C-reactive protein to distinguish pneumonia from acute decompensated heart failure

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Abstract

Background: Patients with acute decompensated heart failure (ADHF) are frequently treated with unnecessary antibiotics since they are confused with pneumonia patients.

Aim: To study the efficacy of measuring C-reactive protein (CRP) levels on admission and CRP velocity in differentiating ADHF from pneumonia.

Methods: A retrospective observational study of ADHF and pneumonia patients admitted to a tertiary hospital during 2 years. Patients who were already treated with antibiotics on admission were excluded. Efficacy of CRP as a diagnostic marker was evaluated by using receiver operator curves (ROC).

Results: Overall, 72 ADHF and 50 pneumonia patients were included in the study. The mean CRP levels on admission were 13.5±13.5 mg/L for the ADHF patients and 127±84 mg/L for the pneumonia patients (p<0.001). CRP increases of ≥0.56 mg/L/h were diagnostic of pneumonia.

CRP levels on admission together with CRP increases had a sensitivity of 0.96 and a specificity of 0.972 (p<0.001) as markers to distinguish pneumonia from ADHF.

Conclusions: This study emphasizes the dynamic nature of biomarkers. Demonstrating the efficiency of repeated CRP measurements in an acute setting will provide clinicians with a valuable tool for establishing the correct diagnosis and refraining from unnecessary use of antibiotics. © 2009 The Canadian Society of Clinical Chemists. Published by Elsevier Inc. All right reserved.

Keywords: C-reactive protein; Pneumonia; Heart Failure

Introduction

Differentiating acute bacterial infections from viral or non-infectious processes in the setting of acute decompensated heart failure (ADHF) poses a clinical challenge. Many of these patients present with dyspnea, mild fever and leukocytosis. Upon auscultation, there are evident crackles and chest X-ray commonly demonstrates interstitial edema and a pleural effusion. All these can either mask or mimic a concomitant pneumonia. The identification of biomarkers, such as procalcitonin and B-natriuretic peptide, for the early detection of bacterial infection could guide treatment, reduce misuse of antibiotics and possibly improve long-term outcomes [1,2].

Among different biomarkers being studied, the C-reactive protein (CRP) shows great promise. Raised levels of CRP on admission have been demonstrated as a relatively more sensitive marker than any clinical symptom or sign in pneumonia patients, and several studies have suggested cutoff values for ruling out pneumonia (20–40 mg/L) or for ruling it in (100 mg/L) [3–6].

Using measurements of CRP in order to diagnose bacterial infections in the setting of ADHF, however, requires special consideration, as elevated CRP levels have been noted in various non-infectious cardiac pathologies [7]. Here, understanding the
kinetics of CRP may be of help in confirming the diagnosis. The plasma half-life of CRP is approximately 19 h and is constant under all conditions of health and disease. Thus, the sole determinant of circulating CRP concentration is its synthesis rate. Following a specific stimulus, CRP concentration will rapidly rise, peaking by 48 h and eventually subsiding once the stimulus disappears [8]. Based on these characteristics, we had speculated that quantitatively following the rate of change in serum CRP concentration will help differentiate between distinct stimulating processes.

In CHF, several studies have suggested serial measurements of CRP as a mean for following disease progression and response to treatment [9,10]. However, this approach has been traditionally qualitative. In this work, we implied a quantitative method and studied the hypothesis that, among ADHF patient, levels and velocity of rise of CRP will be significantly lower than among patients with pneumonia. Our rational was that based on such evidence, we can then speculate that ADHF with a concomitant pneumonia is bound to differ significantly from ADHF alone. To the best of our knowledge, this is the first time CRP velocity is assessed in the acute setting of heart failure.

