High-sensitivity C-reactive protein as an independent predictor of progressive myocardial functional deterioration: The multiethnic study of atherosclerosis

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Background Systemic inflammation has been linked to the development of heart failure in population studies including Multi-Ethnic Study of Atherosclerosis (MESA), but little evidence exists regarding potential mechanism of this relationship. In this study, we used longitudinal magnetic resonance imaging follow-up analysis to examine whether C-reactive protein (CRP) levels relate to progressive myocardial functional deterioration as a potential mechanism of incident heart failure.

Methods Regional myocardial functional data from MESA participants who had baseline CRP measurement and also underwent tagged cardiac magnetic resonance imaging both at baseline and at 5-year follow-up were analyzed. Left ventricular midwall and midslice peak circumferential strain (Ecc), of which a more negative value denotes stronger regional myocardial function, was measured. Circumferential strain change was calculated as the difference between baseline and follow-up Ecc.

Results During the follow-up period, participants (n = 785) with elevated CRP experienced a decrease in strain, independent of age, gender, and ethnicity ($B = 0.081$, ΔEcc change per 1 mg/L CRP change, 95% CI 0.036-0.126, $P < .001$, model 1) and, additionally, beyond systolic blood pressure, heart rate, diabetes, smoking status, body mass index, current medication, and glomerular filtration rate ($B = 0.099$, 0.052-0.145, $P < .001$, model 2). The relationship remained statistically significant after further adjustment for left ventricular mass, coronary calcium score, and interim clinical coronary events ($B = 0.098$, 0.049-0.147, $P < .001$, model 3).

Conclusion Higher CRP levels are related to progressive myocardial functional deterioration independent of subclinical atherosclerosis and clinical coronary events in asymptomatic individuals without previous history of heart disease. (Am Heart J 2012;164:251-8.)

Systemic inflammation has been shown to be related to hospitalization and mortality in patients with heart failure (HF).[1] High-sensitivity C-reactive protein (CRP) is a biomarker of inflammation that has been associated with the development of symptomatic HF in large-scale population studies. Indeed, several prior reports have demonstrated a clear link between elevated levels of CRP and the development of HF, even among asymptomatic individuals.[2,3] Among potential mechanisms, myocardial infarction caused by coronary arterial plaque rupture due to the local activation of proinflammatory cytokines is a well-known determinant of incident HF.[4,5] However, the greater incidence of HF among patients with elevated CRP has been observed to be, in large part, independent of interim myocardial infarction in previous population studies including the Multi-Ethnic Study on Atherosclerosis (MESA).[3] Therefore, the mechanisms by which higher systemic inflammatory markers contribute to the development of HF have not been fully elucidated. Basic research suggests that direct myocardial functional depression may be induced by inflammatory cytokines.[6]

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In this regard, recent population studies have shown that CRP levels are independently related to regional myocardial dysfunction, although causation could not be ascertained in such cross-sectional analyses.[5] Until now, there have been no large-scale longitudinal follow-up studies designed to evaluate the effects of systemic inflammation on progression of regional myocardial dysfunction in community-based populations.

Myocardial circumferential strain (Ecc), defined as proportional myocardial deformation during the cardiac cycle, can be accurately measured regionally by tagged magnetic resonance imaging (MRI) and has been validated and used as a reference index of regional myocardial function.[7] Therefore, in this MESA ancillary study, we used serial cardiac MRI tagging examinations to determine whether elevated CRP can predict progressive regional myocardial functional deterioration independent of interim cardiovascular events, in a multiethnic population without clinically apparent cardiovascular disease at baseline.

