Elevated Levels of Angiotensin-converting Enzyme in *Pneumocystis carinii* Pneumonia*

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Serum angiotensin-converting enzyme (ACE) levels are elevated in sarcoidosis and have been used both to diagnose and to assess response to treatment of this disease. We report significantly (p<.0005) elevated ACE levels in patients with *Pneumocystis carinii* pneumonia (PCP) (49 ± 14 U/L) compared with normal control subjects (32 ± 11 U/L) tested within 48 hours of hospital admission. Serum ACE levels in smoking control subjects (33 ± 11 U/L) were not significantly (α = .05) different from nonsmoking control subjects (32 ± 11 U/L), but the levels in PCP patients who smoked (55 ± 15 U/L) were significantly (p<.025) higher than in those who did not smoke (42 ± 10 U/L). In addition to suggesting a possible clinical use for measuring ACE levels in suspected or confirmed PCP, we speculate that elevations in serum ACE levels may reflect macrophage dysfunction in patients with PCP.  

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**METHODS**

Prospective subjects were identified upon admission to the Beth Israel Medical Center in New York with the admitting diagnosis of PCP. In accordance with protocol approved by the Center's Institutional Review Board, informed consent was obtained before drawing 8 ml of fasting venous blood (or unused serum was obtained from prior phlebotomy) within 48 hours of admission. All samples were centrifuged within four hours, serum removed and kept frozen until ready for assay.

Twenty male patients with the diagnosis of *Pneumocystis carinii* pneumonia (PCP) confirmed by transbronchial biopsy and/or bronchoalveolar lavage were studied. All had the acquired immunodeficiency syndrome (AIDS). Because of possible effects on serum ACE levels, patients were excluded from the study if any of the following was present: (1) pulmonary pathology other than PCP demonstrated on transbronchial biopsy or bronchoalveolar lavage; (2) thyroid disease; (3) diabetes mellitus; (4) alcoholic liver disease, based on a history of alcoholism and a red blood cell mean corpuscular volume of greater than 100 fL; (5) a concurrent diagnosis of Kaposi's sarcoma or retinopathy due to cytomegalovirus or toxoplasmosis; (6) medications likely to affect ACE levels, such as ACE inhibitors.

Twenty healthy male hospital employees without a history of intravenous drug abuse (IVDA) or homosexuality served as control subjects. Both patients and control subjects were stratified to include ten smokers and ten nonsmokers. Smokers were defined as those smoking a minimum of ½ pack of cigarettes per day during the previous year.

Serum ACE concentrations were determined by SmithKline BioScience Laboratories using a spectrophotometric method. In brief, at 37°C ACE from a measured serum sample is used to catalyze the hydrolysis of furylacryloylphenylalanlylglycylglycine (FAPGG) (Sigma Diagnostics) to FAP and GG, resulting in a decrease in absorbance at 340 nm. Absorbance is measured by spectrophotometry in patient samples, a normal control sample (Sigma Diagnostics) and an elevated control sample (Sigma Diagnostics) and is interpreted using an ACE calibrator (Sigma Diagnostics). One unit of ACE activity is defined as that amount of enzyme that catalyzes formation of one micromole of FAP per minute.

A two-tailed Student's t-test with α = .05 was used to test for significance of the difference between means of groups, unless otherwise stated.

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higher than in non-smokers with PCP (42 ± 10 U/L), whereas mean serum ACE levels in control smokers (33 ± 11 U/L) were not significantly different from those in control non-smokers (32 ± 11 U/L).

When serum ACE levels were compared between non-smokers with PCP and non-smoker controls, the PCP patients' ACE levels were significantly higher (p < 0.025). Likewise, when smokers with PCP were compared with smoking control subjects, serum ACE levels in those with PCP were significantly higher (p < 0.005).

Clinical information describing the 20 patients with PCP is presented in Table 1. The mean age for control subjects (33 ± 7.2) was significantly (p < 0.01) lower than that of the PCP patients (38 ± 6.7), but there was no significant correlation between serum ACE level and age in either PCP patients, control subjects, or both groups combined (r = 0.11). There was no significant racial difference among the various subgroups.

Serum ACE levels could not be used to predict the outcome of hospitalization for PCP: the mean age of those who died (n = 5) was 51 ± 13 U/L, not significantly different from the value of 48 ± 15 U/L in those who were discharged (n = 15). Also, although mean serum ACE levels in non-smoker PCP patients with a history of prior PCP (n = 4) were lower (35 ± 8 U/L) than mean levels (47 ± 11 U/L) in those without any history of pulmonary disease (n = 4), this difference did not achieve statistical significance.

**RESULTS**

The distributions of ACE levels for normal control subjects and PCP patients are presented in Figure 1. The mean ± SD for our 20 normal control subjects was 32 ± 11 U/L, not significantly different from the value of 30 ± 10 U/L for 56 individuals reported by Sigma Diagnostics in their commercial literature. The mean for the PCP patients was 49 ± 14 U/L, significantly higher than the 20 normal control subjects (p < 0.0005).

There were six PCP patients out of 20 (30 percent) whose ACE levels were elevated to more than two standard deviations above the mean of the normal group, compared with one normal control subject out of 20 (5 percent). This difference was significant (p < .05), using Yates' correction for continuity and a one-tailed test.