Methods

Study design

This was a retrospective observational study of ADHF patients and pneumonia patients admitted to the internal medicine wards B and D at the Tel Aviv Medical Center between October 1, 2004, and September 30, 2006. Patient selection was based on a search through the medical records database using the terms “CHF exacerbation” and “pneumonia.” Included were only patients in whom CRP levels and WBCC were obtained twice; within the first 24 h of hospitalization and during the next 24 h. CRP and WBCC velocity were calculated by dividing the change in their levels with the hours that went through between the samples. For example, if the first blood sample for CRP (10 mg/L) was obtained 2 h following admission and the second blood sample for CRP (30 mg/L) was obtained 20 h following admission, then CRP velocity would have been equal to 20 mg/L divided by 18 h, i.e., 1.11 mg/L/h. ADHF was defined by a known history of heart failure and a new onset or worsening of dyspnea accompanied by weakness and/or peripheral edema. The definition of pneumonia was consistent with the American Thoracic Society’s guidelines for the management of adults with community-acquired pneumonia; pneumonia was defined by the appearance of a new infiltrate on chest X-ray accompanied by an oral fever of at least 38 °C and/or leukocytosis or leukopenia in a patient who had not been hospitalized in the previous 14 days [11]. Moreover, the appearance of a new infiltrate on chest X-ray was confirmed by a specialist in radiology. Included were only patients admitted without consuming antibiotics. Excluded from this study were patients with evidence of myocardial infarction, active inflammatory disease, immunodeficiency and systemic steroid treatment. Data were collected in accordance with the permission and instructions of the institutional Helsinki committee.

Laboratory variables

Measurements of CRP were preformed according to the Bayer’s wide-range (wr-CRP) method, using an immunoturbidimetric assay on the ADVIA 1650 chemistry system and the Bayer ADVIA kit for wide-range CRP [12]. The white blood cell count (WBCC) was performed by the Coulter STKS (Beckman Coulter, Nyon, Switzerland) electronic analyzer.

Statistical analysis

Statistical analysis was performed by using the SPSS (version 13; SPSS Inc., Chicago, IL) software. All data were summarized and displayed as mean ± standard deviation for the continuous variables and as number of individuals plus the percentage in each group for categorical variables. Comparisons of variables were obtained using Fisher’s exact test, chi-square test, Student’s t-test, Wilcoxon rank sum test, Pearson’s test and Jonckheere–Terpstra test as appropriate. All the above analyses were considered significant at \( p < 0.05 \) (two tailed).

Efficiency of CRP as a diagnostic marker was evaluated in comparison to clinical and radiological diagnosis by using receiver operator curves (ROC) [13] in three steps. First, an ROC curve depicting CRP values of the first 24 h of hospitalization was analyzed, and a cutoff value for ruling-in pneumonia with the highest specificity was chosen. Then, a second analysis was implemented looking only at subjects with values under the cutoff. An ROC curve was constructed comparing CRP velocity to clinical and radiological diagnosis in this particular group, and a second cutoff value was chosen using the Youden index (sensitivity + specificity – 1). Combining these two cutoffs to determine a ruling-in rule for pneumonia was defined and evaluated for specificity, sensitivity and predictive values by the Fisher’s exact chi-square test.

Results

Overall, 72 ADHF patients and 50 pneumonia patients were included. The prevalence of ischemic heart disease (IHD), chronic renal failure (CRF), hypertension (HTN), diabetes mellitus (DM), atrial fibrillation and hyperlipidemia were significantly higher among ADHF patients compared with pneumonia patients, while the prevalence of dementia was significantly higher among pneumonia patients compared with ADHF patients (Table 1). Each of these features was evaluated in a univariate analysis for the presence of correlations to the continuous variables and as number of individuals plus the percentage in each group for categorical variables. Comparisons of variables were obtained using Fisher’s exact test, chi-square test, Student’s t-test, Wilcoxon rank sum test, Pearson’s test and Jonckheere–Terpstra test as appropriate. All the above analyses were considered significant at \( p < 0.05 \) (two tailed).

