

Gallium-67 scanning in the staging of cryptogenetic fibrosing alveolitis and hypersensitivity pneumonitis

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ABSTRACT: Gallium-67 citrate is known to localize within inflammatory sites. Gallium-67 scanning is used for the evaluation of lung inflammation (*i.e.* alveolitis) during interstitial lung diseases. We investigated 27 patients with cryptogenetic fibrosing alveolitis ($n=17$) and hypersensitivity pneumonitis ($n=10$) using gallium-67 lung scanning and lung function tests (forced vital capacity, diffusing capacity, resting and exercise blood gases). Investigations were performed before and after one year of methylprednisolone treatment. None of eight healthy volunteers had any abnormal gallium-67 uptake. In all patients with cryptogenetic fibrosing alveolitis an initial abnormal gallium-67 uptake was observed (mean fixation index: 163 ± 18). In addition, analysis of lung function tests a year after initial evaluation showed that unchanged or improving patients presented initially with a lower gallium-67 index than patients with evidence of deterioration (153.9 ± 23.7 vs 251.0 ± 23.3 ; $p < 0.01$). Similarly, among patients with hypersensitivity pneumonitis the index was lower in unchanged or improving patients than in those with deterioration (74.9 ± 22 vs 226.7 ± 4.9 ; $p < 0.05$). Thus gallium-67 scanning is useful in the management of cryptogenetic fibrosing alveolitis and hypersensitivity pneumonitis.

Eur Respir J. 1988, 1, 517-522.

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Keywords: Bird fancier's lung; cryptogenetic fibrosing alveolitis; farmer's lung; gallium-67 lung scanning; hypersensitivity pneumonitis; interstitial lung diseases; pulmonary fibrosis.

Received: June 5, 1986; accepted after revision August 19, 1987.

This work was partly supported by INSERM, Faculté Grange Blanche et Biologie Humaine and Fonds spécial contre les maladies respiratoires et la tuberculose.

Interstitial lung diseases are a heterogeneous group of diseases characterized by the risk of evolution towards pulmonary fibrosis [1-3]. Some of these conditions, such as hypersensitivity pneumonitis, are due to inhaled antigens, whereas others, such as cryptogenetic fibrosing alveolitis are of unknown aetiology [1]. Recently advances in the understanding of the pathogenesis of interstitial lung diseases have been accomplished. It is now clear that two phases occur: an inflammatory process within the interstitium (*i.e.* alveolitis), followed by fibroblast proliferation and collagen synthesis dysregulation (*i.e.* fibrosis) [1, 3, 4]. Furthermore, the pulmonary fibrosis is modulated by the alveolitis process since inflammatory cells involved in the alveolitis are able to release factors involved in fibrogenesis [1, 3, 4].

So far there is no effective treatment for pulmonary fibrosis. In contrast, the alveolitis process may be controlled, thus reducing the fibrosis. For patients with interstitial lung disease, it is critical to assess the intensity of the alveolitis process. Two approaches are currently used for this purpose: analysis of alveolar cell populations collected by bronchoalveolar lavage and analysis of lung uptake of gallium-67 [5, 6]. These can be used either separately or together. When used in combination, they can assess the intensity of the alveolitis [4]. This has been demonstrated by compar-

ing bronchoalveolar lavage and gallium-67 scan results to the inflammatory cell infiltration within the alveolar structure, *i.e.* alveolitis, on lung biopsies [7, 8]. Such a study has been performed in sarcoidosis [8, 9], where the T-lymphocyte percentage is the critical information, and in cryptogenetic fibrosing alveolitis [7, 10, 11] where the percentage of neutrophils is the critical bronchoalveolar lavage information. We have already demonstrated in sarcoidosis, pulmonary fibrosis and hypersensitivity pneumonitis that the combined use of bronchoalveolar lavage and gallium-67 scanning enables us to assess the intensity of the alveolitis of these diseases [6, 12-14]. In addition, measurement of the alveolitis by bronchoalveolar lavage combined with gallium-67 scanning enables us to predict the functional evolution [1, 4]. The intensity of the alveolitis is predictive of pulmonary function test deterioration either during sarcoidosis or during pulmonary fibrosis [15, 16], although we have reported discrepancies during sarcoidosis [17]. As yet, such information has not been obtained during hypersensitivity pneumonitis. Repeated bronchoalveolar lavage can not always be performed in some patients. We have thus investigated the use of gallium-67 scanning as a means of assessing the intensity of the alveolitis in patients with cryptogenetic fibrosing alveolitis and hypersensitivity pneumonitis.