Methods

Study population

The MESA is a prospective study designed to evaluate mechanisms that underlie the development and progression of subclinical cardiovascular diseases among asymptomatic individuals of the general population. The details of the MESA study design have been previously described.[8] In short, 6,814 American men and women 45 to 85 years of age, free of known cardiovascular disease, of 4 self-reported ethnicities ("non-Hispanic white," "African American," "Hispanic," and "Chinese American") were enrolled by 6 participating centers in the United States. On entry, all participants underwent an extensive evaluation that consisted of clinical questionnaires, physical examination, and laboratory tests. Individuals with symptomatic cardiovascular disease were excluded. Computed tomography (CT) scanning of the chest was performed either with electrocardiogram (ECG)-triggered electron beam CT, or multidetector CT system. Cardiac MRI was done in 5,098 participants, and as an ancillary study, tagged MRI was performed at baseline and repeated at MESA 4 in part of them. The institutional review boards in each of the participating centers approved the study protocol, and informed consent was obtained from each participant.

High-sensitive-CRP concentrations

The serum level of CRP was measured at the baseline MESA examination as a marker of systemic inflammation. The level of CRP was measured using the BNII nephelometer (N High-Sensitivity CRP; Dade Behring, Deerfield, IL). Analytical intra-assay coefficients of variation (CVs) of CRP ranged from 2.3% to 4.4%, and interassay CVs ranged from 2.1% to 5.7%.

Baseline and follow-up tagged MRI studies

The detailed protocol for tagged MRI studies has been previously described.[9] The same tagged MRI protocol was applied at baseline and at follow-up scanning. Images were acquired by whole-body scanners (1.5 CVi; General Electric Medical Systems [Waukesha, WI] and Sonata/Symphony Siemens Medical Solutions [Erlangen, Germany]) using ECG-triggered segmented *k*-space fast-spoiled gradient-echo pulse sequence during breath holds. After completing the standard protocol, 3 tagged short-axis slices (base to apex) were obtained. Parallel striped tags were prescribed in 2 orthogonal orientations (0° and 90°) using spatial modulation of magnetization. Parameters for tagged images were as follows: field of view 40 cm, slice thickness 7 to 8 mm, repetition time 6 ms, echo time 3.0 ms, flip angle 10° to 12°, phase encoding views 128 with 6 phase encoding views per segment, temporal resolution 35 ms, and tag spacing 7 mm. The left ventricular (LV) mass, LV end-diastolic volume, and LV ejection fraction were determined for each participant using dedicated, commercially available software (MASS, version 4.2; Medis, Leiden, the Netherlands), as previously described.[10]