The most prominent complaints were dyspnea (79.2%) among ADHF patients and cough and fever (56%) among pneumonia patients (Table 2). No correlation was found between various symptoms and values of CRP or WBCC. Body temperature was significantly higher among pneumonia patients compared with ADHF patients (38.8 ± 0.8 vs. 36.9 ± 3.4).
and weakly inversely correlated with CRP levels on admission ($r = -0.285, p = 0.022$). The incidence of lung crackles, heart murmurs, atrial arrhythmia (fibrillation/flutter) and severe HTN were significantly higher among ADHF patients compared with pneumonia patients. On univariate analysis, ADHF patients presenting with atrial arrhythmia demonstrated significantly higher levels of CRP ($p = 0.002$).

Pneumonia patients presented to the hospital with significantly higher levels of CRP (127.2±84 vs. 13.5±13.5 mg/L, $p<0.001$) and WBCC (13100±5800 vs. 9250±5800/mL, $p<0.001$) compared with ADHF patients (Figs. 1 and 2). In pneumonia patients, there was an inverse correlation between CRP levels on admission and CRP velocity ($r = -0.689, p<0.001$), which was graphically portrayed by a trend of increase in serum CRP until a peak of 100–200 mg/L followed by a trend of decrease at higher CRP levels (Fig. 3). On the other hand, in ADHF patients, there was a moderate positive correlation between CRP levels on admission and CRP velocity ($r = 0.582, p = 0.001$). A similar analysis was implied with regard to WBCC and WBCC velocity (Fig. 4). We noted a trend of decreased WBCC counts in both pneumonia and ADHF patients. However, the latter trend was much steeper and inversely correlated to WBCC counts upon admission ($r = -0.756, p<0.001$).

Efficacy of CRP measurements in differentiating pneumonia from ADHF was evaluated by ROC diagrams and compared to clinical and radiological diagnosis. The analysis was performed in three steps: first, an ROC curve depicting CRP values upon the first 24 h of hospitalization was analyzed (Fig. 5), demonstrating efficacy of 0.918 (area under the curve) and a specificity of 1.0 for pneumonia patients with CRP values

### Table 1
Demographics and medical history of included patients.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>ADHF patients</th>
<th>Pneumonia patients</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) Mean±SD</td>
<td>76.8±10.4</td>
<td>68.4±20.2</td>
<td>Ns</td>
</tr>
<tr>
<td>Sex (male/female)/n/n (%)</td>
<td>39/33 (54.2%/45.8%)</td>
<td>27/23 (54%46%)</td>
<td>Ns</td>
</tr>
<tr>
<td>Prior medical conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD n (%)</td>
<td>47 (66.2%)</td>
<td>5 (10%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRF n (%)</td>
<td>30 (42.3%)</td>
<td>4 (8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HTN n (%)</td>
<td>49 (69%)</td>
<td>19 (38%)</td>
<td>0.001</td>
</tr>
<tr>
<td>DM n (%)</td>
<td>28 (38.9%)</td>
<td>6 (12%)</td>
<td>0.001</td>
</tr>
<tr>
<td>PAF/CAF n (%)</td>
<td>31 (43.7%)</td>
<td>11 (22%)</td>
<td>0.014</td>
</tr>
<tr>
<td>Hyperlipidemia n (%)</td>
<td>25 (34.7%)</td>
<td>8 (16%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Dementia n (%)</td>
<td>2 (2.8%)</td>
<td>6 (12%)</td>
<td>0.045</td>
</tr>
<tr>
<td>COPD/asthma n (%)</td>
<td>11 (15.5%)</td>
<td>3 (6%)</td>
<td>Ns</td>
</tr>
<tr>
<td>s/p CVA n (%)</td>
<td>9 (12.7%)</td>
<td>8 (16%)</td>
<td>Ns</td>
</tr>
</tbody>
</table>

IHD=ischemic heart disease; CRF=chronic renal failure; HTN=hypertension; DM=diabetes mellitus; PAF/CAF=paroxysmal and chronic atrial fibrillation; COPD=chronic obstructive pulmonary disease; CVA=cerebrovascular accident.