Patients and methods

Study population

Eight control individuals were studied. All of them were free of lung disease, a gallium-67 scan being performed to detect an extrathoracic infectious site.

Twenty-seven patients were investigated: seventeen with cryptogenetic fibrosing alveolitis (10 men and 7 women, aged 60.1 ± 3.5 yr) and ten with hypersensitivity pneumonitis (6 men and 4 women, aged 49.2 ± 2.1 yr). These patients presented with interstitial lung disease, demonstrated by exercise dyspnoea, lung crackles, an interstitial pattern on chest X-ray and abnormal pulmonary function tests including restrictive ventilatory defects, exercise hypoxaemia and a decreased carbon monoxide diffusing capacity. None of the patients had pulmonary infection or left ventricular failure.

Cryptogenetic fibrosing alveolitis was diagnosed in seventeen patients using criteria already reported [18, 19]. These patients had no clinical signs of connective vascular disease, and none of the classical aetiology of interstitial lung disease was found [20]. Baseline pulmonary function tests were established using methods already described [21]. Eleven of the patients had a decreased vital capacity (VC) (<95% of the predicted value), mean VC: 2.6 ± 0.2 l ($87.9 \pm 5.0\%$ of predicted value). Forced expiratory volume in one second (FEV₁) (1.96 ± 0.18 l; $93.1 \pm 5.9\%$), and FEV₁/VC ($75.4 \pm 7.5\%$) were normal. Carbon monoxide diffusing capacity related to the alveolar ventilation (DLCO/VA) was decreased (4.3 ± 0.3 ml·mm⁻¹·Hg·min⁻¹; $89.4 \pm 5.6\%$), oxygen arterial pressure (PaO₂) was 9.2 ± 0.3 kPa and exercise PaO₂ (50 W, 10 min) 7.9 ± 0.3 kPa.

Hypersensitivity pneumonitis was diagnosed in ten patients by evidence in the history of a known inhaled antigen, serum precipitins and in some cases a positive provocation test, as previously described [22]. This group included seven subjects with pigeon breeder's disease, two with farmer's lung and one with isocyanate hypersensitivity pneumonitis. Pulmonary function tests were as follows: VC = 2.12 ± 0.38 l ($68.0 \pm 6.5\%$), FEV₁ = 1.73 ± 0.28 l ($72.9 \pm 6.3\%$), FEV₁/VC = $87.8 \pm 8.9\%$, DLCO/VA = 3.9 ± 0.3 ml·min⁻¹·mmHg·l⁻¹ ($76.4 \pm 23.4\%$), PaO₂ at rest = 8.3 ± 0.6 kPa, exercise PaO₂ (50 W, 10 min) = 6.9 ± 0.5 kPa.

Changes in VC, DLCO/VA, and exercise PaO₂ were used to assess the evolution of pulmonary function tests in these patients. A 20% change in VC or DLCO/VA or a 1 kPa change in exercise PaO₂ were considered significant. Improvement or deterioration were observed in individual patients' pulmonary function tests when at least two of these three values were modified similarly. Patients were assessed at baseline and 12 months later. All patients received methylprednisolone $1 \text{ mg} \cdot \text{kg}^{-1}$ during 15 days, then tapered to $0.25 \text{ mg} \cdot \text{kg}^{-1}$ until the next assessment.

