Predictive value of high sensitivity CRP in patients with diastolic heart failure

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Abstract

Background: C-reactive protein (CRP) has been tested in patients with systolic heart failure (HF) and mixed results have been obtained with regards to its potential predictive value. However, the role of C-reactive protein (CRP) in patients with diastolic HF is not established. We studied the predictive role of high sensitivity CRP (hsCRP) in patients with diastolic HF.

Methods: HsCRP levels were measured in a cohort of CHF outpatients, 77 patients with diastolic HF and 217 patients with systolic HF. Concentrations were compared to a large cohort of healthy population (\(n=7701\)) and associated with the HF admissions and mortality of the patients.

Results: Levels of hsCRP did not differ between patients with systolic and diastolic HF and were significantly elevated compared to the cohort of healthy subjects even after adjustment to various clinical parameters \((p<0.0001)\). In patients with diastolic HF, hsCRP levels associated with New York Heart Association functional class (NYHA-FC) \((r=0.31\ p=0.01)\). On univariate Cox regression model hsCRP levels independently predicted hospitalizations in patients with systolic but not diastolic HF \((p=0.047)\).

Conclusion: HsCRP concentrations are elevated in patients with diastolic HF and correlate with disease severity; their prognostic value in this patient population should be further investigated.

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1. Introduction

Congestive heart failure (CHF) is a common disorder with substantial morbidity and mortality. Despite improved understanding of the underlying pathogenetic mechanisms, the syndrome carries a significant morbidity and mortality burden and is the leading cause of hospitalization among individuals older than 65 years [1–3]. Many CHF patients have preserved systolic function with an ejection fraction greater than 45%. When a valvular cause of symptoms is excluded and echocardiographic study demonstrates impaired diastolic function these patients are diagnosed as having isolated diastolic heart failure (HF) [4–8].

Patients with diastolic HF constitute 40–60% of CHF patient populations. They have different characteristics from patients with systolic HF and their clinical course may not be identical [4–8].

Patients with CHF manifest many aspects of chronic inflammatory disease, including activation of inflammatory markers like IL-6, TNF-alpha and CRP [9–12]. These proinflammatory cytokines probably contribute to the clinical aspects of heart failure including cardiac cachexia and hemodynamic and vascular instability.

CRP has been correlated with the severity, prognosis and response of CHF patients to treatment [9–12]. However, these studies were conducted in patients with predominantly systolic heart failure. As diastolic HF may constitute a group with discrete characteristics, their cytokine profile may differ from that of systolic HF. Our purpose was to study CRP
concentrations among patients with diastolic HF and to define its relevance to clinical outcome.

2. Methods

2.1. Patients

The study included a cohort of clinically controlled CHF patients with New York Heart Association (NYHA) functional class II–IV attending the outpatient clinic of the Tel Aviv Sourasky Medical Center. This is a referral clinic in which all patients have symptomatic severe controlled HF and are under a close follow up. A cutoff of an ejection fraction above 45% was used to classify patients into the diastolic HF group. We used the term diastolic HF instead of HF with preserved systolic function as it describes the dominant underlying pathophysiological mechanism [13]. Patients with valvular heart disease, disease duration of less than 6 months or acute decompensated HF within the last 3 months prior to enrollment were excluded. At baseline, patients answered a thorough questioner on past medical history, performance status, atherosclerotic risk factors and medications. Coronary artery disease (CAD) was diagnosed based on history of myocardial infarction or evidence of diseased vessels in coronary angiography. Thereafter, patients were examined and baseline serum was drawn and kept frozen at −80 °C until performance of the lab assays.

The assay for high Sensitivity CRP (hsCRP) was conducted according to manufacturer’s instructions (Dade Behring Inc.). Shortly, the principle of the method includes, using polystyrene particles coated with monoclonal antibodies to CRP. These particles agglutinate with CRP. HsCRP level was determined according to the intensity of the scattered light in the nephelometer, compared with standards of a known concentration. Mean value of hsCRP in healthy population is 1.6±3.4 mg/L for women and 1±2.7 mg/L for men [14].

