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*Original Article*

# EVALUATION OF SERUM ANGIOTENSIN CONVERTING ENZYME (SACE) AS A DIAGNOSTIC MARKER FOR PULMONARY EMBOLISM

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**ABSTRACT:**

***Objective:*** A number of supportive laboratory tests such as ECG, Chest x-ray, ABGs, SLDH, SGOT, S. Bilirubin and D-dimer with variable sensitivity and specificity are available to facilitate the clinical diagnosis of acute Pulmonary Embolism (PE). Serum Angiotensin Converting Enzyme (SACE) which is produced mainly by the pulmonary vascular endothelial cells, is found altered during a variety of diffuse lung diseases. This study was designed to evaluate the validity of SACE level as a marker for hypoxic damage to the pulmonary endothelium in PE.

***Design:*** A prospective study carried out on forty patients with high clinical suspicion of PE. Besides routine diagnostic tests mentioned above all of them had Ventilation Perfusion isotope (V/Q) scans (as a diagnostic test) and SACE level checked.

***Setting:*** Shaikh Zayed Hospital Lahore.

***Results:*** Among forty consecutive patients with age range 25-59 years (mean: 42 Yr), twenty six patients (65%) with abnormal scans reported as 'High Probability' were included in group-A (True Positive), whereas 14(35%) patients having Low-Probability (Suspected) or Normal scan were included in group-B, Low SACE level (<28iu/L) was found in 19/26 (sensitivity of 73%) in Group-A (Positive Predictive Value: 47%) and 9/14 (sensitivity of 64%) in Group-B, whereas mean levels for both groups were 34.55 and 54.84 respectively. Rise in LDH was pronounced in Group-A. Only chest X-ray and ECGs were found to be more sensitive for group-A than group-B. Changes in ABGs (Type-1 Resp. Failure) had low sensitivity.

***Conclusion:*** Among clinically suspected cases of PE, fall in SACE level can be used as a sensitive and reliable diagnostic marker as more than 75% of the enzyme is produced in the lungs compared with other enzymes which have extra-pulmonary source.

**KEY WORDS:** SACE, Pulmonary Thrombo-embolism.

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## INTRODUCTION

The activity of serum angiotensin converting enzyme (SACE) was recognized in 1954 and isolated in 1956. SACE-kinase-II hydrolyses Angiotensin-1 (decapeptide) to Angiotensin-II (octapeptide) and inactivates bradykinines[1]. Conversion of Angio-I to Angio-II occurs more than 75% in lungs and rest in vasculature of kidneys, intestine, forearm areries and hand veins. Serum Angiotensin Converting Enzyme

(SACE) level is found elevated in different diseases[2] like sarcoidosis, tuberculosis, primary biliary cirrhosis, leprosy; and decreased in Acute Respiratory Distress Syndrome, pulmonary fibrosis and bronchogenic carcinoma producing diffuse lung injury. SACE can be a good index of integrity of pulmonary vasculature. Pulmonary Embolism (PE) results in hypoxic injury to endothelium and fall in SACE level can be a valid diagnostic criteria for acute pulmonary embolism[3] and secondary rise in SACE may be an index of reperfusion. Present study was intended to evaluate validity of fall in SACE as a criteria for diagnosing pulmonary embolism.

## PATIENTS AND METHODS

Fifty-eight consecutive patients with age range 25-75 years having clinical suspicion of PE were followed up. Only 40 cases were enrolled for the study, after clinical diagnosis was established through assessment and evaluation (see below). All these patients had presented in different medical and surgical specialties, with acute respiratory distress in the background of high-risk diseases. All those on ACE inhibitors[4] were excluded. A battery of conventional tests for the diagnosis of pulmonary embolism were carried out, which included chest x-ray, serum enzymes (LDH, SGOT), ECG, ABGs and V/Q scan. D-dimer[6] assay was not available. Relying on these tests and clinical evaluation, patients were diagnosed to have PE and were subsequently categorized as High Probability (Group-A) and Low Probability (Group-B) depending on the findings of V/Q scan. Besides the conventional tests for PE, all cases after being included as study cases, had SACE level checked within 48 hours of making the provisional diagnosis. SACE level was measured using spectrophotometer method utilizing synthetic tripeptide substrate (FAPGG)[7], using heparinised syringe personally by one of the authors. The investigators were not involved in the active management of cases at any stage.

