Original Article

A Study of Association between High Sensitivity C-reactive Protein and Diastolic Dysfunction in Patients with Cardiac Risk Factors

Swapan Sarkar[1], Joydeep Biswas[2]

Background : Diastolic dysfunction (DD) is considered to be associated with inflammatory fibrosis of myocardium. So, this cross-sectional, observational study was done to test the hypothesis that hsCRP, an inflammatory biomarker is associated with diastolic dysfunction and is a predictor of incipient diastolic heart failure in patients with cardiac risk factors.

Methods : 84 patients were selected. hsCRP level was measured and echocardiogram was done to assess ratio of transmitral flow velocity and annular velocity (E/E') and left ventricular end-diastolic pressure (LVEDP). Correlation coefficient was calculated to quantify strength of association between hsCRP and numerical variables. Linear regression was performed to evaluate the association between hsCRP and numerical variables.

Results : The mean age was 59±7years. 40(48%) were men and 44(52%) were female. 27(32.14%) had mild DD(DD1) with normal LVEDP and 29(34.52%) had DD with elevated LVEDP(DD2). E/E´, a parameter of LV diastolic function showed the strongest positive correlation to hsCRP (r=0.653, p<0.001). Linear regression showed that only E/E'(b-coefficient=0.845, p<0.001) was significantly associated with hsCRP.

Conclusion : The data shows that hsCRP is significantly increased in patients with diastolic dysfunction and establishes a close association between hsCRP levels and diastolic dysfunction in patients with diabetes and hypertension.

[*J Indian Med Assoc* 2020; **118(3):** 31-5]

Key words **: Diastolic dysfunction, high-sensitivity C-reactive protein, cardiac risk factors.**

The underlying pathophysiological mechanism in more than half of patients of heart failure (HF) is diastolic dysfunction(DD)[1,2]. Diastolic dysfunction is considered to be associated with inflammatory fibrosis and stiffening of myocardium caused by increased collagen deposition in interstitium[1,3]. Studies have shown that low grade systemic inflammation is associated with arterial and ventricular stiffness, which again is associated with diastolic heart failure[4-6]. So, pro-inflammatory conditions like hypertension (HTN) and diabetes (DM) may predispose to myocardial stiffness and diastolic dysfunction, which ultimately leads to heart failure[7,8].

On the other hand, high-sensitivity C-reactive protein (hsCRP), produced by liver in response to inflammatory conditions has been also shown to predict cardio-vascular events[9,10]. So, hsCRP has been used recently as a therapeutic target for preventing heart disease[11].

Although some data is available about the relationships between hsCRP and echocardiographic parameters[12], but there is few data between hsCRP and left ventricular (LV) diastolic function. Studies have shown an association between hsCRP and diastolic dysfunction in patients with symptomatic heart failure. But very limited data is available about the relationship between hsCRP and diastolic dysfunction in patients with risk factors who are asymptomatic. A study found association between hsCRP and diastolic dysfunction in young African American asymptomatic patients but not much data was found in Indian population where diabetes and hypertension are quite prevalent and have higher level of inflammation as suggested by the raised inflammatory marker levels.

So, this cross sectional, observational study was done to test a hypothesis that hsCRP, an inflammatory biomarker

Department of Medicine, Jagannath Gupta Institute of Medical Sciences and Hospital (JIMSH), Kolkata 700137
[1]MD (Med), Assistant Professor; at present : Associate Professor
[2]DNB (Neurology), Associate Consultant, Department of Neurology, National Neurosciences Centre, Kolkata700094 and Corresponding Author
Received on : 25/04/2019
Accepted on : 05/08/2019

Editor's Comment :

- **hs-CRP level is found to be significantly associated with presence of diastolic dysfunction in asymptomatic patients with cardiovascular risk factors.**
- **It is recommended to measure hs-CRP in these patients to identify the population at risk of diastolic heart failure and to diagnose diastolic dysfunction at an early stage.**
- **hs-CRP may be used as a possible predictor of incipient diastolic heart failure in these patients.**

is associated with diastolic dysfunction and is a predictor of incipient diastolic heart failure in patients with cardiac risk factors.