Bronchoalveolar lavage was performed during baseline assessment as previously described [22].

Gallium 67 scanning was performed using an Anger's tomoscintigram three days after *i.v.* injection of 3–5 mCi of gallium-67 citrate [6, 12]. Gallium-67 uptake index was established according to LINE *et al.* [8]. The fixation index was determined by three independent observers, the mean index of the three observers was used for individual patients [12].

Statistical analysis

Results are expressed as mean \pm standard error of the mean. Mean comparison was performed using a Mann-Witney U-test, linear regression analysis by the least squares method [23].

Results

Control individuals

The gallium-67 scan uptake index was between 0 and 50: 6.3 ± 17.7 demonstrating no uptake in normal lung parenchyma.

Cryptogenetic fibrosing alveolitis

All patients had an abnormal gallium-67 scintigram, indices varying from 90–305 (163.3 ± 18.0). No extrapulmonary uptake was found. During the initial assessment no correlation was found between the gallium index and the pulmonary function tests (VC, DLCO/VA). In addition, there was no correlation between the gallium index and the neutrophil percentage (table 1).

The analysis of pulmonary function tests one year after baseline assessment showed a statistically signifi-

Table 1. - Cryptogenetic fibrosing alveolitis: lack of correlation between gallium-67 uptake and bronchoalveolar lavage data

| | gallium-67 index | cells per μ l | bronchoalveolar lavage | | |
|--------------------------------------------------|---------------------|----------------------|------------------------|------------------|------------------|
| | | | macrophages % | lymphocytes % | neutrophils % |
| mean | 163.3 | 250.3 | 50.8 | 27.9 | 16.6 |
| SEM | 18.0 | 47.8 | 6.2 | 6.7 | 3.3 |
| correlation coefficient with gallium-67 index | | 0.40 | 0.26 | 0.12 | 0.19 |
| | | NS | NS | NS | NS |

cant inverse relationship between the gallium-67 index and VC evolution ($r=0.62$; $p<0.05$). In addition, by analysing pulmonary function test evolution after one year of corticosteroid treatment, it is possible to define two groups of patients. The first group of eight patients remained unchanged or improved, the second group of four deteriorated. Gallium-67 index was lower in the group of patients unchanged or improving when compared to the other group (153.9 ± 23.7 vs 251.2 ± 23.3 ; $p<0.01$; fig. 1A). A similar prognostic value was found for the neutrophil percentage since there was a statistically significant difference between improving or unchanged patients and deteriorating patients (12.3 ± 3.1 vs $26.3 \pm 11.4\%$; $p<0.05$; fig. 1B). The prognostic value of a gallium-67 scan can also be

demonstrated by analysis of the evolution of one of the pulmonary function tests, vital capacity. Patients presenting at baseline with an intense gallium-67 uptake (index >175) had a significantly higher decrease in their VC in one year than patients presenting with a lower uptake (index ≤ 175) (-440 ± 250 ml vs -55 ± 45 ml; $p<0.05$; fig. 2A). Analysis of changes in other pulmonary function tests did not disclose such a significant relationship with the gallium-67 index (fig. 2B and 2C).

Hypersensitivity pneumonitis

Seven patients had abnormal lung uptake while three had a gallium-67 index under 50. No correlation was found between gallium-67 uptake and any of the

