ORIGINAL ARTICLE

The role of high-sensitivity C-reactive protein for assessing coronary artery disease severity and left ventricular end diastolic pressure in patients with suspected coronary artery disease

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Objective Much attention has recently been focused on the underlying role of circulating inflammatory biomarkers such as high-sensitivity C-reactive protein for predicting cardiovascular disease progression. We therefore set out to assess the relationship between the value of high-sensitivity C-reactive protein and (i) coronary artery disease severity, and (ii) left ventricular end diastolic pressure.

Design A cross-sectional study.

Setting The Shafa hospital in Kerman, Iran.

Patients A total of 107 consecutive patients referred for coronary angiography from January 2008 to January 2009 were prospectively studied.

Intervention and main outcome measures All patients underwent coronary angiography. They all had undergone left ventricular end diastolic pressure measurement, involving a 6-Fr pigtail catheter and a properly zeroed fluid-filled pressure transducer. For each patient, the level of high-sensitivity C-reactive protein was also determined using enzyme-linked immunosorbent assay kits.

Results The high-sensitivity C-reactive protein levels could strongly predict increased left ventricular end diastolic pressure (standardised beta=1.010; P=0.008), with other patient variables being confounders, but there was no significant association between these levels and Gensini scores. Multiple linear regression analysis showed that among the study parameters, systolic hypertension (standardised beta=1.611; P=0.047) and a family history of coronary artery disease (standardised beta=1.911; P=0.005) were the main predictors of high Gensini scores in study patients.

Conclusion High-sensitivity C-reactive protein level is a clinical parameter that could predict left ventricular end diastolic pressure and left ventricular dysfunction, but was not associated with the severity of coronary artery disease.

Key words
Coronary artery disease; C-reactive protein; Heart ventricles

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New knowledge added by this study

- The current study could demonstrate the role of assessing high-sensitivity C-reactive protein for predicting left ventricular end diastolic pressure and left ventricular dysfunction in coronary artery disease patients.

Implications for clinical practice or policy

- Because of confirmed potential role of inflammatory processes in ischaemic heart disease, high-sensitivity C-reactive protein can be applied diagnostically as a main indicator for assessment of inflammatory sources in coronary artery disease patients.

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Introduction

Recently, attention has been focused on the role of the circulating inflammatory biomarkers such as C-reactive protein (CRP) for predicting cardiovascular disease progression.[1] A wide variety of clinical investigations in healthy as well as high-risk individuals have shown a relationship between this biomarker and the risk of coronary artery disease (CAD) and its

related life-threatening events.[2-6] Some investigators hypothesised that irrespective of the extent and severity of CAD, serum CRP level is an index of atheromatous plaque activity and vulnerability.[7] In addition, a high normal CRP level might be a reliable marker of cardiovascular risk even if its level is within the physiological range.[8,9] Some researchers have therefore used this parameter to screen patients at risk of developing clinically symptomatic CAD, though some authorities considered this approach to be premature.[10] Besides, as shown by the increment in CRP values, the immune system is frequently activated in patients with the chronic left ventricular dysfunction.[11] However, results from a study of American patients with ischaemic heart disease and left ventricular systolic dysfunction undergoing coronary angiography suggested that those with an elevated high-sensitivity CRP (hs-CRP) had a worse prognosis.[12] A study of the Japanese patients with dilated cardiomyopathy also yielded similar findings.[13]

To date, few studies have examined the relationship between systemic markers of inflammation such as hs-CRP and regional left ventricular dysfunction and its parameters. We therefore set out to assess the value of measuring hs-CRP to determine whether the prevailing level was related to CAD severity and the left ventricular end diastolic pressure (LVEDP).

高敏C反應蛋白在評估懷疑冠心病患者中其冠心病嚴重程度和左室舒張末壓的角色

目的 炎症生物標記物，例如高敏C反應蛋白，對預測心血管病進度的基本作用倍受關注。因此，本文評估高敏C反應蛋白和以下兩者的關係：（1）冠狀動脈病嚴重程度和（2）左室舒張末壓。

設計 橫斷面研究。

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患者 納入2008年1月到2009年1月期間，所有107名轉介至冠狀血管學的患者進行前瞻性研究。

干預及主要結果測量 所有患者接受冠狀動脈造影檢查，並以6-Fr豬尾型導管和已調整的充液壓力傳感器量度他們的左室舒張末壓。研究並使用ELIZA工具檢視每名患者的高敏C反應蛋白水平。

