

Angiotensin converting enzyme and Lung Function Correlation in Sarcoidosis

Siddharth Waghmare, Ketaki Utpat, Jyotsna .M. Joshi

Department of Respiratory Medicine, T. N. Medical College B.Y.L. Nair Hospital, Mumbai.

Correspondence: Dr. J. M. Joshi

Abstract

Background: Sarcoidosis is a multisystemic disease with a myriad of presentations. In sarcoidosis the hunt for a disease activity marker that correlates with lung function status has been extant with paltry breakthroughs. We conducted this study with the endeavour of investigating serum Angiotensin converting enzyme (ACE) levels with lung function parameters.

Methods: We retrospectively studied 39 cases of pulmonary sarcoidosis and analyzed the correlation of their serum ACE levels with lung function parameters namely forced vital capacity (FVC) and forced expiratory volume at 1 second (FEV1). Correlation coefficient (r) was calculated to study the correlation.

Results: There was a weak negative correlation between serum ACE levels and FVC ($r = -0.21$) and FEV1 ($r = -0.26$). However, this correlation was not found to be statistically significant (calculated $r < 0.316$).

Conclusion: Our study shows that serum ACE levels do correlate with lung function parameters however the correlation could not be proved to be statistically significant in our study. More studies with a larger sample size are required to shed light on this insufficiently fathomed domain.

Keywords: Angiotensin converting enzyme (ACE), Forced vital capacity (FVC), Forced expiratory volume at 1 sec (FEV1), Sarcoidosis, Correlation

Date of Submission: 12-01-2018

Date of acceptance: 31-01-2018

I. Introduction

Sarcoidosis is a granulomatous disorder of unknown etiology distinguished by non caseous epithelioid cell granuloma formation in multiple organ systems. It gains momentousness owing to the heterogeneity of its manifestations and the solemn consequences of its delayed diagnosis. It exhibits ubiquity as far as organ involvement is concerned however lung is the most commonly involved organ. Diagnosis of sarcoidosis commands a multi-disciplinary approach as other causes of granulomatous diseases pose a close differential to this entity. A salient marker of disease activity in sarcoidosis is serum angiotensin converting enzyme (ACE) level. It is conjectured that it is secreted by epithelioid cells and macrophages that make up the granuloma. This pathological basis explains its correlation with disease activity in sarcoidosis (1). Although the precise clinical value of this marker is still nebulous it is one of the most serviceable and pragmatic disease activity marker in sarcoidosis diagnostic accoutrements forthwith. It aids in the diagnosis by adding a corroborative value to the clinic radiological and histopathological data. Hence it is a commonly performed investigation in the diagnostic workup of sarcoidosis. Lung functions in pulmonary sarcoidosis are variably affected in sarcoidosis and the stage of the disease and the disease activity cast a major role in the same. In sarcoidosis management the pursuance for a disease activity marker that correlates with pulmonary functions has been unfolding with only a handful markers being added to the basket bit by bit. There are scarce studies available in literature pertaining to this subject matter. Hence we decided to study the association of serum ACE levels with lung function in cases of pulmonary sarcoidosis to attain a better understanding of this linkage.

II. Material and method

We included 51 patients diagnosed with pulmonary sarcoidosis from 2013 to 2015 attending the respiratory medicine department in Topiwala national medical college, Mumbai. Diagnosis was made by clinic-radiological correlation supported by serum ACE levels and histopathology. All the patients were treatment naïve. The serum ACE levels and lung functions in the form of forced vital capacity (FVC), forced expiratory volume at 1 sec (FEV1), and FEV1/FVC were noted in all patients. Of the 51 patients 12 patients were excluded due to lack of data pertaining to ACE levels and lung functions. So the final study population was 39 (Figure:1). The patients were grouped based on FVC and FEV1 values. The patients were categorized based on FVC (litres) in the form of i) 0-0.9 ii) 1-1.9 iii) 2-2.9 iv) 3-3.9 v) 4-0-4.9. Likewise, patients were categorized as per FEV1 (litres) in to the following groups- i) 0.5-1.4 ii) 1.5-2.4 iii) 2.5-3.4 iv) 3.4-4.5.

Statistical analysis

Mean and standard deviations were calculated for FVC, FEV1, Serum ACE levels. Also the mean ACE, FVC and FEV1 were calculated for individual ACE, FVC and FEV1 groups. The correlation between lung functions (FVC, FEV1) and serum ACE level was assessed by calculating Pearson's correlation coefficient (r). The statistical significance of the correlation (r) was assessed by comparing it with the critical r value (the value of r for 0.05 level of significance).

