8-Isoprostane, a Marker of Oxidative Stress, Is Increased in the Expired Breath Condensate of Patients With Pulmonary Sarcoidosis*

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Study objective: 8-Isoprostane is considered an index of oxidative stress. Measurement of 8-isoprostane in the expired breath condensate, a totally noninvasive method, has not been used to explore the level of inflammation in pulmonary sarcoidosis. Therefore, the aim of our study was to measure the levels of 8-isoprostane in the expired breath condensate of patients with sarcoidosis, and to investigate the relation of 8-isoprostane level to disease activity.

Patients: We investigated 30 patients with pulmonary sarcoidosis (active disease, n = 14; nonactive disease, n = 16) and 12 healthy subjects as control group.

Methods: 8-Isoprostane was measured in the expired breath condensate of all subjects, and its levels were compared between the control and sarcoidosis groups as well as between the subgroups of patients with active and nonactive disease. In the group with sarcoidosis, 8-isoprostane levels were further correlated with markers that may reflect disease activity, such as serum angiotensin-converting enzyme (sACE) level, serum calcium level, and pulmonary function test results.

Results: The concentration of 8-isoprostane was increased in patients with sarcoidosis compared to control subjects (mean, 64.23 pg/mL; 95% confidence interval [CI], 37.00 to 91.46 pg/mL; vs mean, 20.75 pg/mL; 95% CI, 16.06 to 25.44 pg/mL; p = 0.04). The difference was primarily due to the patients with active disease, who had significantly higher levels of 8-isoprostane (mean, 111.4 pg/mL; 95% CI, 62.56 to 160.30 pg/mL; p < 0.001) compared to patients with nonactive disease (mean, 22.94 pg/mL; 95% CI, 15.89 to 29.99 pg/mL) or healthy subjects. 8-Isoprostane levels in patients with nonactive disease did not differ from those in healthy subjects (p > 0.05). In the patients with sarcoidosis, 8-isoprostane levels were positively correlated with sACE level (p < 0.0001, r = 0.69), but was not correlated with serum calcium level or pulmonary function test values.

Conclusions: Our data suggest that 8-isoprostane levels are increased in the expired breath condensate of patients with sarcoidosis and might serve as an index of disease activity.

(CHEST 2004; 125:1005–1011)

Key words: 8-isoprostane; expired breath condensate; oxidative stress; sarcoidosis

Abbreviations: ACE = angiotensin-converting enzyme; BALF = BAL fluid; CI = confidence interval; CXR = chest radiography; DLCO = diffusing capacity of the lung for carbon monoxide; HRCT = high-resolution CT; PFT = pulmonary function test; ROS = reactive oxygen species; sACE = serum angiotensin-converting enzyme; TLC = total lung capacity

Oxidative stress is generally considered to be an increased exposure of a cell to oxidants. In the context of local inflammation, inflammatory cells such as neutrophils and macrophages excrete into their local environment so-called reactive oxygen species (ROS), such as superoxide anions, hydrogen peroxide, and hydroxyl radicals, which are metabolic oxygen products and act as oxidants to the neighboring cells. ROS affect cell components such as cell membrane lipids, DNA, and cellular proteins of the cell, changing their structure and/or function and resulting in the malfunction or death of the cell. Oxidative stress can be quantified in a biological specimen by measuring the levels of ROS (such as \( \text{H}_2\text{O}_2 \)) themselves, or the products of the effect of oxidative stress on cell components. \( \text{F}_2 \) isoprostanes are stable prostaglandin-\( \text{F}_2 \)-like compounds formed by oxidation of arachidonic acid in the cell mem-
bran via a nonenzymatic pathway, and they have been advocated as a novel index of oxidative stress. S-isoprostane is the most prevalent F2 isoprostane in humans and has been found to be increased in the expired breath condensate of patients with many pulmonary diseases.