### Table 2
Symptoms, signs and chest X-ray findings of included patients.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>ADHF patients</th>
<th>Pneumonia patients</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>57 (79.2%)</td>
<td>13 (26%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cough</td>
<td>3 (4.2%)</td>
<td>28 (56%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chest pain</td>
<td>16 (22.5%)</td>
<td>5 (10%)</td>
<td>Ns</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>1 (1.4%)</td>
<td>2 (4%)</td>
<td>Ns</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (1.4%)</td>
<td>2 (4%)</td>
<td>Ns</td>
</tr>
<tr>
<td>Weakness</td>
<td>9 (12.7%)</td>
<td>7 (14%)</td>
<td>Ns</td>
</tr>
</tbody>
</table>

### Table 3
Hospitalization duration.

<table>
<thead>
<tr>
<th>Days</th>
<th>Mean±SD</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.9±2.8</td>
<td>6.7±5.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
above 57 mg/L. In light of our relatively small sized cohort, we then chose an even stricter cutoff value of 72.5 mg/L (sensitivity = 0.67, specificity = 1.0) for ruling-in pneumonia, and a second analysis was implemented with regard to only subjects with values under the cutoff. An ROC curve was constructed to compare CRP velocity to clinical and radiological diagnosis in this particular group (Fig. 6), demonstrating an efficacy of 0.967 (area under the curve). A second cutoff value of 0.56 mg/L/h (sensitivity = 0.88, specificity = 0.93) was chosen using the Youden index. The latter analysis included only 30 ADHF and 16 pneumonia patients. Based on these observations, we defined a ruling-in rule for pneumonia as CRP ≥ 72.5 mg/L or CRP velocity ≥ 0.56 mg/L/h, which demonstrated a sensitivity and positive predictive value of 0.96 and specificity and negative predictive value of 0.972 compared to standard clinical and radiological diagnosis (p < 0.001). A multivariate logistic regression did not demonstrate any correlations between background features, including age, and the group allocation by the diagnosis rule.

We evaluated WBCC counts and WBCC velocity in a similar manner but were unable to demonstrate significant diagnostic efficacy. Patients were divided into five ordinal groups based on the duration of their symptoms. We then used the Jonckheere–Terpstra test to check for correlations with CRP, WBCC and the velocity of change in these parameters. In both ADHF and pneumonia patients, as the duration between symptoms and admission prolonged, the levels of CRP increased and the CRP velocity decreased. In respects to WBCC counts, protracted duration was associated with lower counts upon admission and higher velocity. No such association was

![Fig. 3. The relation between CRP levels and CRP velocity.](image)

![Fig. 4. The association between white blood cell count and white blood cell count velocity.](image)

![Fig. 5. Efficacy of CRP in diagnosing pneumonia. ROC chart: evaluation of the efficacy of CRP in diagnosing pneumonia in the setting of ADHF compared to clinical and radiological criteria. 50 ADHF and 72 pneumonia patients. Area under the curve = 0.918.](image)

![Fig. 6. Efficacy of CRP velocity in diagnosing pneumonia. ROC chart: evaluation of the efficacy of CRP velocity in diagnosing pneumonia compared to clinical and radiological criteria, in a select group of patients with CRP values under a cutoff of 72.5 mg/L. 30 ADHF and 16 pneumonia pts. Area under the curve = 0.967.](image)
noted for pneumonia. Among ADHF patients, we found a positive correlation between WBCC counts on presentation and the CRP velocity ($r=0.506, p=0.005$).

