Serum angiotensin converting enzyme in pneumonias

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SUMMARY Serum concentrations of angiotensin converting enzyme (ACE) were studied in pneumonias caused by different pathogens and in cases in which the aetiology could not be defined. In all aetiological groups, except in viral pneumonia, there was a significant increase in ACE during recovery (p < 0·001). In several patients the lowest values during the acute phase of disease and the highest values during recovery were outside the reference limits. In cases with known aetiology the highest ACE values and the difference between the lowest and the highest values correlated positively with C-reactive protein concentrations at admission (p < 0·001). The pathophysiology behind the fluctuations of the ACE concentrations is unknown.

Serum angiotensin converting enzyme (ACE) has been used as a diagnostic tool and a marker of disease activity in sarcoidosis since 1975.[1] Increased values are observed in about half the patients with newly diagnosed sarcoidosis.[2] ACE may also be increased in various non-sarcoid lung diseases, the incidence of increased values generally being less than 5%.[2 3] In histoplasmosis about 25% of patients show slightly increased ACE concentrations.[4] In one report ACE was shown to be decreased during the acute phase of pneumonia.[5]

The present study was undertaken to study the fluctuations of serum ACE values in pneumonias of different aetiology. In our patient population the aetiology of the pneumonias was defined to a larger extent than usual, using viral and bacterial serology and pneumococcal antigen detection in addition to blood cultures. Thus it was possible to relate the aetiology of pneumonias to changes in ACE concentration. We also studied the relation between changes in ACE and the severity of illness as judged by C-reactive protein values.

Material and methods

PATIENTS
The primary patient population consisted of adult patients (over 15 years), who were admitted to the Aurora Hospital, Helsinki, between April 1 1980 and April 30 1981, for a suspected community acquired pneumonia. There were 182 patients on whom the

radiologist verified a pneumonic infiltrate in the chest radiograph. Paired serum samples for serology were obtained from 160 patients. Patients with complicating pulmonary disease, such as tuberculosis or malignancy, were excluded. The aetiological diagnosis of pneumonia was based on blood cultures, aerobic and anaerobic, taken at admission to hospital from all patients, or on confirmation of pneumococcal antigen in urine or serum, or both, as described in detail elsewhere (Y Kerttula, *et al*, unpublished observations).

After patients with mixed bacterial infections had been excluded the following aetiological groups remained:
(1) *Pneumococcal disease with positive blood culture (n = 14)* One patient died before a blood sample for ACE had been taken. One patient with simultaneous myocardial infarction and another with *Escherichia coli* bacteremia were excluded. In one of the remaining 11 patients spontaneous pneumothorax developed one week after admission and he was transferred to a surgical department before more than one blood sample had been obtained. In one of the remaining 11 cases there was also a rise of antibodies to parainfluenza III virus.
(2) *Pneumococcal disease with positive serology and negative blood culture (n = 21)* This group included four cases with simultaneous positive viral serology. One patient with hyperthyroidism was excluded.[6]
(3) *Gram negative infections (n = 18)* This group including five cases caused by *Haemophilus influenzae*, nine cases caused by *Branhamella catarrhalis*, and four cases caused by *Neisseria meningitidis*.
(4) *Psittacosis (Chlamydia) (n = 9)*

Table 1 *Serum angiotensin converting enzyme (ACE) on admission to hospital (ACE_1), maximum value during the follow up (ACE_{max}), and difference between them (ΔACE) in pneumonias of different aetiology (values are given as means (SEM) with No of observations in second parentheses)**

Aetiological group	ACE_1	ACE_{max}	ΔACE
1 Pneumococcal, blood culture positive	26 (3) (11)	53 (5)† (10)	26 (5) (10)
2 Pneumococcal serology positive	30 (2) (20)	39 (2)† (20)	9 (1) (19)
3 Gram negative bacteria	29 (2) (18)	38 (2)† (18)	9 (2) (18)
4 Psittacosis	28 (3) (9)	43 (3)† (9)	15 (2) (9)
5 Viral	35 (6) (5)	38 (5) (5)	0 (5) (4)
6 No defined aetiology	32 (1) (81)	41 (1)† (81)	8 (1) (81)

†Significant difference from ACE_1 at $p < 0.001$ (paired *t* test).
*Reference limits of ACE activity are 23 and 53 U/l.

(5) *Viral infections (n = 5)* There was no evidence of concomitant bacterial infection.

(6) *Pneumonias of no defined aetiology (n = 81)* These cases were probably mostly of bacterial aetiology, as judged by the high C-reactive protein values.

On admission to hospital C-reactive protein was determined in all patients. Blood samples for ACE determinations were taken on the first working day after admission and once a week thereafter during the hospital stay, as well as at the outpatient follow up during recovery—that is, usually three to six weeks from onset of disease.