Sarcoidosis is a chronic inflammatory disease of unknown origin characterized by a histopathologic lesion, the noncaseating epithelioid granuloma. Inflammatory cells, mainly lymphocytes and macrophages, contribute to the inflammatory process in sarcoidosis. It has been shown that alveolar macrophages isolated from patients with sarcoidosis produce increased amounts of superoxide anions when cultured in vitro. Markers of oxidative stress, particularly S-isoprostane, were also found to be increased in BAL fluid (BALF) from patients with sarcoidosis.

We therefore hypothesized that S-isoprostane levels might also be elevated in the expired breath condensate of these patients, and that S-isoprostane levels might differ between patients of different disease activity. Since the collection of expired breath condensate is a noninvasive procedure, it could serve as a convenient and easily repeatable method for monitoring patients with sarcoidosis. The aim of this study was to determine the levels of S-isoprostane in the expired breath condensate of patients with sarcoidosis, and evaluate whether the level of S-isoprostane reflects disease activity.

**Materials and Methods**

**Subjects**

Subject characteristics are summarized in Table 1. In this cross-sectional study, we investigated 30 patients with sarcoidosis and 12 healthy control subjects. All the patients had histologically proven pulmonary sarcoidosis and no history of any coexisting disease. We excluded from the study 18 other patients with sarcoidosis, who also came for consultation to our hospital, because of a history of smoking, bronchial asthma, allergy, recent respiratory infection, or denying the proposed clinical evaluation. The healthy subjects had no history of allergy or any chronic disease, were not receiving any medication, and had normal spirometry findings. All healthy subjects and patients were nonsmokers and free of respiratory infections for at least 6 weeks before the study.

In the group with sarcoidosis, 7 patients had newly diagnosed disease, and 23 came to the respiratory clinic as outpatients for a regular 3-month follow-up of previously diagnosed disease. Nine of the outpatients were receiving low-dose corticosteroids at the time of the study. The duration of disease prior to the study was 3 ± 2 years (mean ± SD). The radiographic stages of all patients are shown in Table 2.

**Assessment of Disease Activity**

The patients were categorized into active and nonactive disease groups using proposed indexes of disease activity in sarcoidosis, as previously described.

**Clinical Indexes:** The patients received a review of their medical history and a physical examination focusing on persistent or progressive respiratory symptoms and physical signs suggestive of the underlying disease.

**Biochemical Indexes:** All the patients underwent serum angiotensin-converting enzyme (sACE), serum calcium (Ca++, +), and liver enzyme measurements. It was considered that any abnormal values that could not be otherwise explained may reflect active disease.

**BAL Fluid Indexes:** Bronchoscopy and BAL were performed on the new cases only, and the differential cell count and CD4/CD8 ratio were determined. Lymphocyte alveolitis (> 18%) and/or a CD4/CD8 ratio > 3.5 were considered markers of active sarcoidosis.

**Radiologic Indexes:** Chest radiography (CXR) and CT of the chest with high-resolution CT (HRCT) scans (1.5 collimation, 10-mm intervals, and high-spatial-resolution reconstruction algorithm) were performed in all but one case. That patient denied permission for radiologic examination but was not excluded from the study because she showed other indications of active sarcoidosis. An experienced radiologist evaluated the radiographs and CT scans and, for the old cases, compared them with previous examinations in order to determine any change. Progressive deterioration on CXR over 3 months was considered a sign of disease activity. Ground-glass attenuation on HRCT was also used as a marker for active disease. All of the patients with previously diagnosed disease underwent HRCT follow-up yearly. HRCT was mainly used to exclude rather than affirm active disease in these cases, because the significance of disease progression on yearly HRCT scans in determining disease activity at the time of the study was rather uncertain if disease activity could not be suggested by any other index. Such uncertain cases were not included in the study.