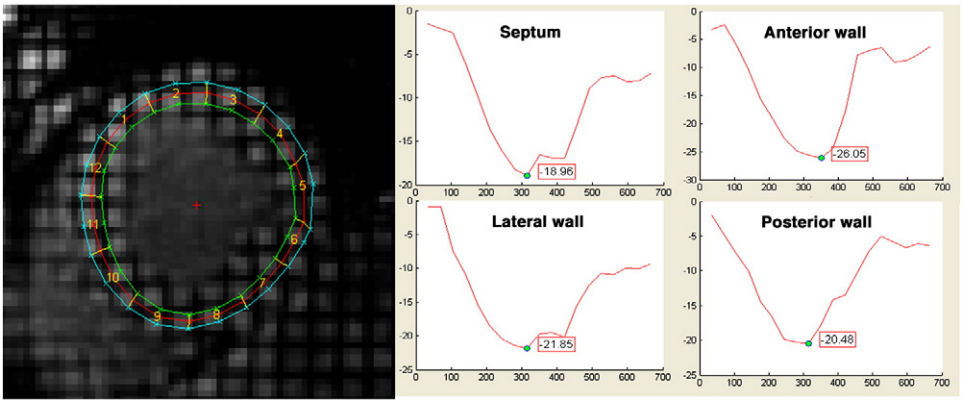
Myocardial strain analysis

Myocardial systolic Ecc was measured to evaluate regional myocardial function. Short-axis tagged slices were analyzed using the HARP method (Diagnosoft, Palo Alto, CA), which enables the fast determination of myocardial strain during the cardiac cycle.[11] Circumferential strain was determined in 4 wall segments (anterior, lateral, inferior, and septal) from the LV midwall layer[9,12] using MATLAB software (The MathWorks, Natick, MA) (Figure). By convention, systolic Ecc is normally negative denoting circumferential shortening, and higher Ecc values reflect decreased regional function (eg, Ecc = −12% reflects lower regional function when compared with Ecc = −18%). Segments without well-defined peak strain curves owing to significant noise were excluded. Intraclass correlation coefficients for interobserver and intraobserver agreement for peak systolic midwall Ecc were 0.81 and 0.84, respectively.[9] *Peak global systolic strain* was defined as the peak midwall Ecc averaged across all midventricular segments. Peak Ecc change during the follow-up period was calculated by subtracting peak global mid-LV slice Ecc at baseline from Ecc at the follow-up examination to reduce mismatching between the 2 examinations.

Interim cardiovascular events

At intervals between 9 and 12 months, interviewers were contacted with each participant by telephone to document interim hospital admissions, cardiovascular outpatient diagnoses, or deaths. Interviewers took history of angina followed by revascularization, stroke, peripheral artery disease, myocardial infarction, resuscitated cardiac arrest, and death from coronary disease. If interviewers failed to contact participants directly, they contacted family members. For participants who had died of cardiovascular causes outside the hospital, interviews were conducted with the next of kin and copies of death certificates were requested. To verify self-reported diagnoses, study personnel requested copies of all medical records for all hospitalizations and outpatient cardiovascular diagnoses. Hospital records were obtained for an estimated 98% of cardiovascular events requiring hospitalization, and some information was available for 95% of outpatient diagnostic encounters. The MESA coordinating center collated the abstracted or original end point records and sent them to 2 paired cardiologists and

Figure



Tagged MRI study with a sample Ecc curve (in %strain on *y*-axis; in milliseconds on *x*-axis) in a cross section of LV.

cardiovascular epidemiologists for independent end point classification and assignment of incidence dates. If disagreements persisted after review and adjudication, a full Mortality and Morbidity Review Committee made the final classification. Reviewers assigned a diagnosis of myocardial infarction based on a combination of symptoms, ECG findings, and cardiac biomarker levels. The definition of angina leading to hospitalization was adapted from the Women's Health Initiative criteria. Reports of percutaneous coronary intervention and bypass surgery were also obtained from medical records.

Statistical analysis

Pearson correlation analysis was performed to evaluate relationships between continuous variables. Comparisons of continuous variables across CRP quartile groups were performed using analysis of variance–*F* analysis or Kruskal-Wallis tests. Comparisons of discrete variables were performed using χ^2 tests, whereas comparisons of Ecc values between 2 examinations were performed using paired *t* tests. For categorical analyses of change in Ecc, we defined a "definite" Ecc deterioration group as participants who had ΔEcc greater than mean ΔEcc + 1 SD and definite improvement as Ecc improvement greater than mean ΔEcc − SD. Comparisons of continuous variables between the definite myocardial functional deterioration group and the remainder group of participants were performed using *t* tests and those of discrete variables by χ^2 tests. Prevalence of definite Ecc deterioration group was compared between groups with CRP >3 and ≤3 mg/L using χ^2 test. Comparison of nonparametric parameters was performed using Mann-Whitney *U* test. Both multivariable linear regression analysis of ΔEcc and logistic regression analysis for definite Ecc deterioration were performed to evaluate the predictability of baseline parameters. We evaluated and compared the fitness, statistical results, and interpretation of findings obtained using the following models: model 1 included age, gender, and ethnicity; model 2 included systolic blood pressure, heart rate, diabetes, smoking status, body mass index, current medications (antihypertensive medication, aspirin, and statin), and glomerular filtration rate in addition to model 1 variables; and model 3 included LV mass, coronary calcium score, interim myocardial infarction, and coronary revascularization in addition to model 2. Because ΔEcc was significantly correlated with baseline Ecc, we adjusted for baseline Ecc in model 4. To examine whether the results were independent of interim coronary events, we repeated the analyses after exclusion of participants who experienced interim coronary events. All statistical analyses were performed using SPSS (version 15.0; SPSS, Inc, Chicago, IL), and we considered 2-sided *P* values <.05 to be significant.

