

## Value of C - Reactive Protein Measurements in Exacerbations of Chronic Obstructive Pulmonary Disease

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### Abstract

**Background** The acute phase protein, CRP, when elevated, provides good evidence of an active tissue-damaging process. Thus; its measurement provides a simple screening test for active organic disease. Increased CRP production is a very early and sensitive response to most forms of bacterial infection.

**Objective** was to ascertain whether infective exacerbations of chronic obstructive pulmonary disease (COPD) and their successful treatment correlate with corresponding changes in CRP level.

**Methods** Fifty Patients (age  $65 \pm 6$  years) diagnosed as COPD on the basis of clinical history and pulmonary function test were enrolled into the study. All those were admitted to Al-Kadhimya Teaching Hospital because of clinical exacerbations of their condition. Serum samples were obtained on admission from the patient for measurement of CRP and full blood count together with sputum sample for microbiological diagnosis (especially culture). CRP measured by semi quantitative method, the cutoff point of this test is 0.6 mg/L. So all positive values were  $\geq 1.2$  mg/L. All these patients with exacerbations were treated by conventional treatments. Blood samples for CRP, full blood count and forced expiratory volume in 1<sup>st</sup> second (FEV1) were repeated 4-5 days thereafter.

**Results** The levels of CRP were elevated  $\geq 1.2$  mg/L in 27 patients who were positive for bacterial culture. The average CRP level after adequate treatment was highly decreased ( $p$  value  $< 0.001$ ). There was a significant improvement in their measured FEV1 ( $p$  value  $< 0.001$ ). The peak CRP level and fall in CRP were significantly correlated with both the corresponding peripheral blood smear white cell count ( $r=0.57$ ,  $p$  value  $< 0.001$ ) and the correlation Coefficient between CRP and FEV1 was ( $r= -0.45$ ,  $p$  value  $< 0.001$ ).

**Conclusions** Since patients with acute exacerbations of COPD had their CRP levels elevated initially and had clinical improvement with lowering of the CRP levels after treatment, there is a strong possibility that CRP is a marker of exacerbation of COPD. We suggest that, in exacerbation of COPD, CRP estimation provides a useful and inexpensive early marker of the exacerbation and provides a useful guide to assess the efficacy of treatment.

**Key words** C, reactive protein. Chronic obstructive pulmonary disease with exacerbation.

### Introduction

Chronic obstructive pulmonary disease (COPD) is defined as a disease state characterized by the presence of airflow obstruction due to chronic bronchitis or emphysema.

The airflow obstruction generally is progressive, may be accompanied by airway hyper-reactivity, and may be partially reversible <sup>(1)</sup>. Pathological changes in COPD occur in the large (central) airways, the small (peripheral) bronchioles, and the lung parenchyma <sup>(2)</sup>.

Although primarily affecting the lungs, the chronic inflammatory process of COPD does have systemic effects <sup>(3)</sup>. There is increasing evidence that COPD is a multiorgan system disease. Skeletal muscle weakness and wasting and impaired exercise tolerance which are frequently occurring symptoms in advanced COPD appear to be linked to a systemic inflammatory response <sup>(4)</sup>. Several systemic inflammatory mediators such as TNF- $\alpha$  <sup>(5)</sup>, the soluble TNF transmembrane receptor-75 (sTNF-R75) <sup>(6)</sup>, soluble adhesion molecules <sup>(7)</sup>, some interleukins, acute phase proteins (CRP, fibrinogen, lipopolysaccharide-binding protein (LBP) ) and leucocytes are increased in the systemic circulation of patients with COPD <sup>(4)</sup>. One of the markers of systemic inflammation that is consistently shown to be slightly increased in patients with COPD compared with healthy controls is CRP <sup>(8)</sup>. Exacerbation is a prominent feature of the natural history of COPD. Exacerbations are commonly considered to be episodes of increased dyspnea and cough and change in the amount and character of sputum. Exacerbations are more frequent as disease progresses and are most often triggered by respiratory infections, often with a bacterial component <sup>(9)</sup>.

Studies have shown that an elevated CRP level is a useful indicator of exacerbation in cystic fibrosis, chronic bronchitis, and COPD <sup>(10-12)</sup>.

## Methods

### Patients

Fifty Patients (age 65 $\pm$ 6 years) with COPD on the basis of clinical history and pulmonary

function test were enrolled into the study, were admitted to Al-Kadhimya Teaching Hospital because of clinical exacerbations of their condition with dyspnea and increased cough with expectoration of yellow-green sputum. All of them had baseline FEV1 of (0.7 $\pm$ 0.2). Pneumonia was excluded by chest radiograph and clinical examinations.