III. Results

Total 39 patients were enrolled in the study. Mean age was 42.10 (-/+13.87) years. There were 18 male and 21 female patients. There was a slight female preponderance (53.84%). The common symptoms were dry cough, dyspnea and fever with Dyspnea being the most common symptom. The average serum ACE level was 75.80 IU. The normal range i.e. 32 +/- 8 IU established has been validated by a number of standard laboratories. Thirty one out 39(79.4%) patients had elevated serum ACE levels. The highest value of serum ACE level was 217 U and lowest value was 23 U. Spirometry was performed in all patients on the same machine which complied all the ATS criteria by the same technician. A restrictive ventilatory pattern (i.e. FEV1/FVC ratio >70) was seen in 82.05% of patients whereas 7 patients had normal lung functions. The mean FVC value and FEV1 values were 1.98L and 1.75L respectively. Normal FVC and FEV1 (i.e. >80% of predicted) were seen in 9 and 15 patients respectively. On further analyzing the FVC values, most of the patients (51.28%) had FVC values between 1-1.99L followed by 2-2.99L. The mean ACE levels were 86.39U and 68.15U in the 1-1.9L and 2-2.9L groups respectively. The most common FEV1 values were 0.5-1.4L and 1.5-2.4L with the average ACE levels were 79.5IU and 88.26IU respectively (table 1 and table 2). We assessed the correlation between FVC and FEV1 with serum ACE levels by calculating the Pearson's coefficient of correlation. The value of r was -0.21 and -0.26 for FVC and FEV1 respectively (figure 2 and figure 3). Therefore, there was a weak albeit a negative correlation between lung functions and ACE levels. However the r values of both FVC and FEV1 were much less than the critical r value (i.e. 0.308 for 0.05 level of significance). Hence this correlation was not statistically significant.

IV. Discussion

Sarcoidosis is a multisystemic disease prevalent since coons-age with the pulmonary system being its most common prey. Timely diagnosis and staging is vital in chalking out the treatment scheme and preventing irrevocable loss of lung function. Hence there is an exigent need for a disease marker that will gauge the disease activity as well as predict the lung function status in unison. Serum ACE level is one such promising crystal globe. ACE is a dipeptidyl hydrolase that converts angiotensin1 to angiotensin2 thereby inactivating bradykinin. It has gained rapid significance in the workup since the unearthing of this fact that its levels are elevated in sarcoidosis and it can be possibly used as a measure of disease activity. However subsequent literature brought forth the fact that serum ACE levels may not accurately correlate with the degree of alveolitis. And hence its correlation with lung function also therefore remains a debate. We therefore conducted this research to shed light on this controversial though intriguing topic.

This was a retrospective study which involved 39 patients of sarcoidosis. There was a slight female preponderance in the study. Like with other autoimmune disorders, sarcoidosis affects women more than men (2). Serum ACE level was elevated in 79.4% of the patients. Serum ACE has low sensitivity and specificity in the diagnosis of sarcoidosis(3). Studies have shown that normal serum ACE level does not exclude the diagnosis of sarcoidosis (4) and hence low or normal serum ACE levels did not challenge the diagnosis of sarcoidosis in our study. Nonetheless, it is very useful test in differentiating sarcoidosis from other granulomatous diseases like tuberculosis(1) in cases of diagnostic dilemmas. Pertaining to spirometry, a restrictive ventilatory pattern was the most common (82.05%) spirometric finding and 24.13% had normal pulmonary functions. One third of patients of sarcoidosis may have normal lung functions(5) Sarcoidosis can affect any part of the lung but mostly affects the airway and interstitium (6). Pulmonary function testing usually demonstrates restriction from parenchymal involvement though airflow obstruction from airway-centred fibrosis is also recognized (7). In a north Indian population based study on sarcoidosis restrictive pattern and normal lung functions were seen in 56% and 8.9% of patients(8). When serum ACE levels were compared with their corresponding FVC values it was found that lower FVC values were associated with higher ACE levels. Similar association was found in a study done to assess correlation between serum ACE level, hypoxia and lung function. It was found that there was a negative correlation between ACE levels and lung functions (9). They postulated that the ACE levels increased due to hypoxia and probably due to poor lung functions. In another study by Kumar Ashutosh and John F. H. Keighley, the serum ACE levels were high amongst patients with active sarcoidosis (10). In sarcoidosis, patients may also suffer from airway involvement in the form of airway hyperresponsiveness (11)(12). As with FVC, higher ACE levels corresponded with low FEV1 values. In a study done in asthmatics, serum ACE levels were found to be elevated in patients with mild asthma compared to control group(13). On

statically analysis, there was a definitive negative correlation. However this correlation was not statistically significant

