and matching abnormalities of isolated decreases in $T_{L,CO}$ but with normal vital capacity: 1) patients with evidence of FA on HRCT, and 2) patients with normal HRCT. For comparison, a group of SSc patients with normal imaging and physiology was also evaluated.

Subjects and methods

Patients

All patients fulfilled the American Rheumatism Association (ARA) preliminary criteria for SSc [15]. Patient groups were then characterized dependent on their presenting lung function and HRCT appearances. An abnormal total gas transfer ($T_{L,CO}$) was defined as ≥70% and normal lung volumes as a forced vital capacity (FVC) of 80%. In the presumed pure vascular disease group (VAS), 14 patients were identified who had isolated $T_{L,CO}$ of ≥70% of predicted, FVC ≥80%, normal chest radiographs

Table 1. – Clinical, demographic and immunological characteristics of 37 patients with systemic sclerosis

Patient No.	Age yrs	Sex	Subject	HRCT	FVC % pred	$T_{L,CO}$ % pred	ECHO	ANA	
								Scl-70	AC
Group 1 (VAS)									
1	56	F	LSSC	N	96	70	N	-	+
2	40	F	LSSC	N	115	66	N		
3	75	F	LSSC	N	122	57		-	+
4	43	M	LSSC	N	104	42	N	-	+
5	63	F	LSSC	N	117	33	PHT	-	+
6	41	F	LSSC	N	95	54	N	-	-
7	62	F	LSSC	N	109	44	PHT	-	+
8	50	F	LSSC	N	106	65	N	-	+
9	38	F	DSSC	N	107	69	N	-	-
10	47	M	LSSC	N	98	58	N	-	+
11	60	F	LSSC	N	108	44	N	-	+
12	52	F	LSSC	N	122	44	N	-	+
13	50	F	LSSC	N	134	60	N	-	+
14	51	F	DSSC	N	113	69	N	-	-
Group 2 (C)									
1	44	F	LSSC	N	103	84		-	-
2	48	F	DSSC	N	113	110	N	-	-
3	52	F	LSSC	N	98	86	N	-	-
4	49	M	LSSC	N	97	105	N	-	-
5	66	F	LSSC	N	137	85	N	-	-
6	50	F	DSSC	N	92	90		-	-
7	79	F	LSSC	N	85	93	N	+	-
8	41	F	DSSC	N	89	80	N	-	-
9	54	F	DSSC	N	148	88	N	-	-
Group 3 (FA)									
1	42	M	DSSC	FA	85	63	N	+	-
2	61	F	LSSC	FA	88	54	N	-	-
3	24	F	DSSC	FA	104	60	N	-	-
4	46	F	DSSC	FA	122	60	N	-	-
5	29	F	LSSC	FA	88	52		-	-
6	49	F	LSSC	FA	88	56			
7	48	F	LSSC	FA	94	69	N	-	-
8	47	F	DSSC	FA	90	54	N	-	-
9	51	F	LSSC	FA	114	64	N	+	-
10	53	F	LSSC	FA	104	63	N	+	-
11	43	F	LSSC	FA	94	61	N	+	-
12	62	F	LSSC	FA	102	46	N		
13	30	F	LSSC	FA	93	69	N	-	-
14	38	F	LSSC	FA	92	52	N	+	-

HRCT: high-resolution computed tomography; FVC: forced vital capacity; $T_{L,CO}$: transfer factor of the lung for carbon monoxide; ECHO: echocardiography; ANA: antinuclear antibodies; AC: anticentromere; VAS: pulmonary vascular; C: control; FA: fibrosing alveolitis; F: female; M: male; LSSC: limited systemic sclerosis; DSSC: diffuse systemic sclerosis; N: normal; PHT: pulmonary hypertension.

and no evidence of parenchymal disease on HRCT appearances. As a matching control group, patients with biopsy-proven FA and SSc were also characterized (n=14). In addition to characteristic biopsies, these patients had HRCT appearances typical of FA and, as in the VAS group, had a $T_{L,CO}$ of $\leq$70% and FVC $\geq$80%. An additional control (C) group comprised nine patients with SSc, but no radiographic or lung function abnormalities.

Full characteristics of all patient groups are given in table 1. All patients were nonsmokers or had stopped smoking at least 6 months before the study.

^{99m}Tc-DTPA clearance

Clearance of aerosolized ^{99m}Tc-DTPA from the lungs to the blood was measured as described previously [16]. An aerosol of ^{99m}Tc-DTPA was produced using an Acorn nebulizer (Medic-Aid, Bognor Regis, UK) and administered for 4 min; the particle size was limited to <2 μm. One-minute frames were acquired by a gamma camera (SMV International, Buc, France) for 45 min, background subtraction was employed, using activity in the central abdomen (not including the kidneys). An exponential fit was derived from the first 15 min of the curve (starting from peak activity) and the half-time of clearance was obtained; slow and fast components were not delineated by curve-stripping. The normal range for ^{99m}Tc-DTPA clear-ance was defined in 22 nonsmoking volunteers (values lying within 2 SD of the mean) [11]; on this basis, a clearance half-time of <40 min was regarded as abnormal.