### Blood samples

Blood was withdrawn and serum was collected for measurement of CRP and full blood count together with sputum sample for microbiological examination (especially culture). CRP measured by using of Wellcotest Latex agglutination test (*Wellcome Diagnostics*) which is semi-quantitative method, the cutoff point of this test is  $\leq 0.6$  mg/dL, so all positive values were  $\geq 1.2$  mg/L.

### Treatment and Follow up

All these patients with exacerbations were treated with antibiotics, bronchodilators, controlled low tension oxygen therapy, low dose diuretics for those associated with right sided heart failure with short course of steroids. Then blood sample for CRP and full blood count (Blood samples were collected for all patients before and after treatment. FEV1 is also repeated after 4-5 days after treatment mentioned above.

### Statistical Analysis

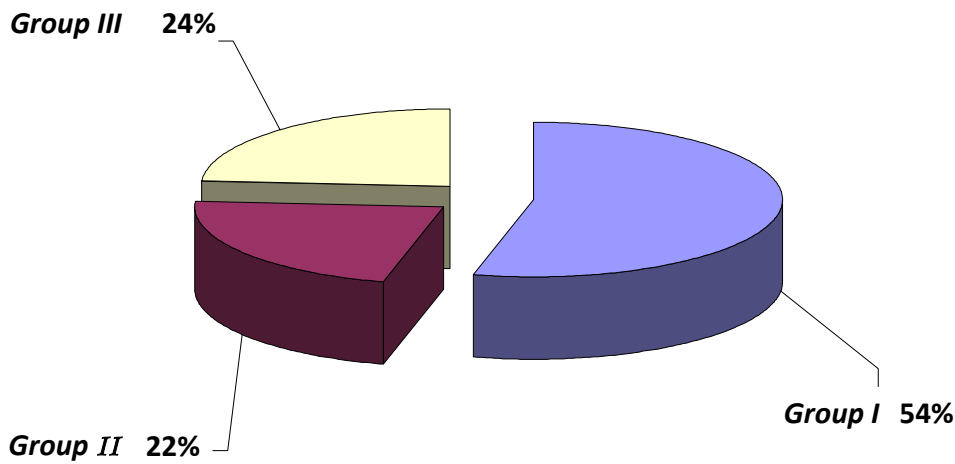
The statistical analysis was done using *t test* and correlation coefficient (*r*). All the results are significant if the *p* value is  $< 0.005$ .

## Results

CRP levels were elevated  $\geq 1.2$  mg/L in 27 patients who were positive for bacterial culture (group I), and 11 of the 23 patients with no clear bacteriological evidence of infection (group II); while those with CRP and culture negative were mentioned as group III (see Figure.1). The average elevated CRP level in group I was (11.2 $\pm$ 6.8); while average

CRP level in those with culture negative (i.e. group II and III) was  $(3 \pm 2.9)$ . The average CRP level after adequate treatment was  $(3.2 \pm 2.9)$  ( $p$  value < 0.001). There was an improvement in their measured FEV1 from  $0.78 \pm 0.2$  before treatment to a mean of  $1.4 \pm 0.2$  after treatment ( $p$  value < 0.001).

The patient characteristics and their relationship to CRP were shown in table 1. The peak level and fall in CRP were both correlated with the corresponding peripheral blood smear white cell count ( $r=0.57$ ,  $p$  value < 0.001) as in Figure 2. Also the correlation Coefficient between CRP and FEV1 was ( $r= -0.45$ ,  $p$  value < 0.001) as shown in Figure 3.