LABORATORY METHODS

ACE was determined by a fluorometric technique.[7] The reference limits for ACE were taken as 23–53 U/l, based on the values from 55 healthy adults (2 SD). C-reactive protein was determined by immuno-

nephelometry using commercially available reagents (Orion Diagnostica, Finland).

STATISTICAL METHODS

The significance of differences between means belonging to the same group (on admission to hospital and during recovery) was calculated by the *t* test for paired samples. The significance of the differences between means belonging to different groups with known aetiology was tested by one way variance analysis.[8] If this analysis showed a significant difference—that is, $p < 0.05$ at least, the means of the different groups were tested against each other by the modified *t* test.[8] The means of the heterogeneous group pneumonias of no defined aetiology, in which the number of observations was much greater than in the other groups, were tested against the other means by the conventional *t* test.

Results

There was a highly significant increase of ACE concentrations during the follow up of patients with pneumonia in most aetiological groups, except those in group 5 ($p < 0.001$) (table 1). In some rare cases the first ACE (ACE_1) value was the highest. In these cases the difference between the lowest value during follow up and ACE was used for calculating the change of ACE (ΔACE), which was negative—that is, ACE decreased during recovery.

The increase in ACE concentration was most prominent in group 1 in which the highest ACE value (ACE_{max}) was greater than that in groups 2 and 3 ($p < 0.005$), groups 4 and 5 ($p < 0.05$), and group 6 ($p < 0.001$). The differences between ACE_{max} and the other groups were not significant. There were no significant differences between ACE_1 concentrations in the groups.

In several patients, most often those in group 1, ACE_1 was below the reference limit (23 U/l) on admission to hospital, but then rose above the upper reference limit (53 U/l) during the follow up (table 2, figure).
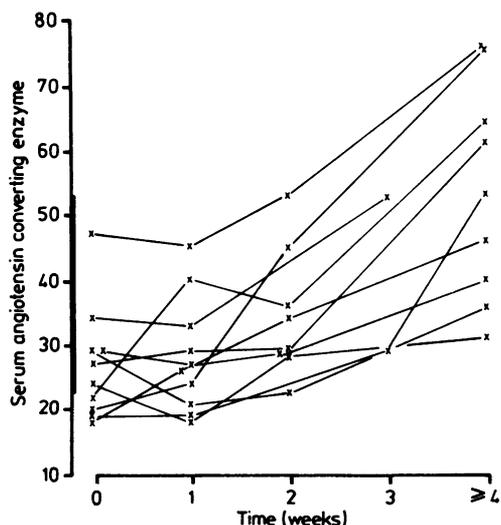

Figure *Changes in serum ACE activity in pneumococcal pneumonias with positive blood cultures. Reference range is indicated by bold part of ordinate.*

Table 2 *No (%) of patients with ACE concentrations below reference limits in acute phase and above during follow up in pneumonias of different aetiology*

Aetiological group	ACE < 23 U/l	ACE > 53 U/l
1 Pneumococcal, blood culture positive	5/11 (45)	4/10 (40)
2 Pneumococcal, serology positive	4/20 (20)	2/20 (10)
3 Gram negative	3/18 (17)	1/18 (6)
4 Psittacosis	1/9 (11)	1/9 (11)
5 Viral	1/5 (20)	0/5 (0)
6 No defined aetiology	13/81 (16)	9/81 (11)

In group 1 Δ ACE was greater than in groups 2, 3, 5, and 6 (p < 0·001), and group 4 (p < 0·025). There were no significant differences between Δ ACE in the groups.

When the groups with defined aetiology (1–5) were taken together, there was a highly significant positive correlation between Δ ACE and ACE_{max} with C-reactive protein (p < 0·001, table 3). Δ ACE showed a positive correlation with C-reactive protein in the group 6 (p < 0·01, table 3).

Discussion

After an initial decrease, observed on admission to hospital, there was a clear increase in serum ACE concentrations in pneumonias of different aetiology, except in group 5, where the number of cases unfortunately was small. The increase was most prominent in group 1. ACE_{max} occasionally exceeded the upper reference limit in all groups of patients with pneumonia but most often in those of group 1. The follow up in our patients was not long enough to show the duration of increased ACE values, mainly because of difficulties in obtaining blood samples from the patients after recovery. In various non-sarcoid lung diseases ACE has been reported to be above reference limits in about 5%,[2] and increased in histoplasmosis in about 25%.[4] These figures were, as shown here, higher in patients with pneumococcal disease with positive blood culture pneumonia; 40% had raised ACE values. Of the entire pneumonia patient series ACE values were raised above the reference limit in 12% during recovery. It has already been emphasised that even if ACE is within the reference limits in sarcoidosis, a rise or fall within these limits may reflect disease activity.[9] The rise of ACE values during recovery of pneumonias, as shown in this study, makes it questionable whether ACE fluctuations in sarcoidosis actually always reflect disease activity.