Measurements of serum NT-pro-BNP were performed by automated immuno-assay (Elecsys proBNP, Roche Diagnostics, Germany). The test principle includes using two polyclonal antibodies directed against NT-pro-BNP; epitope 1: amino acid 1–21 and epitope 2: amino acid 39–50. The results are calibrated against a synthetic NT-pro-BNP (amino acid 1–76). The range of results is between 5–35,000 pg/ml and is normally less than 250 pg/ml for patients’ aged 60 years and older [15].

2.2. Follow-up

Patients were followed every 3–6 months or more frequently as required. The study end points were hospitalizations due to heart failure and all-cause mortality.

2.3. Control healthy population

The control group consisted of patients from the Tel Aviv Medical Center Inflammation Survey (TAMCIS) [16]. TAMCIS is a survey of apparently healthy individuals that is currently taking place at our medical center and includes a relatively large cohort of individuals attending the Tel Aviv Sourasky Medical Center for a routine health examination. Patients’ medical information including atherosclerotic risk factors, baseline physical examination findings, medications and results of laboratory assays are included in the database. All the individuals included in the present survey gave their written consent according to the instructions of the Institutional Ethics Committee.

Patients with a history of heart failure, underlying inflammatory disease or condition were excluded.

3. Statistical analysis

Comparison between systolic HF patients and patients with isolated diastolic HF was performed using Student’s t-test for continuous variables and Chi-square test for categorical variables.

Pearson correlation coefficient was calculated to evaluate the association between various continuous parameters (hsCRP, NT-pro-BNP, and serum creatinine) and the Spearman rank correlation coefficient was calculated to evaluate the association between these parameters and NYHA score.

A multivariate linear regression model was constructed to study the difference in hsCRP levels between the 2 CHF patient groups and an apparently healthy population group after adjustment to the following possible confounder parameters: age, gender, atherosclerotic risk factors and presence of CAD.

Since the distribution of hsCRP does not resemble a normal distribution, it was log-transformed prior to analysis.

An alternative regression model included patients’ age, gender, NYHA-FC, smoking habits and presence of CAD, diabetes mellitus, hyperlipidemia, hypertension, chronic renal failure and permanent atrial fibrillation.

Cox proportional hazard model was applied to the data to study the association of hsCRP levels with risk of mortality and hospitalization due to heart failure exacerbation. Univariate models for hsCRP alone were followed by multivariate models. All statistical analysis was performed using SAS for Windows, version 9.1.

4. Results

In order to avoid selection bias, we included all eligible patients attending our outpatient clinic. Thus, the study cohort included 217 patients with systolic HF and 77 patients with isolated diastolic HF with an ejection fraction >45%. Baseline clinical characteristics of our cohort and comparison of patients with diastolic and systolic HF is presented in Table 1. Disease duration prior to enrollment in patients with diastolic HF was 3.38±4.3 years. Patients with diastolic HF were more likely to be women and suffer from hypertension and less likely to have CAD. Log
transformed hsCRP levels did not differ between patients with systolic or diastolic HF ($p=0.43$) and were significantly elevated compared to a large cohort of healthy subjects (Fig. 1, $p<0.0001$). Levels of hsCRP in both HF groups remained significantly elevated even after adjustment to age, gender, atherosclerotic risk factors and presence of CAD ($p<0.0001$).

HsCRP levels in all HF patients and in patients with systolic HF correlated with NYHA FC ($r=0.3, p<0.0001$, $r=0.31, p<0.0001$, respectively), serum creatinine ($r=0.24$, $p=0.0001$, $r=0.3, p<0.0001$, respectively) and NT-pro-BNP levels ($r=0.19, p=0.003$, $r=0.244, p=0.001$, respectively). However, when examined in diastolic HF patient subgroup hsCRP levels correlated only with NYHA FC ($r=0.31, p=0.01$). There was no correlation in either patient subgroup between hsCRP levels and age, weight or hemoglobin concentrations.

