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Left Ventricular Function and C-Reactive Protein Levels in Acute Myocardial Infarction

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Abstract

To examine left ventricular (LV) function in patients after acute myocardial infarction (AMI) and assess its relation with C-reactive protein (CRP) as a measure of the early inflammatory response. We measured CRP levels early after AMI and correlated them with early structural and functional cardiac alterations. Between November 2002 and December 2007, we prospectively enrolled community subjects who experienced an AMI defined by standardized criteria, measured CRP and obtained an echocardiogram. The study consisted of 514 patients (mean age 67 ± 15 years; 59% men). CRP was measured early after symptom onset (median 6.1 hours; 25th-75th percentile 2.2-11.1 hours). The median CRP was 4.8 (25th-75th percentile 1.8-24 mg/L). Echocardiograms were obtained at a median of 1 day post-AMI. Wall motion score index, LV ejection fraction (EF) and LV diameters were similar across CRP tertiles (all p>0.05). Greater levels of CRP were associated with the presence of moderate or severe diastolic dysfunction (p=0.002) and moderate or severe mitral regurgitation (p<0.001). The association with moderate or severe mitral regurgitation was independent of clinical characteristics and ST segment elevation status. In conclusion, at the initial phase of AMI, CRP elevation is associated with the presence and severity of MR and with diastolic dysfunction. This suggests that inflammation is related to ventricular remodeling processes, independently of LV systolic function.

Keywords

myocardial infarction; inflammation

Introduction

In the community, heart failure (HF) remains frequent after acute myocardial infarction (AMI) even in the current therapeutic era1 HF occurs early at the acme of tissue necrosis and

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inflammation.2,3Conceivably, ischemic injury promotes myocardial inflammation and pro-inflammatory cytokines stimulate CRP (C-reactive protein)4 leading to cardiac remodeling with HF as its clinical manifestation.2 Yet, the mechanisms of HF post-AMI remains poorly understood. Indeed, while CRP is a marker of inflammation4 activated early after AMI5,6 and associated with HF,7-9 the link between CRP and structural and functional cardiac alterations after AMI is not delineated. Studying the association between CRP and cardiac alterations after AMI is complex as it requires early diagnosis of AMI and measurements of CRP and echocardiograms. To optimize its relevance to all patients with AMI, the study should be conducted in the community.[10] The ongoing prospective study of the epidemiology of AMI meets these requirements by enrolling prospectively subjects with AMI in the community and recording echocardiography and biomarkers. Hence, we examined left ventricular (LV) function and its relation with CRP as a measure of inflammation to test the hypothesis that CRP was associated with worse LV function post-AMI.

Methods

In Olmsted County, medical care is delivered by few providers11 including the Mayo Clinic and its affiliated hospitals, Olmsted Medical Center and its affiliated community hospital, local nursing homes, and a few private practitioners. Each provider uses a medical record in which patient care data, regardless of setting, are available. The records are easily retrievable because indices are maintained through the Rochester Epidemiology Project and extended to the records of all providers in the county, resulting in the linkage of all records from all sources of care.[11] Olmsted County residents hospitalized between November 2002 and May 2006 presenting with troponin T values ≥0.03 ng/mL (upper limit of normal for the assay defined as the value at which the coefficient of variation for the assay is < 10%) were prospectively identified within 12 hours of their initial blood draw through the Department of Laboratory Medicine. All patients had troponin measurements[12] as part of clinical practice. Up to three electrocardiograms per episode were coded using the Minnesota Code Modular ECG Analysis System. Myocardial infarctions were classified using the European Society of Cardiology/ American College of Cardiology guidelines,12 Only patients with incident MI were included to ensure that the findings reflected the first infarction.

Clinical data included Killip class and comorbidities.[13] Clinical diagnoses were used to ascertain hypertension, diabetes mellitus, hyperlipidemia, and smoking.

High sensitivity CRP was measured on serum from the first sample drawn after symptom onset using a latex enhanced immunoturbidimetric assay on a Hitachi® 912 automated analyzer and reagents from Diasorin®. CRP was measured in the laboratories of the Department of Laboratory Medicine and Pathology, which is certified by the Clinical Laboratory Improvement Act of 1988 and the College of American Pathologists.