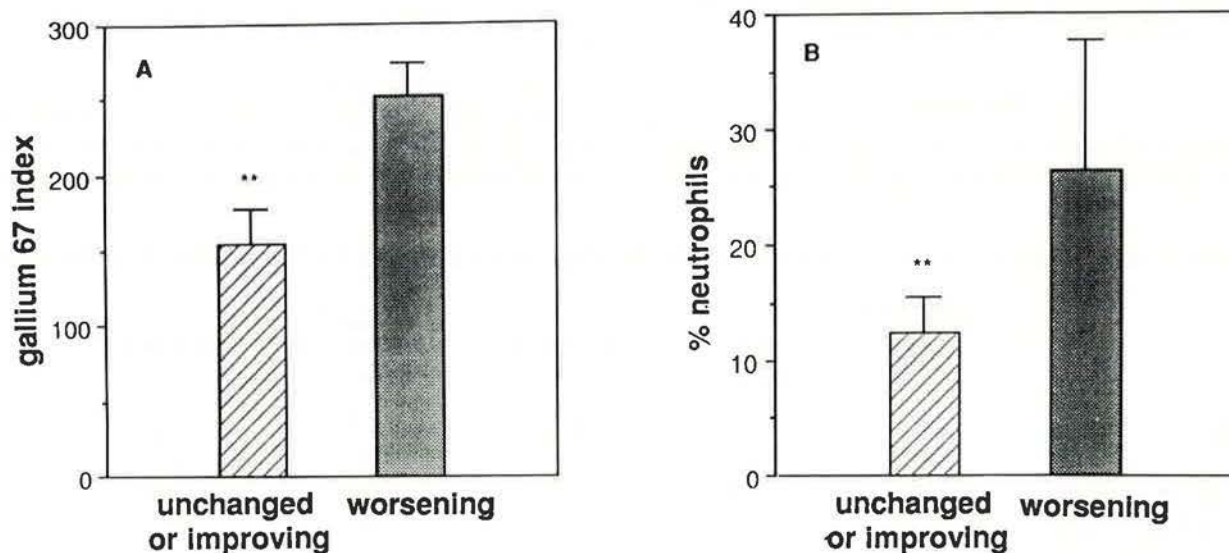


Fig. 1. Analysis of the evolution of patients' status during cryptogenic fibrosing alveolitis. In unchanged or improving patients, and deteriorating patients (for definition see patients and methods) two parameters were compared: gallium-67 uptake (the upper limit of normal is 41.7 (mean ± 2 SEM) (A) and neutrophil percentage in bronchoalveolar lavage (B). **: statistically significant difference.

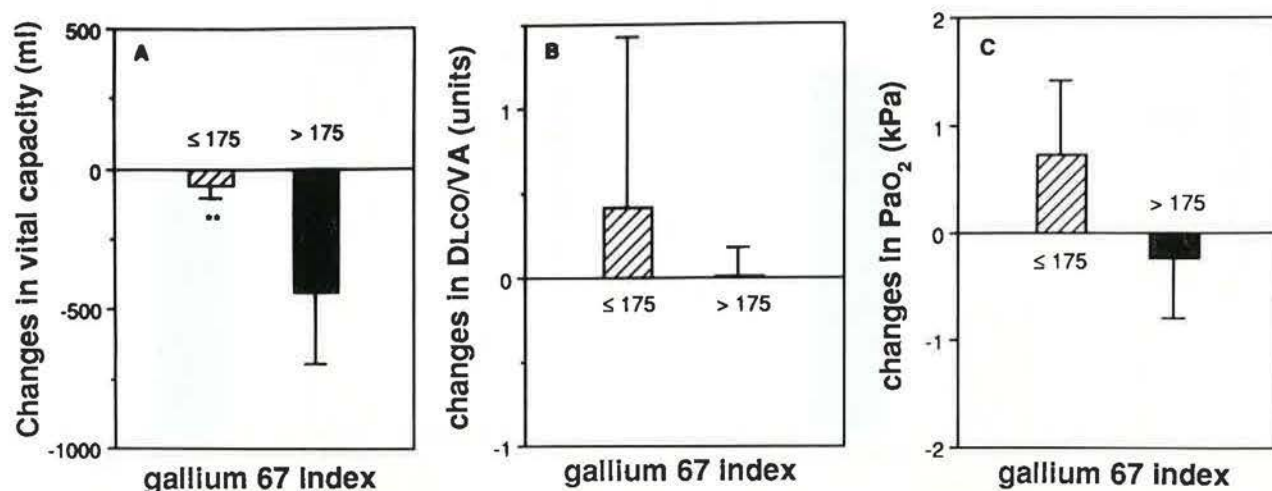


Fig. 2. Pulmonary function test changes in cryptogenic fibrosing alveolitis patients according to initial evaluation. Gallium-67 index (≤ 175 vs > 175), vital capacity (A), DLCO/VA (B) and exercise PaO₂ (C) were measured as described in patients and methods. **: statistically significant difference.

pulmonary function tests. There was no correlation between the gallium-67 index and the bronchoalveolar lavage results: neither total cell number nor lymphocyte percentage (table 2).