Respiratory function tests

In all patients respiratory function tests (expressed as percentages of predicted values based on age, sex, height and ethnic origin) [17] had been performed within 4 weeks of initial ^{99m}Tc-DTPA clearance measurement.

Autoantibody analysis

Autoantibody analysis was performed in the Department of Immunology at the Royal Free Hospital and has been described previously [18].

Statistical analysis

All patients with SSc in the Royal Brompton Hospital database between the years 1986 and 1997 were screened and patients were selected on fulfilling the lung function and radiographic criteria outlined above. The data were collected prospectively and analysed retrospectively. $T_{L,CO}$, FVC and ^{99m}Tc-DTPA clearance half-times were analysed between groups using the Mann–Whitney test.

Results

The C group (n=9, aged 41–79 yrs) had median % pred values (range) for FVC of 98 (85–148)% and for $T_{L,CO}$ of 86 (80–110)%. The FA group (n=14, aged 24–62 yrs) had median % pred values for FVC of 93.5 (85–122)% and for $T_{L,CO}$ of 60 (46–69)%. The (VAS) group (n=14, aged 38–75 yrs) had median % pred values for FVC of 108.5 (95–134)% and for $T_{L,CO}$ of 57.5 (33–70)%. The FVC was similar in all three groups, with no significant differences between groups. However, there was a significant difference in $T_{L,CO}$ between the C group and both the FA (p=0.0001) and the VAS (p=0.0001) groups but no difference was found in $T_{L,CO}$ between the FA and the VAS groups (p=0.66) (fig. 1).

The median ^{99m}Tc-DTPA clearance was rapid in the FA group (21.25 min) but normal in the VAS (46.5 min) and C (84.5 min) groups. In this regard, while all patients in the C group and 12 out of 14 in the VAS group had normal clearance, only three out of 14 patients in the FA group had normal levels. There was a significant difference in DTPA clearance between the FA and VAS groups (p=0.014) and between the FA and C groups (p=0.0004), but no difference was detected between the VAS and C groups (fig. 2).

Follow-up data, including lung function tests and HRCT scans, from the VAS group were available in 13 patients

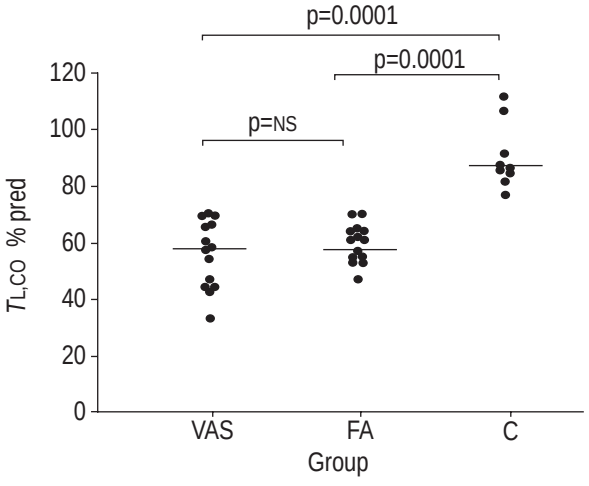

Fig. 1. – Total diffusion capacity of the lung for carbon monoxide ($T_{L,CO}$) expressed as percentage of predicted for the vascular (VAS), fibrosing alveolitis (FA) and control (C) groups. Median values are indicated for each group. Intergroup comparisons are shown with accompanying statistical significances.

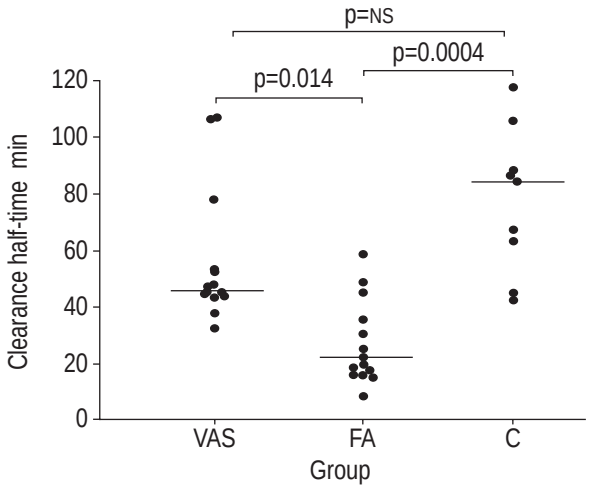

Fig. 2. – Technetium-99m-diethylenetriamine pentaacetate clearance half-times for the vascular (VAS), fibrosing alveolitis (FA) and control (C) groups. Median values are indicated for each group. Intergroup comparisons are shown with accompanying statistical significances.