Data from the echocardiogram during the index hospitalization were retrieved. The parameters of left ventricular systolic function included ejection fraction (EF) and wall motion score index. EF was measured by validated methods using the quantitative bi-dimensional biplane volumetric Simpson method,[14] the Quinones formula, or bi-dimensional estimate method from multiple echocardiographic views, a method comparable to other assessments of EF.15 Values were averaged when multiple measurements were performed. Left ventricular wall-motion score index was calculated.14 Left ventricular end-diastolic diameter, ventricular septal and posterior wall thickness were measured by M-mode or bidimensional echocardiography from the parasternal views at end-diastole as recommended by the American Society of Echocardiography and used to calculate left ventricular mass, indexed to the body surface area. 14 End-systolic diameter was measured at end-systole by M-mode or two-dimensional echocardiography.[14] Diastolic function was assessed by integrating measurements of the mitral

inflow and Doppler tissue imaging of the mitral annulus using the medial annulus velocity and classified into 4 categories: normal diastolic function, mild diastolic dysfunction (impaired relaxation without evidence of increased filling pressures), moderate dysfunction (impaired relaxation or pseudo-normal with moderate elevation of filling pressures), and severe dysfunction (advanced reduction in compliance). The severity of MR was evaluated semi-quantitatively from the area of the regurgitant jet observed by color Doppler and classified as absent or trivial, mild and moderate or severe.[16]

Trends in baseline characteristics across CRP tertiles were tested using the Mantel-Haenszel chi-square test for categorical variables and linear regression for continuous variables. Associations between CRP and the echocardiographic variables were tested using linear regression for the continuous echocardiographic variables and logistic regression for the categorical variables. CRP, wall motion score index, and left ventricular mass index were log-transformed in the regression models. The Institutional Review Board approved the study.

Results

From November 2002 through December 2007, 514 patients with incident AMI had CRP measured and underwent an echocardiogram during hospitalization. The mean age of the population was 67 ± 15 years; 59% were men. CRP was measured at a median of 6.1 hours after symptom onset (25^{th}-75^{th} percentile 2.2 to 11.1 hours). The median CRP was 4.8 mg/L (25^{th}-75^{th} percentile 1.8 to 24 mg/L). Echocardiograms were performed at a median of 1 day after symptom onset (25^{th}-75^{th} percentile 1 to 2 days).

The baseline characteristics of the patients by CRP tertile are shown in Table 1. The cut points for the CRP tertiles were <2.7 mg/L, 2.7-10 mg/L, and >10 mg/L. Patients with higher CRP levels were older, more likely to be women, to have hypertension, diabetes mellitus, and more comorbidities, and to present in a higher Killip class. Patients with higher CRP values were less likely to present with an ST elevation AMI, had lower peak troponin and lower peak creatine kinase-MB (CK-MB) levels. The time from onset of symptoms to blood draw for measurement of CRP was similar across all tertiles as were all other baseline characteristics.

Echocardiographic parameters by CRP tertiles are reported in Table 2. The presence of moderate or severe LV diastolic dysfunction and the presence of moderate or severe MR were associated with higher levels of CRP.

After adjustment for age and sex and further adjustment for comorbidities and Killip class, the associations between higher CRP levels and moderate or severe diastolic dysfunction and moderate or severe mitral regurgitation remained. Table 3 quantifies the strength of these associations by expressing them as odds ratios. After further adjustment for infection within 2 weeks prior to the MI, the association between CRP and diastolic dysfunction was no longer significant, but the association between CRP and MR remained. The association between CRP and MR was also independent of diastolic dysfunction, and was not materially affected by the addition of ST segment elevation status in the models (p-values for the association between CRP and MR after adjustment for diastolic dysfunction and after adjustment for ST segment elevation status were 0.035 and 0.088, respectively).

Discussion

These prospective data from contemporary community patients with AMI provide findings of direct relevance to the pathogenesis of HF after AMI. Worse diastolic function and more severe MR were associated with greater inflammation as measured by CRP. These associations were robust and independent of measured clinical characteristics and echocardiographic indicators

of ventricular systolic function. Further, there was no relationship between CRP and systolic function indices (EF, wall motion score index).

Previous work, including from our group, indicated that CRP predicts HF and death after AMI[8,9]. The mechanisms of these associations, however, remained poorly elucidated.