In our study, higher ACE levels correlated with poorer lung functions. however we failed to proved a statistically significant correlation between ACE and lung function. In spite of this ACE level in the light of clinical information can be used as a predictor of severity of sarcoidosis. However, certain studies done by other authors have found no correlation between ACE levels and lung function or disease severity (14)(15).Hence we conclude that although elevation in serum ACE levels is a common phenomenon in sarcoidosis it may not be universal.Measurement of serum ACE levels is simple, noninvasive and feasible but it cannot be labelled as a surrogate marker of lung function owing to the divergence in literature pertaining to its performance. Therefore more research is required in this sector of respiratory medicine to fully explore the therapeutic and prognostic potentials on serum ACE levels.

Figure 1 Study flow diagram

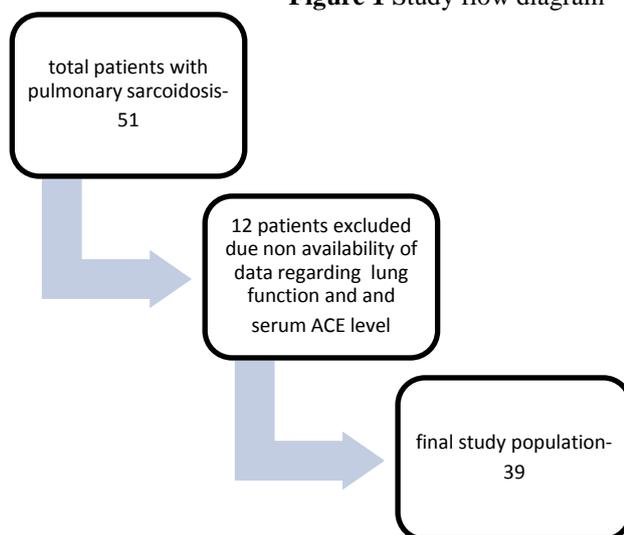


Table-1: average serum ACE level in the various FVC groups

FVC values	Total number of patients	Serum ACE level
0-0.99	5	50.33333
1-1.99	21	86.39091
2-2.99	8	68.15714
3-3.99	5	53.75
4.0-5.0	2	29.5
TOTAL	39	

Table-2: Average serum ACE level in the various FEV1 groups

FEV1 values	Total number of patients	Serum ACE level
0.5-1.4	15	79.50667
1.5-2.4	12	88.26
2.5-3.4	7	42.6
3.4-4.5	5	3.55
TOTAL	39	

Figure 2- A scatter diagram depicting the correlation between serum ACE level and FVC values.