## RESULTS

Out of fifty eight patients, 40 (23 F, 17 M) were confirmed to have Pulmonary Embolism and were managed accordingly by the concerned department. Table-I shows that among these 40 study cases, 26 (65%) had High Probability scan (Group-A), and 14 (35%) had Low Probability Scan (Group-B). Abnormal chest radiographs were observed in 100% of group-A and 70% of group-B. The findings included cardiac enlargment, infiltration or opacities, raised diaphragm and blunting of costophrenic angle. Suggestive ECG abnormalities were detected in 100% of group-A and 56% of group-B. These included right axis deviation, tachycardia, right bundle branch block and $S_1Q_3T_3$. High serum LDH (>350 iu) was seen in 92% of group-A and 37% of group-B, while SGOT and Billirubin levels were not discriminative. Table-II shows that Low serum ACE

*Table - I:* Supportive tests for pulmonary embolism

| *Tests* | *Group-A(n=26) (High probability/ +ve V/Q scan)* | *Group-B (n=14) (Low probability/ Normal scan)* |
|---|---|---|
| SLDH (>350 u/L) | 92% | 37% |
| SGOT (>50 u/L) | 55% | 45% |
| S. Billirubin (1.1 mg/dL) | 30% | 28% |
| Abnormal Chest radiograph | 100% | 70% |
| Suggestive ECG abnormality | 100% | 56% |
| ABGs: $PO_2$ (<85mm Hg) | 50% | 18% |
| $PCO_2$ (<40 mm Hg) | 85% | 10% |

*Table-II:* SACE study results

| | *(High Probability Group-A (n=26)* | *(Low Probability Group-B (n=14)* | *P value* |
|---|---|---|---|
| SACE level (mean) | 34.55 u/L | 54.84 u/L | P < 0.005 |
| Fall in SACE <28 u/L | 19 (73%) | 9 (64%) | P < 0.05 |
| Normal SACE level 33-41 u/L | 4 (15%) | 3 (21.4%) | |
| > Normal level | 3 (11.5%) | 2(14.2%) | |
| Positive Predic. Value | 73% | | |

SACE level = Unit/L (iu)

level (<28 iu) were found in 73% of group-A (Positive Predictive Value: 47%), and 64% of group-B, whereas mean level of SACE in group-A (34.55 u) was much lower than in group-B (54.84 u). About 15% (4/26) of Group-A had normal and 11.5% (3/26) above normal SACE. In Group-B 15% (2/14) had above normal and 21% (3/14) had levels within normal limits.

## DISCUSSION

Pulmonary Embolism (P.E) is a common cause of death even in developed country like USA, where it is responsible for contribution in 500-200000 deaths per annum.[8] The clinical diagnosis of P.E. is difficult. 90% of the patients survive the initial embolic event, while correct diagnosis is not made in more than 2/3rd of them. Overall frequency of undiagnosed Pulmonary Embolism remains same over several decades.[9] This situation largely reflects the non-specificity of the clinical history or physical examination and laboratory finding in PE. As case fatility of Pulmonary Embolism is high i.e. about 15-70%, while appropriate therapy is available but not without risks, the availability of an accurate but noninvasive screening tests for PE is highly desirable.

Pulmonary Embolism can be diagnosed through noninvasive tests.[10] Radionucleide scanning has served as a screening test for the past 20-25 years but its use is not without controversy, as it is time consuming to arrange, require radioactive material and done in a specialized unit. The sensitivity of perfusion scan is well accepted but non-specificity is well documented. The advent of ventilation scan has offered a great improvement in specificity by allowing assessment of ventilation perfusion matching and mismatching. The classical pattern of PE is to have segmental and sub-segmental perfusion defects coupled with normal ventilation study. These findings are categorized as High Probability scan and are diagnostic of PE. A normal perfusion scan may exclude PE[11,12] and even angiography may rarely detect abnormality in this group.[13] Pulmonary angiography is the most specific test available[14] and remains the gold standard for diagnosing PE. Various pattern of vascular deficiencies has been described, which include, filling defects, cut off, pruning, oligemia, asymmetric filling, prolonged arterial phase and bilateral lower zone filling delay. Development of Digital Subtraction Angiography (DSA) has added to the accuracy in providing diagnostic information in patients with suspected PE. Noninvasive contrast enhanced high resolution spiral CT scan may be as valuable as angiography.[15,16] Though highly specific, such test are available only in selected centers and have limited utility.