**Discussion**

Heart failure (HF) is a cardiac disease interspersed with episodes of acute decompensations. Respiratory infections have long been recognized as precipitators of exacerbations and a concomitant pneumonia has been reported in 7–10% of ADHF patients [14–16]. Identifying patients, who present with an ADHF and signs of systemic inflammation, where there is a high likelihood of a concomitant pneumonia, poses a diagnostic clinical challenge. It is our impression that due to the difficulty of establishing a diagnosis based on clinical and radiological findings alone and due to the grave consequences of failing to diagnose a pneumonia or conversely over treating this unique population with antibiotics, which in turn is associated with adverse reactions, high cost and the emergence of bacterial resistance [17], another criteria must be used. In this study, we evaluated CRP as an aid for the diagnosis under these circumstances. CRP is a sensitive marker for pneumonia, and its measurement is nowadays considered common practice [3–6]. However, CRP elevation has also been noted in HF patients and in various other cardiac conditions [7], and it has been therefore imperative to specifically prove its efficacy in differentiating pneumonia from ADHF. We have reviewed data from 72 ADHF and 50 pneumonia patients with a definite clinical and radiological diagnosis. As expected, the ADHF group differed in co-morbidities, of which only hyperlipidemia and atrial arrhythmias were found to be associated with slightly higher levels of CRP. This observation is consistent with prior evidence linking inflammation and specifically elevated levels of CRP with atrial arrhythmias [18].

**CRP for the diagnosis of pneumonia versus ADHF**

We have found ADHF and pneumonia to differ substantially in the observed levels of plasma CRP ($13.5\pm13.5$ vs. $127.2\pm84$ mg/L, $p<0.001$). Employing an ROC diagram, we have demonstrated that using admission CRP as a diagnostic test for differentiating ADHF from pneumonia has an efficacy of 0.918 (area under the curve) compared with common practice clinical and radiological criteria. We then chose 72.5 mg/L as a cutoff value for ruling-in pneumonia. Of note, prior studies have suggested slightly higher cutoff value of 100 mg/L [6], which may be attributed to different study design and population. Though highly specific, our cutoff value was lacking in sensitivity (sensitivity =0.67, specificity =1.0) because of a considerable overlapping of measurements between the two conditions (pneumonia =0.35–317 mg/L vs. ADHF =0.2–54.6 mg/L). A possible explanation for this observation lies in understanding the kinetics of CRP in HF and in systemic inflammation brought on by infection. In the first condition, basal levels of CRP are chronically elevated [7] and are augmented only to a limited extent by episodes of acute exacerbation. In the latter, basal levels are low, then following an infectious stimulus CRP concentration will rapidly and steeply rise, reaching a steady state by 48 h and eventually decreasing once the stimulus has been removed [19]. This translates to an overlap between the early and late phases of pneumonia and the baseline concentration in HF. In accordance with these characteristics, we have noted, in pneumonia patients, CRP serum concentrations as low as 0.35 mg/L and a trend of increase until a peak of 100–200 mg/L followed by a trend of decrease at higher CRP levels. In ADHF patients, on the other hand, change in serum concentration was measured, and the highest noted level was of 54.6 mg/L. Based on these observations, we speculated that quantitatively following CRP velocity will help differentiate between overlapping cases. Monitoring trends of change in serum concentrations of various biomarkers is commonly used in clinical practice but is usually qualitative. Serial measurements of troponin and CK-MB in acute coronary syndrome provide information with regard to infarct size and ongoing myocardial ischemia [20]. Several studies have suggested serial qualitative assessment of CRP as mean for monitoring CHF progression and response to treatment [9,10]. However, to the best of our knowledge, no study has ever quantitatively evaluated the velocity of change in CRP in the setting of an acute HF. We therefore depicted a second ROC diagram comparing CRP velocity to clinical and radiological diagnosis only for subject with CRP concentration under the cutoff value. CRP velocity had an efficacy of 0.967 (area under the curve) for ruling-in pneumonia in this group, and a second cutoff value for CRP, velocity of 0.56 mg/L/h (sensitivity =0.88, specificity =0.93), was chosen using the Youden index. Integrating the two cutoffs, we defined a ruling-in rule for pneumonia in the setting of ADHF, of CRP ≥72.5 mg/L or of CRP velocity ≥0.56 mg/L/h, which demonstrated a sensitivity and positive predictive value of 0.96 and a specificity and negative predictive value of 0.972 compared to standard clinical and radiological diagnosis ($p<0.001$).