Materials and Methods

The study population were the patients visiting outpatient department (OPD) of MR Bangur Hospital, a district hospital in Kolkata from November 2011 to October 2013, for their medical problems. Sample size was 84 patients between 30 to 90 years both male and female.

The patient selection was based on history taking, clinical examination, laboratory investigations and echocardiogram.

Inclusion Criteria :

(1) Hypertension ie, systolic BP ≥140mmHg and/or diastolic BP ≥90mmHg or receiving antihypertensives;

(2) Diabetes ie, history of type 2 diabetes based on American Diabetic Association criteria or on antidiabetic medications.

Exclusion Criteria :

(1) Heart failure signs and symptoms or other cardiac symptoms (chest pain or shortness of breath);

(2) History of cardiac diseases (heart failure, coronary artery disease, myocardial infarction, valvular heart disease, bundle branch block, arrhythmias, wall motion abnormalities, peripheral vascular diseases, stroke);

(3) Digoxin use;

(4) Recently diagnosed (<1 year) DM or HTN;

(5) Pre-existing renal disease (serum creatinine ≥1.6mg/dl);

(6) History of heroine or cocaine use;

(7) History of alcoholism;

(8) Body mass index (BMI)≤18.5 or ≥40;

(9) Situations associated with acute hsCRP elevation (signs of acute systemic infection like fever, collagen diseases like rheumatoid arthritis, lupus,etc.);

(10) Estrogen use.

All patients satisfying the inclusion criteria were interviewed with a standardized proforma. Physical examination was performed. Venous blood was drawn for measurement of routine blood investigations. Latex particle immunoassay with nephelometry was used to measure plasma high-sensitivity C-reactive protein (hsCRP).

Transthoracic echocardiogram was done with M-mode, 2D (two-dimensional), Doppler and tissue Doppler imaging. At first following parameters were measured by M-mode: Interventricular septal thickness (IVST), left ventricular posterior wall thickness (PWT), end-systolic dimension of left atrium (LAD) and left ventricular internal diameter (LVID) at end-diastole (LVIDd) and end-systole(LVIDs). Calculation of left ventricular mass index (LVMI) was done (left ventricular mass)$^{2.7}$ to minimize errors due to overweight. Left ventricular ejection fraction (LVEF) was calculated and wall motion abnormalities noted.

Next, LV diastolic function was estimated by transmitral flow velocity using Doppler. Peak early-diastolic(E) and late-diastolic(A) transmitral flow velocity, deceleration time (DT) and E/A ratio was noted.

Lastly tissue doppler was performed at medial mitral annulus. Peak early(E') and late(A') diastolic mitral annular velocities and ratio(E'/A') was measured. Ratio of transmitral flow velocity and annular velocity(E/E') was calculated to assess LV end-diastolic pressure (LVEDP) that was used as the parameter of LV diastolic dysfunction. Elevated filling pressure was based on E/E' ratio>10. Diastolic function was categorised into : normal(DD0), diastolic dysfunction with normal LVEDP(DD1)(impaired relaxation, grade-1 DD), diastolic dysfunction with high LVEDP(DD2) which includes - impaired relaxation with elevated LVEDP(Grade-1B DD), pseudonormal filling pattern (Grade-2 DD), advanced diastolic dysfunction (Grade-3 DD, restrictive filling pattern).

Written informed consent was taken from all patients. Approval was taken from the Institutional Ethical Committee and Scientific Research Committee.

Statistical analysis :

Data was summarised by descriptive statistics ie, Mean±Standard Deviation for numerical variables and proportions and percentages for categorical variables. Correlation coefficient was calculated to quantify strength of association between hsCRP and different numerical variables. Multiple linear regression analysis was performed to evaluate the association between hsCRP and other numerical variables. $p<0.05$ indicated statistical significance.

Software used : SPSS Statistics version1 [Illinois, Chicago: SPSS Inc, 2008]

Results

A total of 84 patients between 30 to 90 years both male and female were selected by simple random sampling. Majority belonged to age group of 50-60 years with mean age 59±7 years (Table 1). 40(48%) were men and 44(52%) were female. Diabetes was present in 59(70.24%) and hypertension in 49(58.33%) patients. The mean hsCRP level was high (0.782±0.471). Majority had ejection fraction between 60-70% and mean was 65.3±5.3%; all had normal systolic function. Raised mean LVMI indicated LV hypertrophy and decreased mean E/A indicated diastolic dysfunction. Mean E/E' was 9.78±4.4. All variables were normally distributed by Kolmogorov-Smirnov goodness-of-fit test other than LVEF, E/A, E'/A', E/E'.