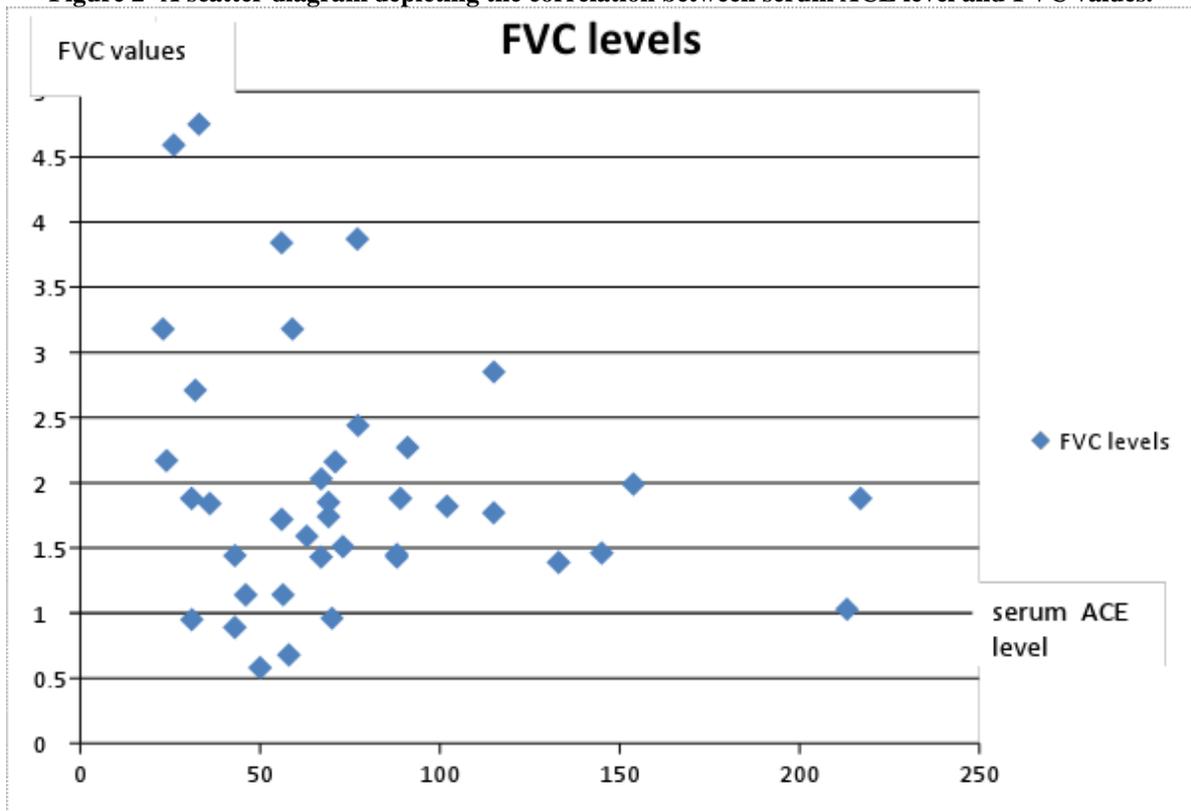
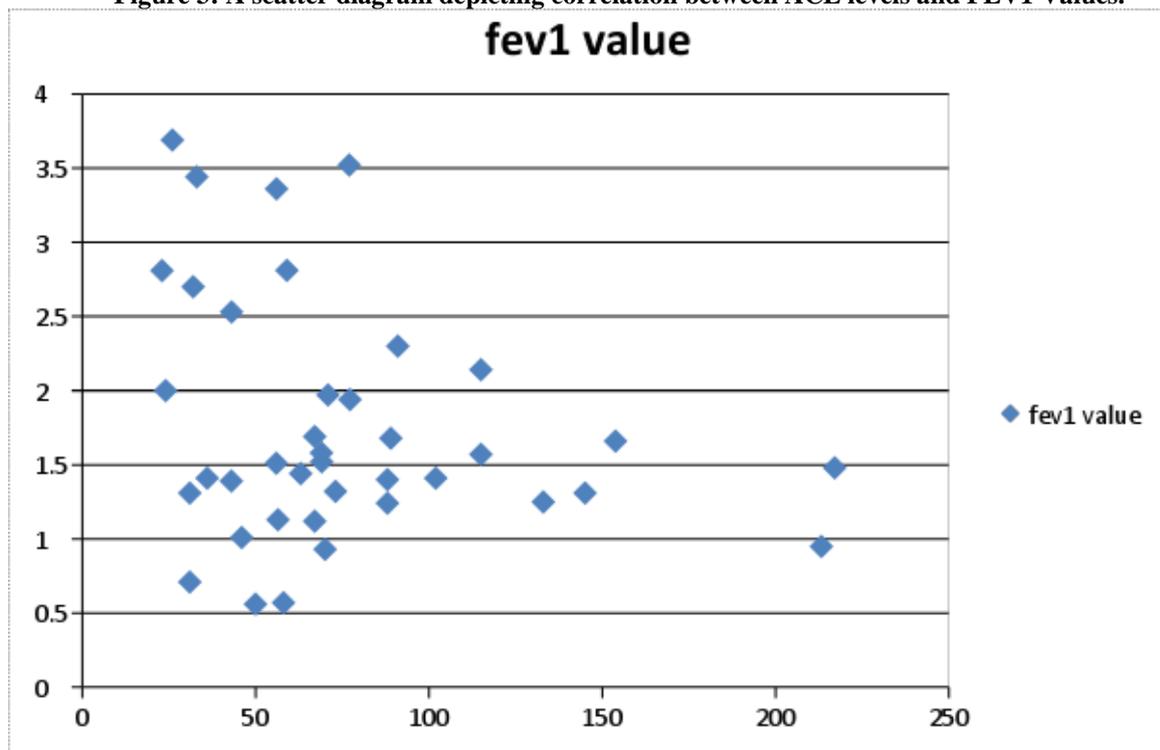


Figure 3: A scatter diagram depicting correlation between ACE levels and FEV1 Values.