**WBCC for the diagnosis of pneumonia versus ADHF**

Understanding the dynamic traits of serum biomarkers and the importance of analyzing their temporal pattern rather than evaluating a single sample, we decided to examine, in a similar fashion, the WBCC count. An elevated WBCC count, probably the most veteran biomarker, has been described in various studies of HF. Cooper et al. [21] found it to be a strong and independent predictor of mortality, while Sheab et al. [22] demonstrated a parallel trend of increasing WBCC counts and CRP in patients who subsequently died. As expected, we found ADHF and pneumonia to differ substantially in observed WBCC counts (9250 ±5800 vs. 13100 ±5800/mL, $p<0.001$). However, a wide distribution of measurements in both groups precluded the use of WBCC as a tool for the diagnosis. Interestingly, when evaluating the velocity of change in WBCC, both groups demonstrated a trend of a decrease in counts in the first hours following admission. Furthermore, in ADHF patients, we found a strong inverse correlation between the WBCC count on admission and the velocity of change ($r=−0.765$, $p<0.001$) while in pneumonia there was no such association.
While leukocytosis in ADHF is mainly derived from the marginal pool as part of a systemic stress response in pneumonia [23], additional prominent systemic inflammation is a possible explanation for this phenomenon. Based on this assumption, we were hoping to demonstrate that WBCC velocity could help differentiate between the two conditions. Using ROC diagrams, we have evaluated WBCC counts and velocity in comparison to clinical and radiological criteria; we were unable to demonstrate any significant efficacy. It might be argued that due to a mutual process of stress leukocytosis, both conditions demonstrate a trend of steep increase and then decrease in leukocyte counts within the first hours of admission. Therefore, the proper period to evaluate WBCC velocity as a biomarker is only once the stress process has subsided.

Symptoms duration and biomarker levels

In accordance with the previously described kinetics of CRP and in both ADHF and pneumonia patients, we have noted a trend of higher concentrations and lower velocity as the duration from symptoms appearance. If in the future we could know the baseline CRP concentration of a patient, we could calculate their CRP velocity based on symptoms duration and CRP sampling on admission.

Study limitations

The main limitation of the present study is its retrospective nature. Inconsistencies in time intervals between CRP measurements limited the number of cases we could use to calculate velocity and prevented us from precisely depicting the temporal pattern of CRP. We therefore assumed a linear pattern though that is probably an over simplification. Apart from the technical limitations, the data gathering and analysis were performed by a sole unblinded researcher. Furthermore, the study design is susceptible to spectrum and test referral biases as the study population is composed of patients with a distinct diagnosis from a tertiary hospital. Have all ADHF patients been treated with antibiotics and therefore excluded from this study? Is the temporal CRP pattern of pneumonia patients in the community similar to that of those hospitalized patients? Notwithstanding the obvious sources of error, we strongly believe the strong statistical significance of our results allows for cautious optimism in regarding CRP and CRP velocity as potential biomarkers for diagnosing pneumonia in the setting of ADHF.

Conclusions

According to our findings, CRP measurements should be used repeatedly since the first day of hospitalization for differentiating pneumonia patients from ADHF patients. Current recommendations promote initiation of antibiotics within 4 h following hospital admission of pneumonia patients [24]. Hence, first CRP measurement should take place within these 4 h in order to avoid unnecessary antibiotic administration to ADHF patients. However, a significant proportion of pneumonia patients do not get their antibiotics within 4 h following hospital admission, especially in cases of diagnostic uncertainty [25]. Hence, first CRP measurement can take place even more than 4 h following hospital admission, as we showed in this study. Due to its limitations, this study must be considered hypothesis generating only; however, we postulate that it will be possible to differentiate pneumonia from other respiratory conditions in which the inflammatory component is less pivotal.

References


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