Results

Baseline CRP and participant characteristics

Among the 1,773 subjects who were enrolled in MESA baseline ancillary tagging study, 851 participants underwent repeated tagged MRI. Among them, 62 cases were excluded because of noise, misregistration of tag, different tagging sequence, and unreadable images by analyzing software. Four cases were lost due to no CRP data. Finally, a total of 785 cases had both CRP value and good quality mid-LV slice strain curve from both baseline and follow-up. The mean age was 64 ± 9 years, and 386 participants were women (49%). The median CRP concentration was 1.7 mg/L (interquartile range, 0.8-3.8 mg/L), and women had higher CRP than did men (2.42 mg/L vs1.25 mg/L, $P < .001$). The mean interval between the baseline and follow-up MRI examinations was 1,713 ± 95 days. During the follow-up period, 6 patients had myocardial infarction (time to interim myocardial infarction 1,390 ± 444 days) and 18 underwent coronary revascularization (time to revascularization 1,176 ± 506 days), with 3,690 person-years of follow-up. Table I shows the baseline characteristics and LV indices for each sex-specific CRP quartile. The higher CRP quartile subgroup was associated with higher body mass index, higher prevalence of hypertension, smokers, African Americans, Hispanics, and

Table I. Baseline characteristics of the study population according to sex-specific CRP quartiles (Q)

	Sex-specific quartiles				
	First quartile (n = 199)	**Second quartile (n = 196)**	**Third quartile (n = 196)**	**Fourth quartile (n = 194)**	***P***
CRP* (mg/L)	0.44	1.19	2.48	6.50	<.001
Age (y)	64 ± 10	64 ± 9	65 ± 9	63 ± 8	.34
Female, n (%)	97 (49)	97 (50)	96 (49)	96 (50)	.998
Ethnicity, n (%)					
Non-Hispanic white	68 (34)	61 (31)	63 (32)	49 (25)	.26
Chinese American	68 (34)	33 (17)	26 (13)	12 (6)	<.001
African American	32 (16)	50 (26)	51 (26)	67 (35)	.001
Hispanic	31 (16)	52 (27)	56 (29)	66 (34)	<.001
Current smoking, n (%)	7 (4)	16 (8)	24 (12)	32 (27)	<.001
Hypertension, n (%)	74 (37)	85 (43)	93 (47)	115 (59)	<.001
Diabetes, n (%)	17 (9)	25 (13)	20 (10)	33 (17)	.06
Body mass index (kg/m^2)	24.9 ± 3.6	27.8 ± 4.4	28.1 ± 4.3	30.2 ± 4.9	<.001
GFR (mL/min)	82.5 ± 15.8	80.5 ± 18.9	79.9 ± 17.3	82.0 ± 18.1	.44
Statin use, n (%)	47 (24)	38 (19)	31 (16)	25 (13)	.04
Aspirin use, n (%)	55 (28)	50 (26)	40 (20)	44 (23)	.35
LV end-diastolic volume (mL)	122.5 ± 33.0	122.8 ± 32.1	122.3 ± 29.9	125.2 ± 29.8	.81
LV ejection fraction (%)	69.0 ± 7.3	69.1 ± 6.6	69.6 ± 7.5	69.3 ± 8.2	.83
LV mass index (g/m^2)	77.3 ± 19.1	77.5 ± 15.6	76.9 ± 13.7	80.1 ± 16.9	.25
LV mass (g)	138.1 ± 42.8	143.2 ± 37.2	143.1 ± 34.6	153.1 ± 39.1	.002
CAC score >0	102 (51)	96 (49)	106 (54)	107 (55)	.61

GFR, glomerular filtration rate; CAC, coronary artery calcium by CT.
*Median. CRP (in milligrams per liter) quartiles for women: first, 0.35-0.90; second, 1.36-2.08; third, 2.88-4.31; fourth, 6.52-11.68; for men; first, 0.30-0.51; second, 0.75-1.06; third, 1.47-2.22; fourth, 3.35-6.49

higher LV mass. Chinese Americans and statin users were associated with lower CRP quartiles.