**Pulmonary Function Tests:** Spirometry (FEV1, FVC, FEV1/FVC ratio), measurement of static lung volumes (total lung capacity [TLC] by body box plethysmography) and measurement of diffusing capacity (diffusing capacity of the lung for carbon monoxide [DLCO] by the single-breath technique) were performed for all cases (Vmax22 SensorMedics; Yorba Linda, CA). In all patients with previously diagnosed sarcoidosis, pulmonary function test (PFT) values were compared with previous results to identify any deterioration of lung function. A decline in PFT values (≥10% or ≥200 mL for lung volumes, ≥15% or ≥3 mL/min/mm Hg for DLCO) in consecutive tests 3 months apart was considered a marker of disease activity.

Patients who had one or more indexes indicative of disease activity were classified in the active disease group. Asymptomatic
Table 1—Subject Characteristics and 8-Isoprostane Measurements*  

<table>
<thead>
<tr>
<th>Variables</th>
<th>All Patients</th>
<th>Active</th>
<th>Nonactive</th>
<th>Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, No.†</td>
<td>30 (9)</td>
<td>14 (3)</td>
<td>16 (6)</td>
<td>12</td>
</tr>
<tr>
<td>Male/female gender, No.</td>
<td>10/20</td>
<td>6/8</td>
<td>4/12</td>
<td>5/7</td>
</tr>
<tr>
<td>Age, yr</td>
<td>48 ± 14</td>
<td>43 ± 15</td>
<td>53 ± 11</td>
<td>39 ± 9</td>
</tr>
<tr>
<td>8-Isoprostane, pg/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>64.23</td>
<td>111.4</td>
<td>22.94</td>
<td>20.75</td>
</tr>
<tr>
<td>95% CI</td>
<td>37.00–91.46</td>
<td>62.56–160.30</td>
<td>15.80–29.99</td>
<td>16.06–25.44</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD unless otherwise indicated. †Data in parentheses represent patients receiving corticosteroid therapy.

Patients with negative clinical examination, normal levels of biochemical indexes, stable CXR findings over a 3-month period, stable findings on HRCT (without ground-glass attenuation) over a 1-year period, and stable lung function were placed in the nonactive disease group.

Expired Breath Condensate Collection and 8-Isoprostane Measurement

Expired breath condensate was collected in the morning using an alternative way of cooling the tubes in order to enhance formation of condensate. A heat exchanger unit (RHES, model 6V3; Jaeger; Wuerzburg, Germany) was used to produce cold air of –15° to –18°C at airflow of 80 L/min. A double-jacketed glass tube of 30 cm in length was specifically adapted to the cold air system, and a Hans Rudolf two-way unidirectional valve was connected to the tube in order to separate inspiration from expiration. After rinsing their mouth, subjects were comfortably seated in a chair wearing nose clips and breathed in a relaxed manner (tidal breathing) into the tube for 10 min. The breath condensate was collected at the other end of the tube and was immediately stored at –70°C for later analysis. Approximately 1 mL of breath condensate was collected in a 2 mL sterile plastic tube. 8-Isoprostane was measured in the expired breath condensate with a specific enzyme immunoassay kit (Cayman Chemicals; Ann Arbor, MI), as described previously. Amylase determination was carried out on all samples to exclude saliva contamination. To examine the reproducibility of 8-isoprostane measurements in individual subjects, condensate was collected from five normal subjects and five patients on 2 consecutive days, and reproducibility was estimated as previously described.

Statistical Analysis

Data concerning the subject characteristics are expressed as mean ± SD. The concentrations of 8-isoprostane in the expired breath condensate of the various study groups are given as means with 95% confidence intervals (CIs). Data were examined for normally distributed values (8-isoprostane levels in the control and sarcoidosis groups), we used the unpaired t test for statistical comparison. 8-Isoprostane levels were compared among the control, nonactive sarcoidosis, and active sarcoidosis groups as well as among the different radiographic stages, using the one-way analysis of variance with an appropriate post hoc test (Bonferroni) for multiple comparisons. The levels of sACE were not normally distributed, and the Spearman correlation coefficient was used to examine the relation between 8-isoprostane and sACE levels in patients with sarcoidosis. The Pearson correlation coefficient was employed to examine the relation between 8-isoprostane level and PFT values or serum Ca++. levels in patients with sarcoidosis; these data were normally distributed. A p value < 0.05 was considered significant.