In some studies of patients who underwent echocardiography or left ventriculography, systolic function was worse among those with higher levels of CRP.[8,9] Conversely, other reports failed to show an association between admission CRP and EF measured by radionuclide angiography or echocardiography or with AMI size measured by thalium-201 single-photon emission computed tomography.17 These discrepancies likely reflect methodological issues. Indeed, most studies included both incident and prevalent AMI cases[8,9] such that ventricular function parameters reflected both chronic and acute changes, and samples were often obtained at disparate times and thus influenced by the degree of necrosis to an unknown degree. The present study contributes to resolve this controversy and extends prior reports due to several distinct methodological advantages which leads to more robust inference. Indeed, all patients underwent echocardiography after the first (incident) MI such that the findings cannot by design reflect preexisting alteration in ventricular function due to prior ischemic injury. As patients were prospectively recruited in the community, the entire spectrum of disease severity is represented. By contrast, in prior studies evaluating CRP and LV function after AMI, patients were selected within intensive care units.[8,9] Finally, CRP, which rises within a few hours after AMI to peak within 2 to 4 days and return to baseline after a few weeks,6 was herein systematically and consistently measured early after the event.

While the association of CRP and diastolic function has previously been reported in established coronary disease, both in the setting of preserved[18] and reduced left ventricular systolic function,[19] little is known about its association with ventricular function acutely. In the present study, elevated CRP was not associated with EF or WMSI but, importantly, exhibited a graded positive and independent association with diastolic dysfunction. The cascade of post-AMI tissue necrosis, healing and scarring leads to ventricular dilatation, i.e. remodeling.[2] A key consequence of remodeling is the development of MR. Indeed, as the ventricle dilates and the heart assumes a more globular shape, the geometric relation between papillary muscles and mitral leaflets is altered, causing tethering of the leaflets, distortion of the mitral apparatus and regurgitation. Thus, after MI, MR is not related to intrinsic valvular abnormalities but rather serves as a marker of ventricular remodeling.[20] Small case series had suggested that CRP was associated with ventricular remodeling in anterior wall AMI.[21,22] The present data extend these reports by indicating that CRP exhibited a robust association with MR independently of clinical and echocardiographic characteristics among all patients presenting with MI in the community. These mechanistic insights resonate with reports from our group on the association of MR and HF on one hand[23] and CRP and HF post-AMI on the other hand[7] and suggest that inflammation and MR are part of a complex pathway leading to HF post-MI, independently of ventricular systolic function. Indeed, the severity of the MR relates to the extent of ventricular geometric changes rather than to the severity of ventricular dysfunction.[24] After MI, MR creates a self-perpetuating deleterious situation, in turn leading to further LV dysfunction and mortality.[25,26] As remodeling is defined as a change in ventricular geometry, its detection occurs at a stage which precludes early intervention. Thus, it is essential to predict and prevent remodeling to improve outcomes. The present data suggest that early CRP can serve as a marker of the propensity to remodel and resonate with the benefits of statin therapy after MI, thought to be in part related to the prevention of inflammation. As our study is cross sectional, longitudinal studies are needed to confirm and extend our findings. Conducting such studies is important as the clinical application of CRP measurement after MI could be to extend the use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers to subjects with elevated early CRP who do not meet current indications for these drugs.

MR was evaluated semi-quantitatively. This is unlikely to affect our results, however, as the central jet of ischemic MR correlates with the regurgitant volume.[16] Further, we previously evaluated MR semi-quantitatively and reported a graded positive association between its severity and outcomes.[23] MR might have been present beforehand in some patients, a limitation shared by all studies on this topic.[23,26-28] However, the frequency of MR observed herein largely exceeded that in the general population,[29] and was similar to that observed in patients post-MI.[23] Thus, the degree of MR described herein can be attributed to the MI. Serial measurements are needed to assess temporal changes in ventricular function and MR post-MI.

Strengths of our study include the prospective evaluation of community patients with a first AMI validated with rigorous criteria[12,30] who all underwent early CRP measurements and echocardiography with assessment of ventricular size, function and MR. These methodological strengths allowed this study to address the gap in knowledge and support the hypothesis of a link between inflammation with structural and functional cardiac alterations after MI.