結果 當其他患者變數是共同物時，高敏C反應蛋白水平能強烈預測左室舒張末壓上升（標準化beta值=1.010；P=0.008），但這些數值水平與冠脈評分間沒有顯著相關。多線性回歸分析顯示在多個研究參量中，收縮期高血壓（標準化beta值=1.611；P=0.047）和冠狀動脈病家族史（標準化beta值=1.911；P=0.005）是患者高冠脈評分的主要預測因子。

結論 高敏C反應蛋白水平是可預測左室舒張末壓和左心室功能異常的臨床參量，但其與冠心病嚴重程度並無顯著相關。

Methods

We measured the plasma hs-CRP levels in 107 consecutive patients (mean ± standard deviation [SD] age: 55 ± 8 years, range: 40-85 years); of these, 78 were males. They all underwent elective coronary angiography for suspected CAD at the Shafa hospital in Kerman, Iran from January 2008 to January 2009. This is a referral hospital for Kerman Province, Iran. The results were compared with the coronary angiography findings. None of these patients had experienced myocardial infarction (MI) within the last 6 months, or unstable angina with anginal pain at rest within 1 month, nor had they undergone a percutaneous coronary intervention or coronary artery bypass within 12 months before assessment. None of the patients had congestive heart failure, life-threatening arrhythmias, renal or liver diseases, or malignancies, nor had they endured any infectious or inflammatory disorders within the last 2 weeks. At the time of diagnostic angiography, clinical data were collected on all the patients, including age, gender, and coronary risk factors. Relevant risk factors were current smoking history (ie regularly smoked once or more daily or smoked in the 30 days prior to admission),[14] presence of hypercholesterolaemia (total cholesterol of ≥5.0 mmol/L, high-density lipoprotein–cholesterol of ≤1.0 mmol/L in male / ≤1.1 mmol/L in female, and triglycerides of ≥2.0 mmol/L),[15] a family history of CAD (first-degree relatives; men aged <55 years and women <65 years),[16] hypertension (systolic blood pressure of ≥140 mm Hg and/or diastolic pressure of ≥90 mm Hg and/or on antihypertensive treatment),[17] and diabetes mellitus (symptoms of diabetes plus at least one of the following: plasma glucose concentration of ≥11.1 mmol/L, fasting plasma glucose of ≥7.0 mmol/L, and 2-hour postprandial plasma glucose ≥11.1 mmol/L).[18]

The entire study protocol was approved by the ethics committee of the Kerman University of Medical Sciences, and written informed consent was obtained from the patients. Blood samples were taken from the patients for laboratory testing within 24 hours of hospital admission. Blood obtained from the coronary sinus was collected in EDTA bottles for CRP measurement. The samples were centrifuged (3000 revolutions/min at 4°C for 15 minutes) and the plasma separated. The hs-CRP level was determined using a commercial enzyme-linked immunosorbent assay kits (Monobind, US).

All coronary angiography procedures were performed via the femoral approach using the standard Judikin's technique, and the images were

analysed separately by two independent investigators. For each patient, the mean reported Gensini score from the two blinded cardiologists were used. Images of the coronary tree were obtained in routine standardised projections with the digital Integris H3000 System (Siemens, Germany). Any significant lesions (>50% stenosis) in the left main coronary artery (LM), left anterior descending coronary artery (LAD), left circumflex coronary artery (LCX), and right coronary artery (RCA) were recorded, in which case patients were classified as having 1-vessel, 2-vessel, or 3-vessel disease. The Gensini scoring system was utilised in the evaluation of coronary lesion severity. The Gensini score for each patient was inferred from the coronary arteriogram by assigning a severity score to each coronary stenosis according to the degree of luminal narrowing and its geographical importance. Reduction in the lumen diameter, and the roentgenographic appearance of concentric lesions and eccentric plaques were evaluated; reductions of 25%, 50%, 75%, 90%, 99%, and complete occlusion were given scores of 1, 2, 4, 8, 16, and 32, respectively. Each principal vascular segment was assigned a multiplier in accordance with the functional significance of the myocardial area supplied by that segment: LM×5; the proximal segment of LAD×2.5; the proximal segment of LCX×2.5; the mid-segment of the LAD×1.5; the RCA, the distal segment of the LAD, the posterolateral artery and the obtuse marginal artery×1; and others×0.5.[19] All patients underwent recording of their LVEDP using a 6-Fr pigtail catheter and a properly zeroed fluid-filled pressure transducer. The pressure was recorded using a 50 mm Hg scale at 50 mm/s paper speed. A blinded physician measured the post–A wave LVEDP based on a minimum of five consecutive cardiac cycles.