As was found in cryptogenetic fibrosing alveolitis there was an inverse correlation between the gallium-67 index and the evolution of vital capacity ($r=0.60$; $p<0.05$), but there was no correlation between pulmonary function tests and alveolar lymphocyte percentage. Contrary to what was observed with alveolar lymphocyte percentage (fig. 1B), there was a statistically significant difference between the gallium-67 index in unchanged or improving patients and deteriorating patients (74.9 ± 22.0 vs 226.7 ± 4.9 ; $p<0.05$; fig. 3A). Furthermore, although an improvement in all three function tests studied (VC, DLCO/VA and exercise P_{aO_2}) was observed in patients with a low gallium 67 uptake, differences did not reach statistical significance (fig. 4A, 4B, 4C).

Discussion

Gallium-67 scanning is a useful tool for assessing the intensity of the alveolitis process [6]. Gallium-67,

carried by transferrin, is taken up by the cells of the alveolitis process; neutrophils, activated T-lymphocytes and macrophages possess a transferrin receptor [24–26]. It has been demonstrated that during cryptogenetic fibrosing alveolitis gallium-67 is taken up *in vivo* by both neutrophils and macrophages [16, 27]. No such study has been performed during hypersensitivity pneumonitis, but in sarcoidosis the uptake is mainly due to macrophages [9]. As previously shown in pulmonary fibrosis and sarcoidosis, the present study found a relationship between gallium-67 uptake and pulmonary function test evolution. This is true both for cryptogenetic fibrosing alveolitis and for hypersensitivity pneumonitis, no prospective study having been published so far regarding the latter.

Analysis of gallium-67 uptake during the baseline study

In both disease groups, there is no correlation between gallium-67 uptake and pulmonary function tests. This is consistent with the fact that pulmonary function tests enable us to assess the disruption of the

Table 2. - Hypersensitivity pneumonitis: lack of correlation between gallium-67 uptake and bronchoalveolar lavage data

| | gallium-67 index | cells per μ l | bronchoalveolar lavage macrophages % | lymphocytes % | neutrophils % |
|--------------------------------------------------|---------------------|----------------------|--------------------------------------------|------------------|------------------|
| mean | 116.8 | 331.1 | 51.6 | 36.5 | 10.3 |
| SEM | 26.3 | 55.8 | 8.0 | 7.1 | 4.3 |
| correlation coefficient with gallium-67 index | | 0.50 | 0.27 | 0.47 | 0.23 |
| | | NS | NS | NS | NS |