Table 2—Radiographic Stage of Patients With Pulmonary Sarcoidosis

<table>
<thead>
<tr>
<th>Variables</th>
<th>0</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>4</td>
<td>6</td>
<td>11</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Active</td>
<td>4</td>
<td>7</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonactive</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

Results

All newly diagnosed patients with sarcoidosis (n = 7) demonstrated lymphocyte alveolitis and CXR/HRCT findings compatible with sarcoidosis. Presenting symptoms and signs included dry cough, dyspnea on exertion, polyarthralgia, and erythema nodosum, although three patients were asymptomatic. sACE levels were increased in all but one patient. At the time of the study, none of the patients demonstrated evidence of extrapulmonary disease, except for two new cases who had increased levels of liver enzymes.

Among patients with previously diagnosed sarcoidosis (n = 23), 5 patients presented with symptoms of dry cough or dyspnea. Five patients showed disease progression on CXR or new areas with ground-glass attenuation on HRCT. One of them revealed worsening PFT values as well. In the remaining patients, PFT values and radiographic findings were stable. In one patient (who was categorized in the active group), the only evidence of active disease was an increase of previously normal sACE level; 1 month later, this patient was admitted with a full picture of relapse.

The 8-isoprostane concentration in the expired breath condensate of patients with sarcoidosis was significantly higher than that of the control group (mean, 64.23; 95% CI, 37.00 to 91.46 pg/mL; vs mean, 20.75; 95% CI, 16.06 to 25.44 pg/mL;
The 8-isoprostane concentration in patients with active sarcoidosis (mean, 111.4 pg/mL; 95% CI, 62.56 to 160.30 pg/mL) was significantly increased (p < 0.001) compared to patients in the nonactive group (mean, 22.94; 95% CI, 15.89 to 29.99 pg/mL) and the control group.

The difference between 8-isoprostane levels in healthy control subjects and those in patients with nonactive sarcoidosis was not significant (p > 0.05, Fig 2). In patients with sarcoidosis, 8-isoprostane level was positively correlated with sACE level (p < 0.0001, r = 0.69, Fig 3, Table 3). The 8-isoprostane level did not show any significant correlation with PFT values (FEV₁, FVC, FEV₁/FVC ratio, TLC, DLCO) or serum Ca²⁺ level (Table 3).

8-Isoprostane did not differ among the patients of different radiographic stages (p = 0.2).

**DISCUSSION**

The levels of oxidative stress indexes in expired breath condensate had not been previously evaluated in an interstitial lung disease. We studied for the first time 8-isoprostane levels in the expired breath condensate of patients with sarcoidosis, and found that 8-isoprostane was increased, but only in patients with signs of active disease.

It has been shown¹¹ that 8-isoprostane is increased in BALF of patients with sarcoidosis, and it was suggested that this elevation could reflect the underlying pathophysiologic process of this disease. In our study, we showed that 8-isoprostane is increased in the expired breath condensate in patients with sarcoidosis. The patients in our study did not all have markers indicative of active disease, and the difference in 8-isoprostane levels between healthy subjects and patients with sarcoidosis was primarily due to the subgroup of patients who showed signs of active disease. When the patients were separated into active and nonactive disease subgroups using proposed markers of activity, we found that those with active disease showed significantly increased levels of 8-isoprostane compared to those with nonactive disease and healthy subjects. The level of 8-isoprostane in patients without evidence of active disease did not differ from that in healthy control subjects, and this seems an expected result since nonactive disease should not produce any signs of pulmonary inflammation (Figs 1, 2).