In order to define the determinants of hsCRP in patients with diastolic HF we performed a multivariate linear regression model. The model included different clinical parameters including patients’ age, gender, NYHA FC, smoking status and presence of CAD, diabetes mellitus (DM), hyperlipidemia, hypertension, chronic renal failure and permanent atrial fibrillation. Only NYHA and DM significantly predicted log-transformed CRP levels ($p=0.02$, $p<0.05$ respectively).

For exploring the clinical significance of hsCRP levels, patients were followed for the occurrence of CHF related hospitalizations or death. During follow-up of 34.1±11.2 months there were 90 hospitalizations, 71 (32.7%) in patients with systolic HF and 19 (24.6%) in patients with diastolic HF, and 95 deaths, 72 (33.1%) in patients with systolic HF and 23 (29.8%) in diastolic HF. The percentage of events was not significantly different between these two CHF patient subgroups (for hospitalizations $p=0.14$ and for mortality $p=0.59$). Results of hsCRP as predictor of these events on univariate and multivariate Cox regression model are presented in Table 2. As it shows, in our cohort the main predictive value of hsCRP seems to be in patients with systolic HF.

| Variable in the model include: age, gender, weight, NYHA FC, smoking status and presence of CAD, DM, hyperlipidemia, hypertension, chronic renal failure and permanent atrial fibrillation. Only NYHA and DM significantly predicted log-transformed CRP levels ($p=0.02$, $p<0.05$ respectively). |

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**Table 1**

<table>
<thead>
<tr>
<th>Clinical data of the 2 different groups of patients</th>
<th>Systolic HF ($n=217$)</th>
<th>Diastolic HF ($n=77$)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD), years</td>
<td>72.4±10.8</td>
<td>71±11.2</td>
<td>0.34</td>
</tr>
<tr>
<td>Males (%)</td>
<td>176 (81.1)</td>
<td>47 (61)</td>
<td>0.0004</td>
</tr>
<tr>
<td>NYHA (mean±SD)</td>
<td>2.7±0.58</td>
<td>2.69±0.66</td>
<td>0.43</td>
</tr>
<tr>
<td>Permanent atrial fibrillation, n (%)</td>
<td>45 (20.7)</td>
<td>21 (27.2)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

| Past history | CAD, n (%) | 181 (83.4) | 39 (50.6) | <0.0001 |
| Previous PTCA/CABG, n (%) | 115 (52.9) | 30 (38.9) | 0.04 |
| Previous TIA/CVA, n (%) | 28 (12.9) | 11 (14.2) | 0.72 |

| Risk factors | Hypertension, n (%) | 124 (57.1) | 54 (70.1) | 0.03 |
| Diabetes, n (%) | 83 (38.2) | 31 (40.2) | 0.69 |
| Smoking n (%) | 66 (30.4) | 20 (25.9) | 0.49 |
| Hyperlipidemia, n (%) | 139 (64) | 42 (54.5) | 0.17 |
| Chronic renal failure* | 104 (47.9) | 38 (49.3) | 0.81 |

| Medications | Beta-blockers, n (%) | 140 (64.5) | 58 (75.3) | 0.08 |
| ACEI/ARB n (%) | 174 (80.1) | 57 (74) | 0.19 |
| Aspirin, n (%) | 154 (70.9) | 41 (53.2) | 0.004 |
| Statins, n (%) | 137 (63.1) | 46 (59.7) | 0.59 |
| Diuretics, n (%) | 195 (89.8) | 64 (83.1) | 0.11 |

| Biochemistry | hsCRP mg/L | 7.8±11.6 | 9.5±16.3 | 0.43 |
| NT-pro-BNP pg/ml | 4195±6119 | 2688±2920 | 0.01 |

Data are in number (range) or mean±SD.

NYHA-FC = New York heart functional class; CAD = coronary artery disease; CAGB = coronary artery bypass graft; PTCA = percutaneous transluminal coronary angioplasty; CVA = cerebrovascular accident; TIA = transient ischemic attack; ACEI = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blocker; hsCRP = High Sensitivity C-reactive protein; NT-pro-BNP = N terminal pro-B type natriuretic peptide.