References

- [1]. Lieberman J. Elevation of serum angiotensin-converting-enzyme (ACE) level in sarcoidosis. *Am J Med.* 1975;59(3):365–72.
- [2]. Judson M a, Boan a D, Lackland DT. The clinical course of sarcoidosis: presentation, diagnosis, and treatment in a large white and black cohort in the United States. *Sarcoidosis Vasc Diffuse Lung Dis* [Internet]. 2012;29(2):119–27. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23461074>
- [3]. Ungprasert P, Carmona EM, Crowson CS, Matteson EL. Diagnostic Utility of Angiotensin-Converting Enzyme in Sarcoidosis: A Population-Based Study. *Lung.* 2016;194(1):91–5.
- [4]. Alston C, Hull R, Sinclair D, Ledingham J, McCrae F, Shaban R, et al. Serum ACE for sarcoidosis is not such an ACE test. *Ann Rheum Dis* [Internet]. 2013;72. Available from: http://ard.bmj.com/content/72/Suppl_3/A330.2.abstract?sid=0fce4c11-4d25-4af6-b804-1265fde28372%5Cnhttp://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed11&AN=71332997%5Cnhttp://lib.exeter.ac.uk:4556/resserv?sid=OVID:embase&id=pmid:&id=d
- [5]. Baughman RP, Lower EE, Gibson K. Pulmonary manifestations of sarcoidosis. *PresseMedicale.* 2012.
- [6]. Valeyre D, Bernaudin J-F, Jeny F, Duchemann B, Freynet O, Planès C, et al. Pulmonary Sarcoidosis. *Clin Chest Med* [Internet]. 2015;36(4):631–41. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0272523115001069>
- [7]. Patterson KC, Strek ME. Pulmonary fibrosis in sarcoidosis clinical features and outcomes. *Annals of the American Thoracic Society.* 2013. p. 362–70.
- [8]. Kumar R, Goel N, Gaur SN. Sarcoidosis in north Indian population: a retrospective study. *Indian J Chest Dis Allied Sci* [Internet]. 2012;54(2):99–104. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22973778>
- [9]. Ucar G, Yildirim Z, Ataol E, Erdogan Y, Biber C. Serum angiotensin converting enzyme activity in pulmonary diseases: correlation with lung function parameters. *Life Sci.* 1997;61(11):1075–82.
- [10]. Ashutosh K, Keighley JF. Diagnostic value of serum angiotensin converting enzyme activity in lung diseases. *Thorax* [Internet]. 1976;31(5):552–7. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=470474&tool=pmcentrez&rendertype=abstract>
- [11]. Kaneko K, Sharma OP. Airway obstruction in pulmonary sarcoidosis. *Bull EurPhysiopatholRespir.* 1977;13(2):231–40.
- [12]. Baughman RP, Teirstein a S, Judson M a, Rossman MD, Yeager Jr. H, Bresnitz E a, et al. Clinical characteristics of patients in a case control study of sarcoidosis. *Am J RespirCrit Care Med.* 2001;164:1885–9.
- [13]. Tutluoglu B, Inan A, Cersek A. The relationship between serum ACE activity and total IgE levels in patients with bronchial asthma. *Pneumoftziologia.* 1998;47(2):95–7.
- [14]. Lieberman J, Schleissner LA, Nosal A. Clinical correlations of serum angiotensin-converting enzyme (ACE) in sarcoidosis. A longitudinal study of serum ACE, 67gallium scans, chest roentgenograms, and pulmonary function. *Chest.* 1983;84(5):522–8.
- [15]. Mimori Y. Sarcoidosis: correlation of HRCT findings with results of pulmonary function tests and serum angiotensin-converting enzyme assay. *Kurume Med J* [Internet]. 1998;45(3):247–56. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9787595>

SiddharthWaghmare "Angiotensin converting enzyme and Lung Function Correlation in Sarcoidosis" *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, vol. 17, no. 1, 2018, pp. 42-46.