On admission to hospital, ACE activity was below the reference limits in several cases, most often in those with pneumococcal disease with positive blood culture—that is, in 45%—and in the whole series in 19%. ACE has been reported to be decreased in adults with respiratory distress syndrome, possibly due to damaged pulmonary endothelial cells.[10] In another study ACE values were decreased in adult respiratory distress syndrome only with concomitant sepsis.[11] In our study, however, sepsis was not a prerequisite for decreased ACE values, although they occurred most commonly in group 1. Decreased ACE values in the acute phase of pneumonia have been described in a Japanese study.[5] It was suggested that they resulted from a decreased pulmonary vascular bed. In that study no increases of ACE activity were reported.

The strong positive correlations of Δ ACE and ACE_{max} with C-reactive protein especially in groups with defined aetiology, indicate a relation between changes in ACE and the severity of pneumonia and the extent of pulmonary tissue damage.

ACE is localised to the vascular endothelial cells in the lungs.[12] ACE also occurs, however, in macrophages and monocytoid cells.[13] The pathophysiology of increased serum ACE concetrations in sarcoidosis and other diseases is still unknown. The decreased ACE concentrations during the acute phase of pneumonia may be related to a decreased pulmonary vascular bed or damaged endothelial cells.[5 10] Decreased ACE activity could also be due to the release of ACE inhibitors from necrotic tissue.[14] This alternative explanation could be examined by comparing enzymatic activity with molar concentrations of ACE in serum, which was not possible in this study. Increased ACE values during recovery could be a reflection of the numbers and activity of tissue macrophages during the reparation of damaged tissues.

Table 3 *Correlation coefficient (r) of C-reactive protein values with ACE_1, ACE_{max}, and Δ ACE in patients with pneumonias of defined aetiology (groups 1–5) and in pneumonias of no defined aetiology*

Aetiological group	ACE_1	ACE_{max}	Δ ACE
Defined aetiology (groups 1–5)	−0·09	0·47*	0·56*
No defined aetiology (group 6)	−0·20	0·04	0·34†

*Significant correlation at p < 0·001; †significant correlation at p < 0·01.

References

1 Lieberman J. Elevation of serum angiotensin-converting-enzyme (ACE) level in sarcoidosis. *Am J Med* 1975;**59**:365–72.

2 Grönhagen-Riska C. Angiotensin-converting enzyme I. Activity and correlation with serum lysozyme in sarcoidosis, other chest or lymph node diseases and healthy persons. *Scandinavian Journal of Respiratory Disease* 1979;**60**:83–93.

3 Lieberman J, Nosal A, Schlessner LA, Sastre-Foken A. Serum angiotensin-converting enzyme for diagnosis and therapeutic evaluation in sarcoidosis. *Am Rev Resp Dis* 1979;**120**:329–35.

4 Ryder KW, Jay SJ, Kiblawi SO, Hull MT. Serum angiotensin converting enzyme activity in patients with histoplasmosis. *JAMA* 1983;**249**:1888–9.

5 Mizuki M, Yamamoto T, Yamagishi M, Ishihara Y, Kitamura S. Changes in serum ACE activity in patients with pneumonia. *Nippon Kyobu Shikkan Gaggai Zasshi* 1982;**20**:798–802.

6 Silverstein E, Schlusser GC, Friedland J. Elevated serum angiotensin-converting enzyme in hyperthyroidism. *Am J Med* 1983;**75**:233–6.

7 Friedland J, Silverstein E. A sensitive fluorimetric assay for serum angiotensin-converting enzyme. *Am J Clin Pathol* 1976;**66**:416–24.

8 Wallenstein S, Zucker CL, Fleiss JL. Some statistical methods useful in circulation research. *Circulation* 1980;**47**:1–9.

9 Selroos O, Grönhagen-Riska C. Angiotensin-converting enzyme III. Changes in serum level as an indication of disease activity in untreated sarcoidosis. *Scandinavian Journal of Respiratory Disease* 1979;**60**:328–36.

10 Bedrossian CWM, Woo J, Miller WC, Cannon DC. Decreased angiotensin-converting enzyme in the adult respiratory distress syndrome. *Am J Clin Pathol* 1978;**70**:244–7.

11 Casey L, Krieger B, Kohler J, Rice C, Oparil S, Szidon P. Decreased serum angiotensin converting enzyme in adult respiratory distress syndrome associated with sepsis: A preliminary report. *Crit Care Med* 1981;**9**:651–4.

12 Caldwell PRB, Seegal BC, Hsu KC, Das M, Soffer RL. Angiotensin-converting enzyme: Vascular endothelial localization. *Science* 1976;**191**:1050–1.

13 Fyhrquist F, Grönhagen-Riska C, Hortling L, Forslund T, Tikkanen I. Regulation of angiotensin converting enzyme. *Journal of Hypertension* 1983;**1** (suppl 1):25–30.

14 Ryan JW, Martin LC, Chung A, Pena GA. Mammalian inhibitors of angiotensin converting enzyme (kininase II). *Adv Exp Med Biol* 1979;**120** (B):599–606.