Grade-2(DD2) diastolic dysfunction patients were maximum in number (29). Echocardiogram showed any DD in 56(66.66%) patients, 27(32.14%) had mild DD(DD1) with normal LVEDP(E/E' ratio≤10) and 29(34.52%) had DD with elevated LVEDP(DD2)[E/E ratio>10 and a decrease in E/A ratio by 0.5 with Valsalva maneuver]. The mean hsCRP level progressively increased across the 3 diastolic dysfunction grades and gradually increased as the E/E' increased (Fig 1).

Association between hsCRP and other variables :

Correlation coefficient was calculated to quantify

Table 1 — *Clinical and Echocardiographic Features*

Characteristics	*Participants (mean±SD)*
Number (male/female)	84 (40/44)
Age (years)	58.6 ± 7.4
BMI (kg/m^2)	23.5 ± 1.7
Hypertension (*n* (%))	49 (58.3)
Diabetes mellitus (*n* (%))	59 (70.2)
Pulse (beats/min)	78.9 ± 4.4
Systolic BP (mmHg)	136.5 ± 10
Diastolic BP (mmHg)	85.3 ± 5.8
FBS (mg/dL)	152 ± 46.4
PPBS (mg/dL)	240 ± 63.9
HbA1c (%)	6.9 ± 0.57
Urea	28.2 ± 6.7
Creatinine	1.09 ± 0.26
hsCRP (mg/dL)	0.78 ± 0.47
LV structural parameters :	
LAD (mm)	35.4 ± 5.9
LVMI (g/m$^{2.7}$)	37.5± 7.8
LV functional parameters :	
LVEF (%)	65 ± 5
E/A	1.19 ± 0.36
E´/A´	1.13± 0.38
E/E´	9.78 ± 4.39

LV, left ventricular; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LAD, left atrial dimension;E, peak early diastolic transmitral flow; A, peak late diastolic transmitral flow; peak early diastolic annular velocity; A´, peak late diastolic annular velocity.

strength of association between hsCRP and different numerical variables. hsCRP was correlated with age, hypertension, diabetes, HbA1c, creatinine, LAD, LVMI, LVEF, E/A, and E/E´ (Table 2). E/E´, a parameter of LV diastolic function showed the strongest positive correlation to hsCRP among all variables (r=0.653, p<0.001)(Fig 2). These results indicate that elevated hsCRP reflects LV diastolic dysfunction rather than LV hypertrophy. Age and BMI may be confounding variables in the association between hsCRP and E/E'. So the correlation coefficient was calculated between hsCRP with age and BMI. But there was poor correlation between hsCRP levels with both age (0.257) and BMI (0.170).

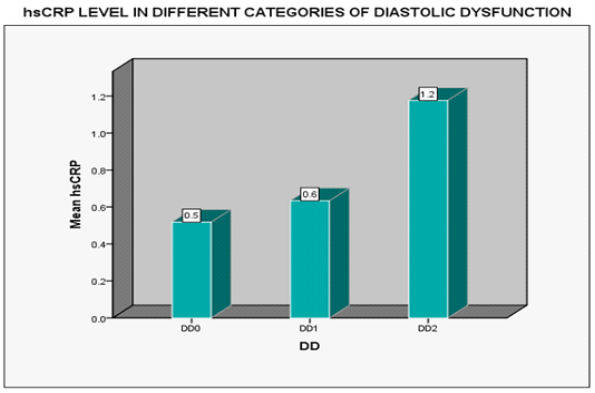

Fig 1 — Bar Diagram showing hsCRP level in different categories of Diastolic Dysfunction

Assessment of the factors related to hsCRP :

Multiple linear regression analysis was performed to evaluate the association between hsCRP and other numerical variables in all subjects. Only E/E'(β coefficient=0.845, p<0.001) was significantly associated with hsCRP (Table 3).