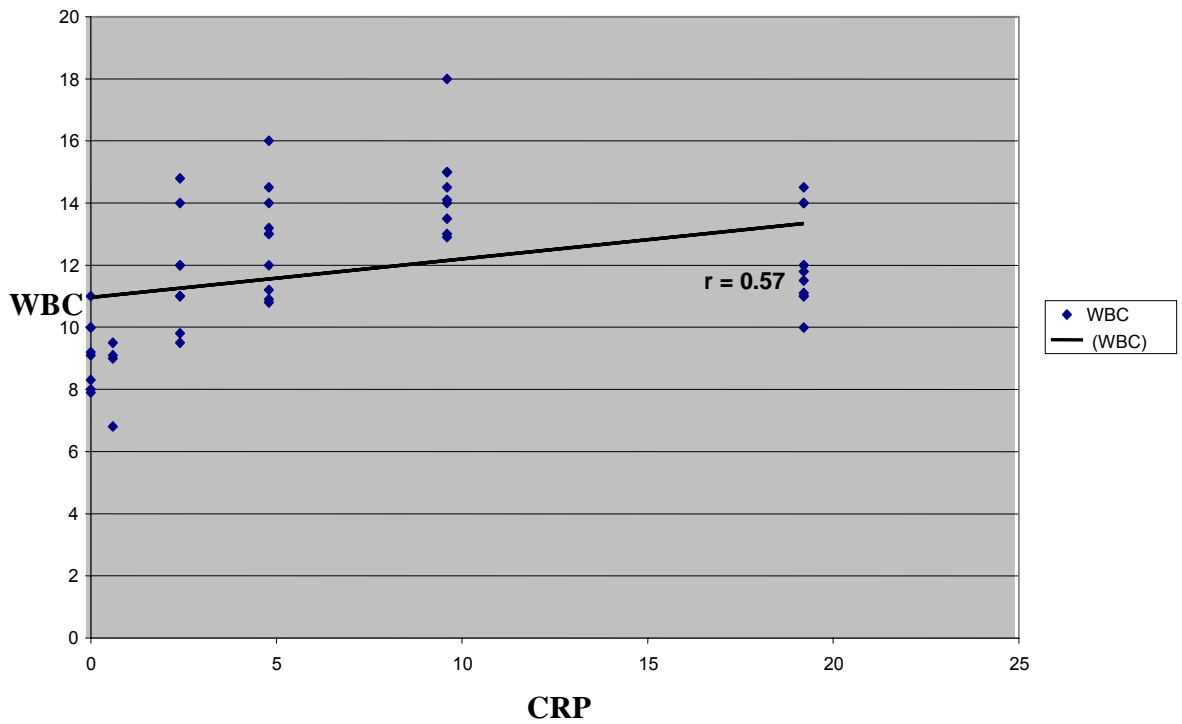


**Figure 1: Groups of the patients in the study**

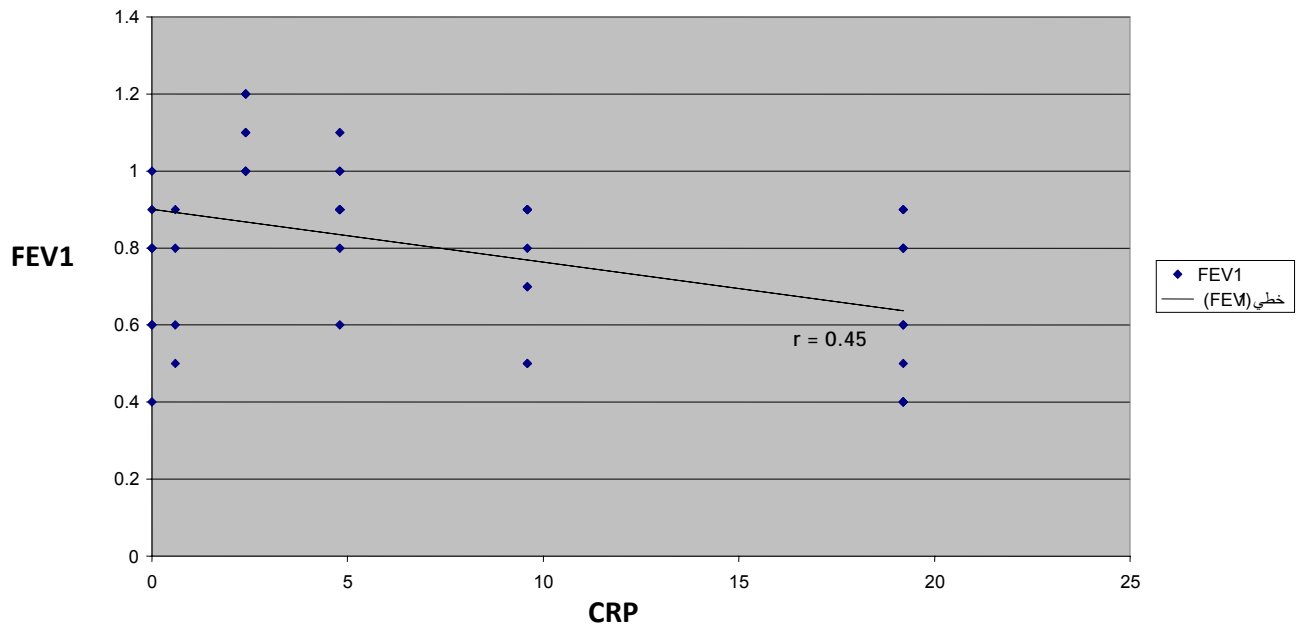
- Group I – Those with elevated CRP and culture positive (54%)
- Group II- Those with deviated CRP and culture negative (22%)
- Group III- Those with normal CRP and culture negative (24%)