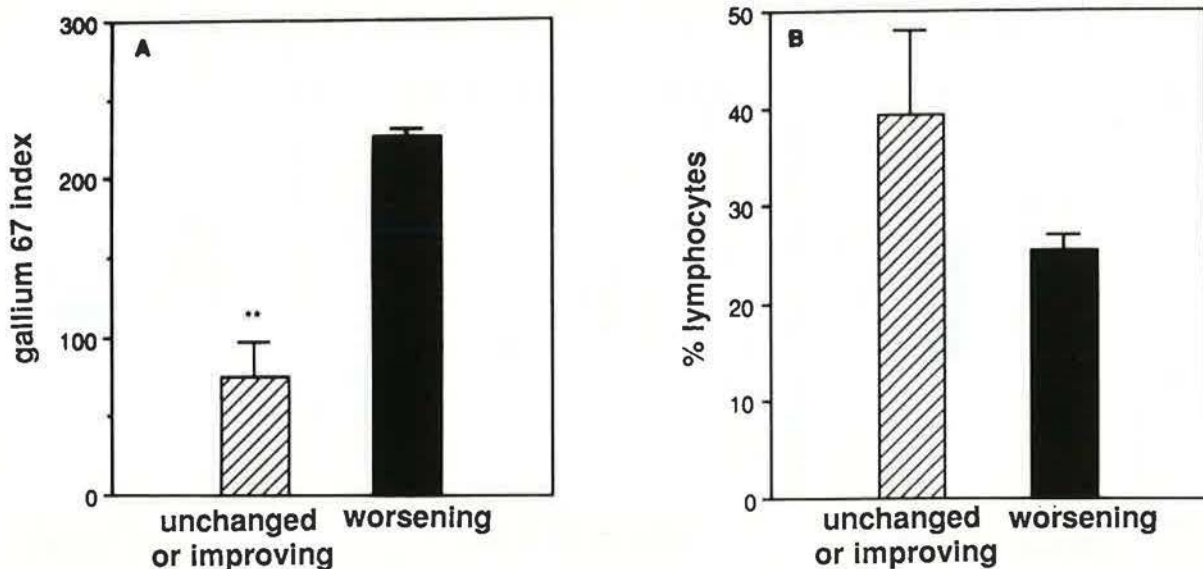


Fig. 3. Analysis of the evolution of patients' status during hypersensitivity pneumonitis. In unchanged or improving patients and deteriorating patients (for definition see patients and methods) two parameters were compared: gallium-67 uptake (the upper limit of normal is 41.7 (mean \pm 2 SEM)) (A) and lymphocyte percentage in bronchoalveolar lavage (B). **: statistically significant difference.

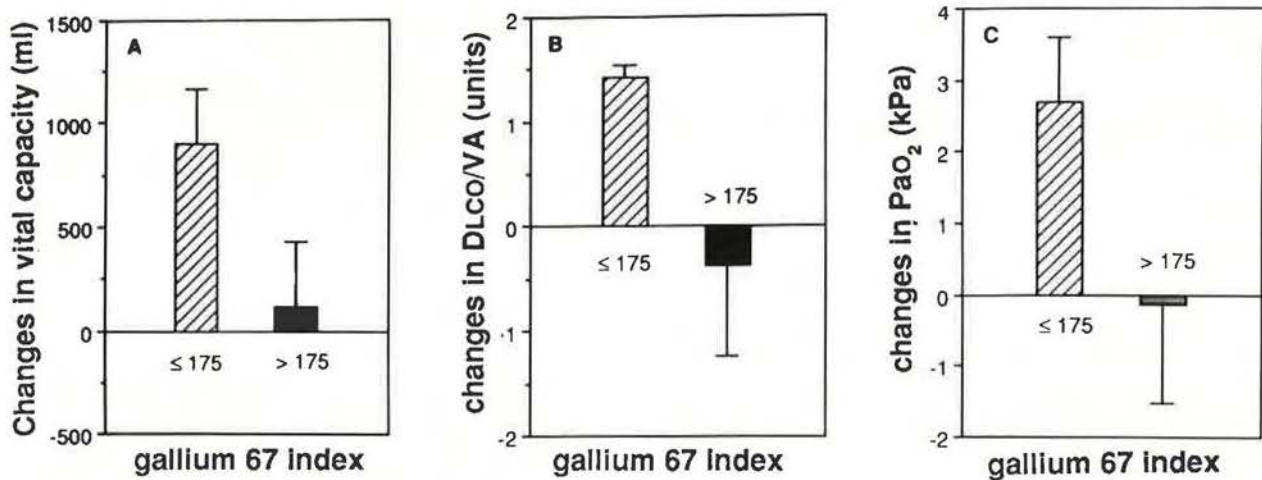


Fig. 4. Pulmonary function test changes in hypersensitivity pneumonitis patients according to initial evaluation. Gallium-67 index (≤ 175 vs > 175), vital capacity (A), DLCO/VA (B) and exercise Pao₂ (C) were measured as described in patients and methods. *: statistically significant difference.