Discussion

In our study, there was high prevalence of DD with high LVEDP(34.5%). The most significant finding was the strong association between diastolic dysfunction ie, E/E' and elevated hsCRP levels, which was much greater than with DM, HTN, LV hypertrophy, and BMI. Patients having higher hsCRP levels were shown to have advanced DD with elevated LVEDP. Our study shows that there is a strong association between hsCRP level, a marker of inflammation and LVEDP in asymptomatic DD patients. This indicates that inflammation has a prominent role in development of

Table 2 — *Correlation of hsCRP levels with numerical variables for entire study sample (n=84)–Pearson correlation coefficient*

Variables	Pearson correlation (r)	P value
Age	0.257	0.009
BMI	0.170	0.061
Pulse	0.126	0.127
Systolic BP	0.238	0.015
Diastolic BP	0.218	0.023
FBS	0.303	0.003
PPBS	0.297	0.003
HbA1c	0.300	0.003
Urea	0.210	0.028
Creatinine	0.283	0.005
LAD	0.221	0.022
LVMI	0.289	0.004
LVEF	-0.326	0.001
E/A	0.222	0.021
E´/A´	0.150	0.086
E/E´	0.653	0.000

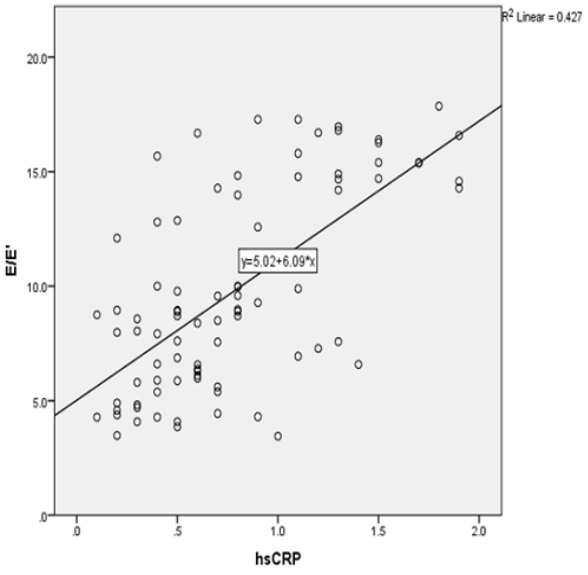

Fig 2 — Scatter Plot showing Correlation between hsCRP and E/E'

diastolic dysfuncton.

HsCRP appeared to be a stronger clinical predictor of DD than age, HTN and DM. DM and HTN leads to ventricular stiffness and diastolic dysfuncton and ultimately to heart failure by a common pathway of inflammation. If this association between diastolic dysfunction and inflammation is confirmed by further prospective long term observational studies, inflammation control may become a target for diastolic dysfunction therapy and heart failure prevention. HsCRP level could be useful in finding patients at risk for diastolic dysfunction and predict the likelihood of progression to heart failure.

The strong association between hsCRP and diastolic dysfunction in our study may be due to the high prevalence of hypertension (58.3%) and diabetes(70.2%). In our study, hsCRP is associated with presence of hypertension (p=0.029) and diabetes (p=0.005)(Table 2). Earlier studies have shown that in diabetic and hypertensive patients, there is an association between hsCRP and microvascular complications like retinopathy and nephropathy. Diastolic dysfunction being also produced by microvascular complication in hypertension and diabetes, is likely to be associated with raised hsCRP.

Study Limitations :

E/E´ was measured at septal mitral annulus. But some studies recommended measuring velocities of lateral mitral annulus or averaged velocities of septal and lateral mitral annulus.

There was no information regarding insulin resistance and atherosclerosis which are microvascular complications and have a common inflammatory background.

The variability of hsCRP levels produced by alcohol intake, medications and exercise were not included. Other markers of inflammation and some non inflammatory causes may be more strongly associated with diastolic dysfunction. So, a prospective longitudinal study with serial measurements of hsCRP along with other inflammatory markers will be needed.

The patients were not investigated for coronary artery disease, which can have inflammatory origin and present as diastolic dysfunction, as further invasive testing was considered unnecessary.