**Table 1: Characteristics of patients and their relationship to CRP**

Characteristic of patients	Elevated CRP N=38	Normal CRP N=12	<i>p</i> value
Age (Mean ± SD)	63±6.14	68±5.8	0.359
Sex ♂/♀	30/8	10/2	0.741
FEV1 (Mean ± SD)	0.739±0.20	0.89±0.18	0.029
FEV1-5d (Mean ± SD)	1.423±0.23	1.32±0.18	0.193
WBC (Mean ± SD)	12.77±1.86	8.99±1.12	0.0001
WBC-5d (Mean ± SD)	8.27±1.86	4.88±0.68	0.0001
Culture P/N	27/11	0/12	0.0001



**Figure 2: Correlation between CRP before and after treatment with corresponding peripheral blood white cell count**  
 $r = 0.57, p \text{ value} < 0.001$



**Figure 3: Correlation between CRP before and after treatment and corresponding FEV1**  
 $r = -0.45, p \text{ value} < 0.001$

## Discussion

The acute phase protein, CRP, when elevated, provides good evidence of an active tissue-damaging process. Thus; its measurement provides a simple screening test for active organic disease. Increased CRP production is a very early and sensitive response to most forms of bacterial infection<sup>(11)</sup>. Studies have shown that it can be a useful indicator in differentiating between bacterial meningitis and viral meningitis<sup>(13)</sup>, CRP levels also have been previously found to be of value in discriminating between bacterial and viral pneumonia<sup>(30)</sup>.

In one study by Nel et al<sup>(31)</sup> showed a significantly increased level of CRP during infective exacerbations in emphysema. However, there has not been any assessment of the value of CRP in exacerbations of COPD, which is one of the commonest causes of hospital admissions. In this context, routine bacteriological analysis of sputum is often unreliable and slow. It is well established that the respiratory tract may be asymptotically colonized; for example *Haemophilus influenzae* in chronic bronchitis<sup>(32,33)</sup>. Thus it may be difficult to distinguish active infection from colonization on the basis of sputum culture. In this situation, serial CRP assays which are cheap, sensitive and rapid to perform provide a useful quantitative measure of exacerbation in COPD.

There have been few studies to assess the value of measuring CRP in clinical exacerbations of COPD. Our study results were compatible with the study by Dev et al<sup>(34)</sup> in whom two group of patients have exacerbation of COPD, one with proven bacterial infection (by sputum culture – group I) and the other in which there is no bacterial cause of infection (group II). The results of our study showed that in both of these groups who had exacerbations of

COPD; there was an elevated CRP at the time of admission to the hospital. In group II, clinical improvement occurs following treatment during their hospital stay with an associated dramatic fall in their CRP levels. This is attributed to the following reasons:

1. Inadequate improper sputum sampling
2. Problems with the analysis of sputum
3. Unusual behavior of the strain
4. viral infection could be responsible pathogen in patients in whom sputum was negative for bacterial pathogens

On the other hand, some patients may be chronically colonized with potential bacterial pathogens. Therefore, microbial examination of sputum may not always be useful indicator of active infectious state.

Consequently, since both groups of patients with clinical exacerbations have their CRP levels elevated initially show clinical improvement with lowering of CRP levels after treatment, there is strong probability that CRP is a marker of an exacerbation of COPD, but not necessarily a marker of bacterial infection.

The fall in CRP level after treatment with the clinical improvement could be due to:

1. The antibiotics used to treat the bacterial infection
2. Several other factors such as steroid treatment, O<sub>2</sub> therapy, bronchodilator and other treatments used in the treatment of COPD exacerbations

However, twelve of patients from the culture-negative group did not show a rise in CRP levels despite the evidence of acute exacerbations (group III). These patients may have viral infection that does not cause a rise in CRP or several other physiological defects interfering with CRP response.

Since patients with acute exacerbations of COPD had their CRP levels elevated initially and had clinical improvement with lowering

of the CRP levels after treatment, there is a strong possibility that CRP is a marker of exacerbation of COPD.

### Recommendation

We suggest that, in exacerbation of COPD, CRP estimation provides a useful and inexpensive early marker of the exacerbation and provides a useful guide to assess the efficacy of treatment

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