Results were reported as mean±SD for quantitative variables and percentages for the categorical variables. Continuous variables (Gensini score and LVEDP) in different risk subgroups were compared using the Student's *t* test or the Mann-Whitney *U* test. Multiple linear regression analysis was used to investigate the association between hs-CRP and these two variables in the presence of baseline data as confounders. Standardised beta was calculated. Any P value of <0.05 was considered statistically significant. All the statistical analyses were performed using the SPSS version 13.0 (SPSS Inc., Chicago [IL], US) and SAS version 9.1 for Windows (SAS Institute Inc., Cary [NC], US).

Results

The baseline characteristics of the study subjects are summarised in Table 1. The most frequent risk factor for CAD was hypercholesterolaemia (48%) followed by opium addiction (44%) and systolic hypertension (37%). The mean LVEDP in different

TABLE 1. Baseline demographic and clinical data of study patients (n=107)

Characteristic*	Data†
Male gender	78 (73)
Age (years)	55 ± 8
Diabetes mellitus	23 (21)
Systolic hypertension	40 (37)
Diastolic hypertension	12 (11)
Hypercholesterolaemia	51 (48)
Hypertriglyceridaemia	41 (38)
Total cholesterol to HDL ratio of >4	48 (45)
Family history of coronary disease	31 (29)
Current smoking	31 (29)
Opium addiction	47 (44)
Gensini score	42.4 ± 36.2
High-sensitivity C-reactive protein	16.1 ± 7.1
LV end diastolic pressure (mm Hg)	8.6 ± 13.5

* HDL denotes high-density lipoprotein, and LV left ventricular
† Data are shown as mean ± standard deviation or No. (%) of patients

TABLE 2. Left ventricular end diastolic pressure (LVEDP) measurement and Gensini score in different risk factors subgroups*

Item	LVEDP	Gensini score
Male	16.2 ± 2.2	43.3 ± 1.3
Female	16.5 ± 1.8	45.2 ± 0.9
P value	0.493	<0.001
With diabetes	16.2 ± 1.5	45.4 ± 1.2
Without diabetes	16.4 ± 1.3	42.2 ± 1.2
P value	0.578	<0.001
With systolic hypertension	16.5 ± 1.1	47.2 ± 1.5
Without systolic hypertension	16.2 ± 1.2	40.4 ± 1.1
P value	0.147	<0.001
With hyperlipidaemia	15.8 ± 1.1	49.7 ± 1.6
Without hyperlipidaemia	16.7 ± 1.2	38.8 ± 1.1
P value	<0.001	<0.001
With a family history of CAD†	17.8 ± 2.0	51.6 ± 1.8
Without a family history of CAD	15.5 ± 1.8	17.8 ± 0.3
P value	<0.001	<0.001
With cigarette smoking	16.9 ± 1.2	45.9 ± 1.2
Without cigarette smoking	16.0 ± 1.1	44.1 ± 1.2
P value	<0.001	<0.001
With opium use	16.9 ± 1.2	51.2 ± 2.3
Without opium use	15.6 ± 1.3	39.0 ± 1.1
P value	<0.001	<0.001

* Data are presented as mean ± standard deviation; data were analysed by *t* tests
† CAD denotes coronary artery disease

risk subgroups (Table 2) was similar in patients with and without many of the study risk factors/profiles (gender, diabetes mellitus, and hypertension), while it was significantly higher in those without hyperlipidaemia, with a family history of CAD, history of smoking, or opium use than in those without. With respect to the differences in Gensini scores in different risk subgroups, subjects with at least one of these risk factors had higher scores. As shown in Table 3, hs-CRP measurement could strongly predict increased LVEDP (standardised beta=1.010; P=0.008) in the presence of other variables as confounders. Multiple linear regression analysis also showed that among study parameters, systolic hypertension (standardised beta=1.611; P=0.047) and a family history of CAD (standardised beta=1.911; P= 0.005) were main predictors of high Gensini score (Table 4). However, hs-CRP level had no significant association with Gensini score.