Lastly, a multicenter trial with larger population is needed to further investigate the role and clinical significance of hsCRP in diastolic dysfunction.

Table 3 — *Linear regression analysis to evaluate association between hsCRP and other numerical variables*

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	0.709[a]	0.503	0.384	0.3698

a. Predictors: (Constant), E/E', Pulse, E'/A', LAD, Urea, DBP, LVMI, PPBS, Cr, BMI, AGE, LVEF, FBS, SBP, HBA1c, E/A

ANOVA[a]

Model		Sum of Squares	df	Mean Square
1	Regression	9.263	16	0.579
	Residual	9.160	67	0.137
	Total	18.423	83	

a. Dependent Variable : hsCRP

b. Predictors:(Constant)E/E', Pulse,E'/A', LAD, Urea, DBP, LVMI, PPBS, Cr,BMI, AGE, LVEF, FBS, SBP, HBA1c, E/A

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	1.744	1.842		0.947	0.347
	AGE	-0.004	0.008	-0.065	-0.502	0.617
	BMI	-0.060	0.031	-0.217	-1.959	0.054
	Pulse	0.013	0.010	0.119	1.244	0.218
	SBP	-0.001	0.010	-0.025	-0.118	0.906
	DBP	-0.004	0.017	-0.055	-0.267	0.790
	FBS	0.001	0.002	0.144	0.922	0.360
	PPBS	0.000	0.001	-0.015	-0.085	0.933
	HBA1c	-0.139	0.173	-0.169	-0.804	0.424
	Urea	-0.004	0.008	-0.063	-0.560	0.577
	Cr	0.093	0.200	0.052	0.465	0.643
	LAD	0.001	0.009	0.012	0.114	0.910
	LVMI	0.000	0.006	-0.003	-0.025	0.980
	LVEF	2.737E-005	0.012	0.000	0.002	0.998
	E/A	0.088	0.300	0.068	0.292	0.772
	E'/A'	0.002	0.301	0.002	0.008	0.994
	E/E'	0.091	0.019	0.845	4.748	0.000

a. Dependent Variable: hsCRP

Conclusion

The data obtained shows that hsCRP is significantly elevated in patients with diastolic dysfunction and establishes a close association between hsCRP levels and diastolic dysfunction in asymptomatic patients with diabetes and hypertension. This provides evidence that systemic inflammation is a cause of myocardial fibrosis and LV dysfunction. HsCRP is more strongly related to diastolic dysfunction which is assessed by E/E' than to LV hypertrophy, assessed by LVMI. This finding suggests that hsCRP may be a possible marker of subclinical diastolic dysfunction in patients with cardiac risk factors, like hypertension and diabetes. If this is supported by further multicenter, longitudinal, prospective studies it may be used to identify the people at risk for heart failure and to establish new targets for management of diastolic dysfunction and prevention of heart failure. HsCRP levels may also be used to detect patients with advanced diastolic dysfunction without symptomatic heart failure.

Funding : None

Conflict of Interest : None

References

1 Gaasch WH, Zile MR — Left ventricular diastolic dysfunction and diastolic heart failure. *Annu Rev Med* 2004; **55**: 373-94.

2 Redfield MM, Jacobsen SJ, Burnett JC, Jr Mahoney DW, Bailey KR, Rodeheffer RJ — Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the