The 8-isoprostane level in expired breath condensate...
sate was correlated with sACE level, irrespective of disease activity (Fig 3). It is well known that angiotensin-converting enzyme (ACE) is produced at the site of granulomas by epithelioid cells and alveolar macrophages. sACE level reflects the whole-body burden of granulomas and is an indirect index of the extent and activity of the disease throughout the body. 16 8-Isoprostane in the expired breath condensate is an index of oxidative stress, isolated from the respiratory system. All of our patients had pulmonary sarcoidosis, and consequently one would expect the lungs of these patients to be the main source of sACE. The common source of ACE and 8-isoprostane, from the local lung inflammation, might explain the correlation between the levels of these two substances. Nevertheless, their relation may be only statistically, and not clinically, meaningful. It has been found that sACE levels are affected by ACE gene polymorphism. 17,18 The correlation of the expired 8-isoprostane with sACE levels might also imply a correlation of 8-isoprostane with the genomics of sarcoidosis, but this hypothesis is still uncertain.

8-Isoprostane levels did not show any correlation with PFT values, also an expected result since oxidative stress marker levels reflect a process going on at the time of the measurement, while PFT values reflect the result of a previous process. This observation is in accordance with the studies of Montuschi et al. 11,14 Perhaps for the same reason, we could not find any correlation of the expired 8-isoprostane with the radiographic stages in sarcoidosis.

The analysis of breath constituents has gained increasing interest during recent years, mainly because it represents a completely noninvasive method to collect samples directly from the respiratory system. Expired breath condensate is a sample in liquid form, and many condensate compounds have already been measured in various lung diseases. 19,20 The levels of oxidative stress indicators such as H2O2 or 8-isoprostane in the expired breath condensate have been shown to reflect the intensity of the underlying inflammation in asthma, 14,21 COPD, 22,23 bronchiectasis, 24 cystic fibrosis, 25 ARDS, 26,27 and cigarette smokers. 23,28

Our results generate the hypothesis that 8-isoprostane level in the expired breath condensate might be used as an index of disease activity in pulmonary sarcoidosis. Some of the proposed markers of activity in sarcoidosis require the detection of a change on consecutive tests in order to classify the disease as active or inactive (eg, PFTs or CXRs), but measurement of 8-isoprostane in expired breath condensate may enable underlying disease activity to be detected more promptly and accurately. This measurement may reflect disease activity in the airways as well as the lung parenchyma, which is significant because sarcoidosis affects the airways in up to 62% of cases. 29 In this study, we have not followed up our patients with the expired 8-isoprostane, and we do not know the “behavior” of this index during the course of the disease. This issue could be addressed in future studies.

If 8-isoprostane were proved to be a good marker of the evolution of the disease in pulmonary sarcoidosis, an emerging question would be whether measurement of 8-isoprostane in the expired breath condensate is superior to measurement of 8-isoprostane in BALF. One clear advantage of the expired breath condensate method is that it is totally noninvasive and can be repeated at any time during the course of the disease, while BAL in contrast requires bronchoscopy. From this point of view, the expired breath condensate method would be very convenient in monitoring the course of the disease or the response to therapy. Moreover, expired breath condensate represents a whole-lung sample, in contrast to BALF, which is a sample from only a portion of the lung and does not capture events in the airways. Further studies are needed to compare the two methods and their possible role in the following up of pulmonary sarcoidosis.

### Table 3—Mean Values of Disease Activity Markers and Their Relation to Expired 8-Isoprostane Level

<table>
<thead>
<tr>
<th>Variables</th>
<th>All Patients</th>
<th>Active (n = 14)</th>
<th>Nonactive (n = 16)</th>
<th>Correlation With 8-Isoprostane</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1, % predicted</td>
<td>101 ± 20</td>
<td>104 ± 18</td>
<td>99 ± 21</td>
<td>0.4</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>103 ± 18</td>
<td>105 ± 16</td>
<td>102 ± 19</td>
<td>0.4</td>
</tr>
<tr>
<td>FEV1/FVC, %</td>
<td>105 ± 10</td>
<td>104 ± 4</td>
<td>105 ± 13</td>
<td>0.6</td>
</tr>
<tr>
<td>TLC, % predicted</td>
<td>103 ± 15</td>
<td>97 ± 16</td>
<td>108 ± 13</td>
<td>0.5</td>
</tr>
<tr>
<td>DLCO, % predicted</td>
<td>96 ± 21</td>
<td>96 ± 22</td>
<td>97 ± 19</td>
<td>0.6</td>
</tr>
<tr>
<td>sACE, IU/L</td>
<td>40 ± 34</td>
<td>64 ± 38</td>
<td>19 ± 6</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Ca++, mg/dL</td>
<td>9.4 ± 0.4</td>
<td>9.4 ± 0.4</td>
<td>9.3 ± 4</td>
<td>0.7</td>
</tr>
</tbody>
</table>