* Defined as baseline serum creatinine above 1.5 mg/dl.
5. Discussion

We found that levels of hsCRP are increased in patients with diastolic HF compared to a large cohort of healthy population, and are comparable to those of patients with systolic HF. In patients with diastolic HF, levels of hsCRP correlated with NYHA FC and on a multivariate linear regression model we found that the main predictors of hsCRP levels are NYHA FC and the presence of DM.

In our cohort prognosis in terms of CHF related hospitalizations and mortality was not statistically different between subgroups of HF patients. The predictive value of hsCRP was limited to HF related hospitalizations and was limited only to patients with systolic HF. Whether this is related to the smaller cohort of patients with diastolic HF, or reflects inferiority of the predictive value of CRP in the latter population needs further investigation.

The prevalence of diastolic HF has increased over the last years [4–8]. This may be attributed to population aging and increased incidence of diabetes. Two recently published large-scale population based studies [5,6] demonstrated a similar prognosis for patients with systolic and diastolic HF further emphasizing the clinical significance of this entity. Nevertheless, diastolic HF is far less studied in terms of its pathogenesis, prognosis and treatment. Several studies demonstrated activation of the neurohormonal axis as reflected by elevated BNP levels in patients with diastolic HF [17,18], however information regarding the inflammatory axis was not reported.

HsCRP, a marker of inflammatory activation is strongly related to atherosclerotic coronary disease [19]. Pathogenetically systolic HF is more closely related to CAD as the main contributor leading to LV systolic dysfunction is an ischemic occlusive event with myocardial necrosis. Additionally, the prevalence of CAD in several studies was higher in patients with systolic compared to diastolic HF [7,8]. However, cardiac ischemia also predisposes to diastolic dysfunction, and results of CRP levels in patients from the Valsartan Heart Failure Trial (Val-HeFT) showed that in patients with systolic HF, levels of CRP were not related to the occurrence of CAD but to the severity of the disease [9]. In our cohort, despite the lower prevalence of CAD in patients with diastolic compared to systolic HF, levels of hsCRP did not differ between these 2 patients groups and correlated with NYHA FC. Thus it appears that that the severity of HF and not its etiological determinant is the principal factor influencing CRP levels.

A recently published study [20] conducted among patients referred for cardiac catheterization, of which one third had clinically diagnosed HF, demonstrated that principal determinant of CRP levels is left ventricular end diastolic pressure which is increased both in systolic and diastolic HF, thus further validating our results.

The mechanism of CRP elevation among patients with HF is not completely defined. Possible theories include organ congestion and hypoperfusion which influences secretion of IL-6 by hepatic, renal, endothelial, mononuclear and even cardiac myocytic cells [9,21–23]. IL-6 in turn promotes CRP production by the liver. Alternatively, elevated CRP levels may reflect an antedating inflammatory state that promoted diastolic HF development. Indeed, it was shown that elevated inflammatory markers were associated with increased risk of developing CHF [24].

CRP may also be an active participant in diastolic HF development and clinical deterioration. CRP may inhibit nitric oxide production [25], impede endothelial function [26] and activate the complement cascade [27]. IL-6 which affects CRP secretion was shown to promote myocyte hypertrophy [28]. The fact that the inflammatory axis is activated among patients with diastolic HF may have therapeutic implications. Fukuta et al. demonstrated the beneficial survival benefit of statins therapy among patients with diastolic HF [29]. This effect was independent of their lipid lowering properties. Thus it is possible the anti-inflammatory properties of statins are the beneficial components in diastolic HF patients. This assumption however, should be further investigated.

It should be emphasized that we tested a cohort of chronic diastolic HF patients treated in an expert referral outpatient clinic. Whether these results are also true for patients treated in the community needs further testing. Nevertheless it seems that like systolic HF, diastolic HF represents a chronic inflammatory condition with elevated inflammatory cytokines.

In conclusion patients with diastolic HF have elevated hsCRP levels that are related to disease severity. Whether hsCRP levels have prognostic implications among these patients needs further investigation.

References


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