scope of the heart failure epidemic. *JAMA* 2003; **289**: 194-202.
3 Nicoletti A, Michel JB. Cardiac fibrosis and inflammation: interaction with hemodynamic and hormonal factors. *Cardiovasc Res* 1999; **41**: 532-43
4 Yambe M, Tomiyama H, Hirayama Y — Arterial stiffening as a possible risk factor for both atherosclerosis and diastolic heart failure. *Hypertens Res* 2004; **27**: 625-31.
5 Pirro M, Schillaci G, Savarese G —. Low-grade systemic inflammation impairs arterial stiffness in newly diagnosed hypercholesterolaemia. *Eur J Clin Invest* 2004; **34**: 335-41.
6 Kass DA — Ventricular arterial stiffening: integrating the pathophysiology. *Hypertension* 2005; **46**: 185-93.
7 Zile MR, Brutsaert DL — New concepts in diastolic dysfunction and diastolic heart failure:Part II:Causal mechanisms and treatment. *Circulation* 2002; **105**: 1503-08.
8 Kuwahara F, Kai H, Tokuda K — Hypertensive myocardial fibrosis and diastolic dysfunction:another model of inflammation? *Hypertension* 2004; **43**: 739-45.
9 Ridker PM, Hennekens CH, Buring JE, Rifai N — C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000; **342**, 836-43.
10 Olsen MH, Hansen TW, Christensen MK, Gustafsson F, Rasmussen S, Wachtell K, *et al* — Cardiovascular risk prediction by N-terminal pro brain natriuretic peptide and high sensitivity C-reactive protein is affected by age and sex. *J Hypertens* 2008; **26**: 26-34.
11 Pepys MB, Hirschfield GM, Tennent GA, Gallimore JR, Kahan MC, Belloti V, *et al* — Targeting C-reactive protein for the treatment of cardiovascular disease. *Nature* 2006; **440**, 1217-21.
12 deFilippi C, Wasserman S, Rosanio S, Tiblier E, Sperger H, Tocchi M, *et al* — Cardiac troponin T and C-reactive protein for predicting prognosis, coronary atherosclerosis, and cardiomyopathy in patients undergoing long-term hemodialysis. *JAMA* 2003; **290**: 353-59.

Learning Points on CRP :

- **CRP was first discovered in 1930 by William Tillet and Thomas Francis at the Rockefeller Institute for Medical Research, in New York.**
- **Inflammation plays an important role in the initiation and progression of atherosclerosis and the development of atherosclerotic events.**
- **The C-reactive protein (CRP) is one of the most reliable biomarker of underlying systemic inflammation.**
- **CRP an acute phase protein is synthesized by hepatocytes in response to proinflammatory cytokines, in particular interleukin-6.**
- **CRP plays a pivotal role in many aspects of atherogenesis including, activation of complement pathway, lipids uptake by macrophage and release of proinflammatory cytokines. It induces the expression of tissue factor in monocytes, promotes the endothelial dysfunction and inhibits nitric oxide production.**
- **Unlike other markers of inflammation, CRP levels are stable over long periods, have no diurnal variation. It can be measured with high-sensitivity assays and it can predict the risk of cardiovascular events.**
- **Many large-scale prospective studies demonstrate that CRP strongly and independently predicts adverse cardiovascular events, including myocardial infarction, ischemic stroke, peripheral arterial disease and sudden cardiac death in individuals both with and without overt CHD**
- **Significance of elevated hs-CRP levels is as follows :**
  - **< 1 mg/L Low risk**
  - **1-3 mg/L Moderate risk**
  - **>3 mg/L High risk**
- **Stable plaque shows modest elevation and there is marked elevation in hs-CRP in ruptured plaque.**
- **Elevated hs-CRP levels in stable patients after myocardial infarction can predict recurrent infarction and cardiovascular death.**
- **Determination of hs-CRP can assist physicians to evaluate cardiovascular risk and to monitor therapeutic interventions.**
- **The measurement of plasma CRP is reasonable for assessing absolute risk for coronary artery disease in primary prevention - particularly in intermediate risk individuals.**
- **Elevated hs-CRP has been recognized as moderate risk in the recent ESC/EAS Guidelines for management of dyslipidemia and Canadian cholesterol guidelines.**
- **In the prospective Physicians' Health Study, Men in the quartile with the highest CRP values had three times more risk of myocardial infarction compared with men in the lowest quartile, and the risk of stroke was approximately also doubled.**
- **In women also hs-CRP levels have been found to be highly predictive of future CVD risk.**
- **In the JUPITER, TIMI 22 and the REVERSAL (reversal of Atherosclerosis with Lipitor) trials. The greatest clinical benefit of statin therapy occurred among patients who had lowering of both LDL-C and hs-CRP**
- **Determination of CRP may provide additional information regarding which patients may benefit from statin treatment irrespective of cholesterol level.**

— DR GURPREET SINGH WANDER,
Prof. & Head, Dept of Cardiology, Dayanand Medical College, Ludhiana