The mean serum ACE level of all smokers (controls plus PCP patients; n = 20) was not significantly different from that of all non-smokers (controls plus PCP patients; n = 20) (44 ± 17 vs 37 ± 12 U/L). However, when the smokers and non-smokers were subdivided into patients and control groups, a significant effect of smoking emerged in the patients (Fig 2), but not in the control group; mean serum ACE levels in smokers with PCP (55 ± 15 U/L) were significantly (p < .025)
Table 1—Clinical Characteristics of Patients with Pneumocystis carinii

<table>
<thead>
<tr>
<th>Angiotensin- Converting Enzyme</th>
<th>Age</th>
<th>Smoker</th>
<th>Risk Factor</th>
<th>Previous Lung Disease</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>78</td>
<td>36</td>
<td>+</td>
<td>Denied</td>
<td>Pneumonia</td>
<td>Discharged</td>
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<tr>
<td>67</td>
<td>43</td>
<td>+</td>
<td>Homosexual</td>
<td>—</td>
<td>Discharged</td>
</tr>
<tr>
<td>66</td>
<td>35</td>
<td>+</td>
<td>Homosexual</td>
<td>Pneumonia</td>
<td>Discharged</td>
</tr>
<tr>
<td>66</td>
<td>34</td>
<td>+</td>
<td>IVDA</td>
<td>—</td>
<td>Died</td>
</tr>
<tr>
<td>58</td>
<td>50</td>
<td>+</td>
<td>Homosexual</td>
<td>PCP</td>
<td>Discharged</td>
</tr>
<tr>
<td>52</td>
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<td>+</td>
<td>Homo/IVDA</td>
<td>Pneumonia</td>
<td>Died</td>
</tr>
<tr>
<td>50</td>
<td>42</td>
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<tr>
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<td>46</td>
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<tr>
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<td>29</td>
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<td>—</td>
<td>Discharged</td>
</tr>
<tr>
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<td>+</td>
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<td>—</td>
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<td>PCP</td>
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<td>-</td>
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<td>PCP</td>
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DISCUSSION

The results of this study show that serum ACE levels in patients with PCP (and AIDS) were elevated compared with normal (non-AIDS) control subjects and that in a significant proportion of cases these elevations fall outside the normal range. The mean level of ACE for patients with PCP in our study was about 50 percent above the mean of normal controls, similar to what has been reported in leprosy. Thus, Pneumocystis carinii pneumonia can be added to the list of conditions associated with increased serum ACE levels.

Increased ACE activity has been found in the pulmonary alveolar macrophage of normal smokers, as well as in patients with sarcoidosis. To our knowledge, a comparison of serum ACE levels in normal smokers and normal nonsmokers has not yet been reported. Despite the increased ACE activity in their pulmonary alveolar macrophages, we report that normal persons who smoke do not exhibit increased ACE concentrations in peripheral blood.

In contrast, ACE levels in patients with PCP who smoke are significantly higher than in those who do not smoke. This appears to represent a synergistic effect on ACE levels between smoking and PCP, though it is possible that the PCP patients were heavier smokers than the smoking control group; we do not report the precise smoking history of subjects in this study because of the vagueness in history given by the patients with PCP.

The observed synergism may be between smoking and PCP or, alternatively and less specifically, between smoking and severe illness. In favor of the latter possibility is the finding that the pulmonary alveolar macrophage of the rabbit does not normally exhibit ACE activity, but when cultured in the presence of dexamethasone, ACE activity is induced. Elevated corticosteroid levels may be a necessary condition for smoking to increase ACE levels significantly. The reason corticosteroid treatment of sarcoidosis does not lead to increased serum ACE levels in smokers but to decreased levels may be that the inducing effect of the corticosteroid is outweighed by its disease-suppressing effect.

If elevated serum ACE levels in sarcoidosis and PCP are derived from macrophages (or their descendants), the elevation found in PCP could be due to an increased rate of production of ACE by activated macrophages or to a dysfunctional release of ACE from damaged or immature macrophages. Several reports suggest that the latter is more likely. First, studies of pulmonary alveolar macrophages in patients with sarcoidosis show that this disease is associated with a less mature population of these macrophages than in normals subjects; second, monocyte chemotaxis in response to soluble products of the parasite Giardia lamblia is impaired in patients with AIDS, and third, tissue macrophages can be infected with the human immunodeficiency virus in vitro, suggesting possible alteration of their in vivo function.

Although we found both a significantly increased mean serum ACE concentration in patients with PCP and a significantly higher proportion of values above the normal range in these patients, the clinical usefulness of measuring ACE levels in patients suspected of having or already diagnosed as having PCP is not clear for several reasons. First, stratification of our study patients according to smoking history revealed the importance of this variable in predicting serum ACE elevations in PCP: serum ACE levels may be more useful in making the initial diagnosis of PCP among patients who smoke than among those who do not smoke. Second, the specificity of a serum ACE elevation in a patient with AIDS who presents with pneumonia and/or a diagnosis to rule out PCP can be questioned because of the reported elevation of serum ACE concentrations in 17 percent of patients with disease due to Mycobacterium avium intracellulare; the rate of false positives due to bacterial pneumonia is also not known. Third, although we found elevated serum ACE levels within 48 hours of admission to PCP, we do not as yet know what happens to these levels after successful vs unsuccessful treatment of the disease. The role of serum ACE levels in diagnosing PCP and following response to therapy awaits further clarification.

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REFERENCES

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Elevated Levels of ACE in PCP (Singer, Talavera, Zumoff)