Discussion

Despite confirmed relationship between the levels of circulating inflammatory biomarkers and coronary atherosclerosis and its related life-threatening events in some previous studies,[20-25] we could not demonstrate this association. In current study, hs-CRP concentrations were similar in patients with suspected CAD and did not correlate with the index of Gensini in these patients. Thus, serum CRP might not be a main predictor of disease activity; such findings are similar to others. For example, Veselka et al[26] reported that the CRP level was not related to the extent of coronary atherosclerosis assessed by coronary angiography, a history of MI or stable angina, in patients referred for coronary angiography or abnormal exercise test results. Another study[27] also did not show a correlation between CRP and the extent of CAD. However, their study defined coronary atherosclerosis by a scoring system incorporating nine coronary artery segments. Interestingly, Hunt et al[28] confirmed by electron-beam computed tomography that of those generally known risk factors of atherosclerosis, only low-density lipoprotein–cholesterol, and not CRP, was related to the extent of coronary calcifications. It therefore seems that the purported relationship between inflammatory biomarkers and the appearance or progression of coronary atherosclerosis might be spurious, possibly due to small-sample-size studies, methodology, or technical details for measuring these markers, and lack of control subjects without CAD. Thus, this association should be re-evaluated in further prospective cohort studies with larger sample sizes, and preferably in CAD patients and suitable controls.

Other studies noted that CRP levels were higher in patients with left ventricular dysfunction than that in the healthy population, and our study also found that hs-CRP was strongly predictive of increased LVEDP. Other multivariate analyses have also explored the presence of underlying risk profiles and elevated CRP levels.[29,30]

After adjustment for potential confounders, we demonstrated an independent association between hs-CRP and elevated left ventricular filling pressures as opposed to systolic or diastolic dysfunction. This finding indicates that CRP elevation is closely related to the overall syndrome of left ventricular dysfunction and volume overload. Similarly, Huang et al[31] reported a modest statistically significant correlation coefficient of 0.26 between LVEDP and CRP; however, this was only associated with those with heart failure. Thus, it seems probable that elevations in CRP lead to increases in left ventricular filling pressures that progress to acute heart failure, or vice versa. In this context, assessment of changes in all left ventricular parameters following progression of inflammatory processing (in both animal and

TABLE 3. Linear regression model indicating relationship between the left ventricular end diastolic pressure and other study parameters*

Variable†	Beta	P value	Standardised beta	P value
hs-CRP	1.008	0.009	1.010	0.008
Male gender	1.020	0.848	1.090	0.509
Age	1.112	0.222	1.150	0.257
Diabetes mellitus	1.002	0.989	1.117	0.380
Systolic hypertension	1.284	0.787	1.002	0.987
Hyperlipidaemia	1.033	0.666	1.014	0.899
Family history of CAD	1.071	0.444	1.078	0.471
Current smoking	1.051	0.611	1.132	0.287
Opium addiction	1.084	0.356	1.198	0.111

* $R^2 = 0.761$

† hs-CRP denotes high-sensitivity C-reactive protein, and CAD coronary artery disease

TABLE 4. Linear regression model indicating relationship between Gensini score and other study parameters*

Variable†	Beta	P value	Standardised beta	P value
hs-CRP	1.001	0.974	1.006	0.477
Male gender	1.132	0.555	1.400	0.225
Age	1.006	0.602	1.001	0.922
Diabetes mellitus	1.087	0.724	1.044	0.866
Systolic hypertension	1.444	0.050	1.611	0.047
Hyperlipidaemia	1.299	0.192	1.445	0.091
Family history of CAD	1.824	0.005	1.911	0.005
Current smoking	1.118	0.601	1.034	0.888
Opium addiction	1.325	0.154	1.398	0.151

* $R^2 = 0.658$

† hs-CRP denotes high-sensitivity C-reactive protein, and CAD coronary artery disease

humans) is recommended.

Limitations of this study included its cross-sectional design and small sample size, which could potentially affect extrapolation of the data to predict future angiographic parameters and CAD severity. Moreover, other putative factors that could affect the predictive power of hs-CRP (eg nutritional status and physical activity) were not included in the regression analyses.

Conclusion

Our study attempted to explore the relationship of hs-CRP level with the CVD progression and left ventricular function. We could only demonstrate its role for predicting increased LVEDP and left ventricular dysfunction.

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