alveolar structure by the fibrotic process more than the alveolitis process itself [28]. Discrepancies between a gallium scan and pulmonary function tests have been reported in sarcoidosis and idiopathic pulmonary fibrosis [7, 8] reflecting the inability of pulmonary function tests to assess the alveolitis process. During cryptogenic fibrosing alveolitis and hypersensitivity pneumonitis, there is no correlation between the gallium-67 index and bronchoalveolar lavage results (tables 1 and 2). LINE *et al.* [8] have reported in idiopathic pulmonary fibrosis a correlation between alveolar neutrophil percentage and gallium-67 index [7], but we were unable to find this in our patients. Nevertheless, the neutrophil percentage in bronchoalveolar lavage is difficult to use as an index since it can be modified by bronchial and/or blood contamination.

Analysis of the evolution of pulmonary function tests

The present study demonstrates a deterioration of pulmonary function tests when the gallium-67 index is elevated during cryptogenic fibrosing alveolitis as previously reported [15]. A gallium-67 scan alone can thus be used as a prognostic tool, and can be repeated whereas bronchoalveolar lavage is usually difficult to perform sequentially. During the monitoring of patients with cryptogenic fibrosing alveolitis a persistently increased gallium-67 uptake suggests that the alveolitis process is not controlled by the treatment used and may lead to an increase in the drug dosages or changes of treatment [2]. Such monitoring by gallium scanning is restricted by the level of radiation delivered to the gonads. Using low doses of isotope may solve this problem [29].

Similarly, the evolution of vital capacity is related to the value of the gallium-67 scan index in hypersensitivity pneumonitis. Treatment of hypersensitivity pneumonitis includes withdrawal from antigen exposure and corticosteroids. In this context a

persistent abnormal gallium scan uptake must suggest a prolonged exposure to the causative antigen.

Acknowledgements: We thank C. Quintin for her help in completing this work.

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RÉSUMÉ: Au cours de la pathologie interstitielle pulmonaire l'analyse de la fixation pulmonaire du gallium-67 permet de mesurer l'activité de l'alvéolite. Vingt-sept patients atteints de fibrose pulmonaire idiopathique (n=17) et de pneumopathie d'hypersensibilité (n=10) ont été évalués lors du premier examen par scintigraphie pulmonaire au gallium-67, lavage broncho-alvéolaire et épreuves fonctionnelles respiratoires (capacité vitale, capacité de diffusion de l'oxyde de carbone, gazométrie artérielle au repos et à l'exercice). Après un an de traitement par méthylprednisolone une deuxième évaluation a été faite par épreuves fonctionnelles respiratoires. Huit sujets témoins indemnes de toute pathologie pulmonaire ont subi une scintigraphie au gallium-67, aucune fixation significative au gallium-67 ne fut trouvée au niveau du poumon. Au cours des fibroses pulmonaires idiopathiques, une fixation anormale du gallium-67 au niveau pulmonaire a été observée (indice moyen de fixation 163 ± 18). De plus, l'analyse des données fonctionnelles respiratoires un an après l'examen initial, montre que l'indice de fixation du gallium-67 était inférieur dans le groupe des patients stables ou améliorés ($153,9 \pm 23,7$) par rapport au groupe des patients aggravés ($251,2 \pm 23,3$); $p < 0,01$. Les mêmes constatations ont été faites dans le groupe des patients atteints de pneumopathie d'hypersensibilité: patients stables ou améliorés $74,9 \pm 22$; patients aggravés: $226,7 \pm 4,9$ ($p < 0,05$). Il en résulte que l'importance de la fixation pulmonaire du gallium-67 est liée à l'évolution dans les fibroses pulmonaires idiopathiques et les pneumopathies d'hypersensibilité.