and the mean time from initial assessment to the most recent HRCT and lung function measurement was 42 months (range 2–134 months). None of the follow-up VAS patients developed FA up to the time of the last follow-up, as assessed by normal HRCT and lung function volume measurements. All patients in the VAS group had a normal FVC in the subsequent months. Four patients died 1.5, 4, 36 and 43 months, respectively, after their first assessment, three of whom had documented evidence of pulmonary hypertension on echocardiography or cardiac catheterization (pulmonary artery pressure range ~50–80 mmHg) during the period of follow-up. None of the patients in the VAS group were on any treatment with corticosteroids and/or immunosuppressive agents (table 2).

Antinuclear antibody data were available in all patients in the C group, 13 of the 14 VAS group patients and 12 of the 14 FA group patients. Sclerosis (Scl)-70 antibodies were detectable in five patients in the FA group (41.6%), one

Table 2. – Follow-up findings in the vascular group

Patient No.	Duration months	HRCT	FVC % pred	$T_{L,CO}$ % pred	Notes
1	134	N	93	67	No treatment
2	108		131	70	No treatment
3	14	N	109	51	Died
4	73	N	160	41	No treatment
5	2		115	33	Died
6	9	N	87	51	Died
7					Died
8	42		100	58	Died
9	47	N	114	80	No treatment
10	28	N	111	52	No treatment
11	36	N	109	39	No treatment
12	14				No treatment
13	27	N	120	53	No treatment
14	13		114	91	No treatment

Length of follow-up with lung function or computed tomography scan following initial assessment. HRCT: high-resolution computed tomography; FVC: forced vital capacity; $T_{L,CO}$: transfer factor of the lung for carbon monoxide; N: normal.

patient in the VAS group (7.69%) and one patient in the C group (11%). Anticentromere antibodies were found in 10 patients in the VAS group (76.9%), but they were not detected in either the FA or the C group (table 1).

Discussion

These results show that the ^{99m}Tc-DTPA clearance time is normal in a group of patients with SSc with a significant loss of transfer factor and normal CT scans, compared with the group with FA and a similar severity of lung disease, consistent with these features being due to vascular disease. Isolated decreases in diffusion capacity have been described in SSc [7, 9, 19, 20] and it is possible that they are either due to primary pulmonary vascular changes or reflect early parenchymal fibrosis. The present study has shown that there was no evidence for the development of FA on further follow-up visits in the VAS group and that DTPA scanning may play a role in identifying this group of patients with pulmonary vascular disease. Furthermore, the control group of patients with SSc and biopsy-proven and radiographic FA was matched with respect to lung volumes and $T_{L,CO}$ but had abnormal DTPA scans.

The specific mechanism of increased clearance times in FA is still unclear but has been thought to be secondary to the stretching of epithelial junctions in the alveolar wall as a result of fibrotic traction or lymphocytic infiltration [12, 21]. The present findings support the hypothesis that the alveolar–capillary barrier is intact in cases of SSc with vascular disease and that the alveolar epithelial integrity is significantly impaired in matching patients with parenchymal fibrosis.

Ten of the evaluated VAS subjects were positive for anticentromere antibodies, with only one subject having Scl-70 positivity. In contrast, all of the patients with diffuse fibrosis were found to be negative for anticentromere antibodies but five were Scl-70 antibody positive. These findings confirm that the isolated $T_{L,CO}$ reduction group with no FA was associated with anticentromere antibodies and pulmonary vascular disease [9].

The measurement of pulmonary technetium-99m-diethylenetriamine pentaacetate (DTPA) clearance is noninvasive and simple and has been demonstrated to be reproducible [22]. In the clinical setting of assessing breathless systemic sclerosis patients with isolated diffusion deficits on lung function testing, technetium-99m-DTPA scans may be a useful additional noninvasive measure to high-resolution computed tomography in confirming the suspicion of vascular disease rather than early fibrosing alveolitis being present in systemic sclerosis. Given that early fibrosing alveolitis may be below the sensitivity of high-resolution computed tomography, a normal technetium-99-DTPA clearance time may obviate the requirement for an open lung biopsy as the definitive diagnostic measure of the presence of fibrosing alveolitis or pure vascular disease in such patients. In addition, this measurement may potentially indicate vascular disease before the development of measurable pulmonary hypertension by other measures such as echocardiography. A normal technetium-99m-DTPA clearance time in the context of isolated diffusion deficits may, therefore, help the clinician to decide on the subsequent follow-up of these patients, with particular regard to more frequent and specific measures of vascular disease such as echocardiography.

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