*p* Value

*r* Correlation With 8-Isoprostane

*Data are presented as mean ± SD.*

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The majority of our patients were not receiving therapy with corticosteroids. Those who did receive this treatment (n = 9) were receiving maintenance low doses, and this may be the reason that three patients showed signs of disease activity (Table 1). These three patients had 8-isoprostane levels similar to or even higher than those of the rest of the active disease group. The number of these patients and the corticosteroid doses they received were not great enough for separate analysis, and further investigation is necessary to determine the role of corticosteroids in the expression of oxidative stress in sarcoidosis.

“Activity” reflects a process that is still evolving. In sarcoidosis, because of the variability of the pathologic picture (lymphocyte/macrophage inflammation, granuloma formation, fibrosis), and the involvement of multiple systems, many activity markers have been developed, each one assessing one aspect of the evolution of the disease.30,31 This definition of activity, which has been used for sarcoidosis, seems rather “descriptive” and imprecise if one would like to strictly define which patients are “active” and which are not. One reason for this vagueness may be the long list of activity markers that have been proposed, which are often not in concordance between each other. Another reason may be that the issue of activity itself is not correlated with prognosis and is different with the concept of response to therapy or the need of treatment and, for this reason, has limited clinical value in sarcoidosis.32,33 For the purposes of our study, we have categorized in the active disease group patients who had any sign of active disease, according to the markers of activity described above, and placed in the nonactive disease group patients who had none of these signs. Certainly, this categorization is empiric and cannot be used as a “definition” of activity. The markers that were used are those that are routinely used in our institute in the evaluation and follow-up of sarcoidosis. These markers are mainly clinically oriented: they are designed to assess the impact of sarcoidosis on the systems that most affect the patient’s activity and quality of life or that may lead to premature death.7,31 As a result, the use of these markers to estimate the relationship between the activity of the inflammatory process in sarcoidosis and expired oxidative stress indicators has inherent limitations because it can underestimate activity as defined above. For example, as we have not performed BAL in patients with previously diagnosed sarcoidosis, we cannot exclude a subclinical lymphocyte alveolitis that would move some patients in the nonactive group to the active group. But in clinical practice, in an asymptomatic patient with negative clinical and laboratory evaluation we do not perform bronchoscopy and BAL to exclude the possibility of subclinical inflammation. Even if such inflammation were present, it would not alter the management of the patient. At present, “clinical activity” is considered the best way to assess activity in sarcoidosis.31 As it was mentioned previously, one of the limitations of this study was that we have not followed up our patients with the expired 8-isoprostane. The study of a relatively small group of patients once in time during the course of their disease may have inserted bias. The value of expired 8-isoprostane in sarcoidosis should therefore be further explored, in a larger sample of patients, during different phases in the course of the disease and in relation to the need for therapy and the prognosis.

We conclude that 8-isoprostane is increased in the expired breath condensate of patients with sarcoidosis. Patients with evidence of active disease seem to be mainly responsible for this increase, as the level of 8-isoprostane in patients with no such evidence does not differ from that in healthy subjects. 8-Isoprostane in the expired breath condensate is an emerging index of the underlying inflammation in sarcoidosis, and its precise role in the assessment and management of this disease is still to be determined.

ACKNOWLEDGMENT: The authors thank Mrs. Despina Moraitaki for technical support in the pulmonary function testing laboratory.

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