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Table 1

Clinical characteristics by tertiles of C-reactive protein (mg/L) levels

Variable	Tertile 1 <2.7 mg/L N=172	Tertile 2 2.7 to 10 mg/L N=169	Tertile 3 > 10 mg/L N=173	P value*
Age, mean ± sd (years)	65 ±14	65 ±15	71 ±17	<0.001
Women	62 (36%)	65 (38%)	86 (50%)	0.023
Body mass index, mean ± sd (kg/m^2)	28± 5	30 ± 7	28± 7	0.539
Hypertension	108 (63%)	107 (63%)	129 (75%)	0.029
Hyperlipidemia	112 (65%)	103 (61%)	107 (62%)	0.702
Current smoker	35 (20%)	47 (28%)	31 (18%)	0.584
Diabetes mellitus	20 (12%)	44 (26%)	54 (31%)	<0.001
Killip class 2, 3 or 4	31 (18%)	42 (25%)	67 (39%)	<0.001
Infection within 2 weeks prior	7 (4%)	18 (11%)	77 (45%)	<0.001
Comorbidity index				<0.001
0	88 (51%)	42(35%)	26 (15%)	
1-2	57 (33%)	65 (38%)	62 (36%)	
≥ 3	27 (16%)	44 (26%)	85 (49%)	
Electrocardiogram				
Inferior location	64 (38%)	60 (37%)	59 (36%)	0.629
Presence of Q waves	88 (56%)	85 (57%)	90 (59%)	0.579
ST elevation myocardial infarction	49 (29%)	45 (28%)	32 (19%)	0.039
Biomarkers				
Time from symptoms to C-reactive protein measurements, median (25th- 75th percentile)	6.3 (3.1-10.5)	6.9 (2.8- 12.2)	4.0 (0.7- 10.7)	0.091
Peak troponin, median (25th-75th percentile)	1.08(0.31-3.57)	0.94 (0.30, 3.93)	0.52 (0.18, 1.520)	0.001
Peak creatine kinase-MB, median (25th- 75th percentile)	42 (11-135)	31 (11-113)	14 (7-30)	<0.001

Table 2

Echocardiographic characteristics by tertiles of C-reactive protein (mg/L) levels

Variable	Tertile 1 <2.7 mg/L (N=172)	Tertile 2 2.7 to 10 mg/L (N=169)	Tertile 3 > 10 mg/L (N=173)	P value*
Wall motion score index, median (25th 75th percentile)	1.28 (1.00- 1.63)	1.31(1.13- 1.69)	1.25 (1.00- 1.82)	0.122
EF, median (25th- 75th percentile)	57 (48- 63)	55(47- 62)	57(45- 64)	0.077
Left ventricular end-diastolic diameter, (25th- 75th percentile), mm	48 (46-52)	50 (46-53)	50 (44-53)	0.781
Left ventricular end-systolic diameter, (25th- 75th percentile), mm	33 (29-36)	33 (29-38)	33 (28-39)	0.124
Left ventricular mass index, median (25th- 75th percentile), g/m2	99 (82- 118)	95 (80- 115)	103(83-125)	0.459
Diastolic dysfunction moderate/severe, n (%)	85 (49)	81(48)	107(62)	0.002
Mitral regurgitation				<0.001
None/mild, n (%)	158 (94)	149 (90)	133 (81)	
Moderate/severe, n (%)	9 (5)	17 (10)	31 (19)	

* From regression models including the logarithm of CRP.

Table 3

Odds ratios (95% CI) for the association between diastolic dysfunction and mitral regurgitation and C-reactive protein

Variable	Unadjusted	Adjusted for age, sex	Adjusted for age, sex, comorbidity, and Killip class	Adjusted for age, sex, comorbidity, Killip class, and infection
Moderate or severe diastolic dysfunction				
CRP tertile 2	0.94 (0.62, 1.44)	0.93 (0.60, 1.43)	0.94 (0.61, 1.46)	0.92 (0.60, 1.43)
CRP tertile 3	1.66 (1.08, 2.55)	1.43 (0.92, 2.22)	1.53 (0.96, 2.44)	1.35 (0.82, 2.23)
p-value*	0.002	0.028	0.021	0.10
Moderate or severe mitral regurgitation				
CRP tertile 2	2.00 (0.87, 4.63)	2.01 (0.86, 4.72)	2.00 (0.85, 4.72)	1.92 (0.83, 4.61)
CRP tertile 3	4.09 (1.88, 8.90)	3.13 (1.41, 6.95)	2.60 (1.14, 5.89)	2.32 (0.98, 5.50)
p-value*	<0.001	0.002	0.009	0.030

* From logistic regression models with the logarithm of CRP modeled continuously.