Among the conventional tests, ABGs are checked routinely, Fall in $PO_2$ or widening of A-a $O_2$ gradient, together with fall in $PCO_2$, increases the value of ABG analysis as screening test in a patient with suspected PE. ECG changes when present are more specific but not sensitive. Routine chest radiographs are highly suggestive test with sensitivity of >90% in established cases. Radiological changes are variable[17] depending upon the number and size of emboli. These include, elevated diaphragm on same side, plate like atelactasis, pleural effusion, dilated central pulmonary artery, abrupt cut off of peripheral arteries, dilated right ventricle, superior vena cava or azygos vein, oligemia, change in vessel size and loss of lung volume. A normal chest radiograph is highly valuable while isotope scan is abnormal. Liver and cardiac enzymes can also be used as an index of PE. Raised LDH with normal SGOT is found in 50% of cases, while raised LDH normal AST and raised serum billirubin though seen only in 12% of cases, has high reliability.

ACE is widespread in body organs but plays especially important role in pulmonary circulation. Pulmonary circulation is uniquely placed in modifying level of circulating vasoactive substances. Angiotensin-I and bradykinin are inactivated in lungs to Angiotensin-II and III[18] which are responsible for homeostatis of BP. SACE is present on or within the endothelial cells, and conversion of enzymes can be

sensitive to changes in $PO_2$[19] or $PCO_2$. More than 75% of Angio-II is produced in lungs, rest is generated in other tissues locally but gets destroyed before reaching the circulation. Thus serum ACE activity reflects pulmonary ACE activity. SACE is a potential marker of pulmonary endothelial cell injury[20] and fall in plasma level has been found in diseases like ARDS[21], diffuse pulmonary fibrosis, bronchogenic carcinoma and advanced COPD[22]. SACE level is found elevated in different diseases such as, Sarcoidosis[23], histoplasmosis, tuberculosis[24], leprosy, primary biliary cirrhosis, hyperthyroidism, diabetes, Gauchers disease, silicosis[25] and asthma.

In 1990 it was suggested that SACE level could be useful biological marker for reduction in vascular bed or diffuse injury, as in pulmonary thromboembolism. SACE activity returns to normal in a few days probably in relation to the spontaneous reperfusion of the pulmonary vascular bed. Measurement of SACE activity may provide useful information in the diagnosis and prognosis of pulmonary vascular endothelial damage in pulmonary embolism.

In this study cases were included which have been selected on high clinical suspicion, supported by highly suggestive conventional tests and abnormal V/Q scans. All these cases were treated as pulmonary embolism by the admitting unit.

Study cases were grouped as High Probability (Group-A) and Low Probability (Group-B) as reported on radionucleide scanning. A mean SACE level of 34.55 u was found in Group-A and 54.84 u in Group-B. Fall in SACE with cut off value of <28 u was observed in 73% (19/26) of Group-A and 64% (9/14) of Group-B. An overall decease in SACE level was more pronounced in Group-A. High Probability scan indicates recently compromised pulmonary vasculature or injury but preserved ventilation, while Low Probability scan more likely indicates loss of vascular bed due to previous or chronic pathology with compromised ventilation as well.

Lowering of cut off value may prove more discriminative but at the cost of missing more cases. Fall in SACE level is probably resultant of hypoxic state of pulmonary vasculature or loss of vascular bed after thrombo embolism. Serial value of ACE could be more valuable for prognostic significance, as serum level may rise with improved circulation during recovery. Serial changes can be used for its prognostic significance. Changes in SACE level among patients with strongly suspected cases of PE can be either diagnostic or may provide supporting evidence which will supplement other diagnostic strategies. It is appropriate to consider how often decreased SACE level will accurately predict a diagnosis of PE, as fall in SACE levels in other conditions can reduces its diagnostic specificity. In this study Positive Predictive value of 47% and sensitivity of 73% was observed for Group-A having high probability diagnosis. The specificity could not be checked as study did not include true negative cases.

SACE is a useful simple noninvasive test which can be repeated at intervals. It provides strong supporting evidence and can be used as a complimentary test to other conventional diagnostic tests. More studies are needed to determine the significance of serial measurement in monitoring the progression in embolic phenomenon and its response to treatment or spontaneous recovery.

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