Longitudinal myocardial functional changes

Temporal change in circumferential myocardial shortening was used to index changes in myocardial function across time. Negative ΔEcc values reflect functional improvement, whereas positive ΔEcc indicates functional deterioration. The mean midventricular Ecc did not significantly change for the entire study group during the follow-up period (from −17.8% ± 2.6% to −17.9% ± 2.8%, P = .26), and average ΔEcc (ie, Ecc at follow-up − Ecc at baseline) was −0.1% ± 3.3%. Therefore, we considered ΔEcc >3.2% (Ecc deterioration >1 SD) as definite myocardial functional deterioration and ΔEcc <−3.4% as definite Ecc improvement. The definite deterioration group (n = 112) had higher baseline CRP. The prevalence of current smokers was significantly higher, and the prevalence of Chinese was significantly lower in the definite deterioration group (Table II). Higher body mass index was related to definite deterioration group in men (odds ratio [OR] 1.1, 1.03-1.18, P = .004) but not in women (1.04, 0.99-1.11, P = .13). Hypertension (OR 1.64, 1.09-2.48, P = .018) and angiotensin-converting enzyme inhibitor users (OR 2.02, 1.21-3.38, P = .008) were significantly related to definite Ecc improvement.

Predictors of regional myocardial functional deterioration

Baseline CRP was weakly but significantly correlated with change in myocardial shortening (ΔEcc, r = 0.11, P = .002), indicating that increased CRP is associated with myocardial functional reduction. In univariate analysis, higher CRP was significantly correlated with definite myocardial functional deterioration (OR 1.07 per 1-mg/L increase, 95% CI 1.03-1.11, P < .001). Because ΔEcc was significantly correlated with baseline Ecc (r = −0.59, P < .001), we reanalyzed the data after adjusting for baseline Ecc. Higher CRP, indexed LV mass, male gender, current smoking, and diastolic blood pressure were all significantly correlated with the myocardial functional deterioration after adjustment for baseline Ecc values both in categorical and continuous variable analyses (Table III). Participants with CRP >3 mg/L had a higher prevalence of Ecc deterioration compared with participants with CRP ≤3mg/L (20% vs 12%, P = .003).

C-reactive protein as an independent predictor of regional myocardial functional deterioration

In linear regression analysis, higher CRP was related to functional deterioration independent of age, gender, and ethnicity (B = 0.08; ΔEcc change per 1-mg/L CRP change, 95% CI 0.04-0.13, P < .001, model 1). In model 2, which included systolic blood pressure, heart rate, diabetes,

Table II. Comparisons of baseline demographics, risk factors, and medications between the definite deterioration group and the other group

	Definite deterioration (n = 112)	Remainder (n = 673)	*P*
Age (y)	64.5 ± 9.9	63.7 ± 9.2	.45
Female, n (%)	50 (45)	336 (50)	.30
Body mass index (kg/m^2)	27.4 ± 5.1	27.8 ± 4.6	.48
Heart rate (beats/min)	62.4 ± 9.9	62.3 ± 9.2	.96
Hypertension, n (%)	54 (48)	313 (47)	.74
Diabetes, n (%)	14 (12)	81 (12)	.89
Ethnicity, n (%)			
Non-Hispanic white	41 (37)	200 (30)	.14
Chinese American	12 (11)	127 (19)	.04
African American	36 (32)	164 (24)	.08
Hispanic	23 (21)	182 (27)	.15
Current smoking, n (%)	19 (17)	60 (9)	.008
LDL cholesterol (mg/dL)	118.7 ± 32.0	118.9 ± 31.5	.95
HDL cholesterol (mg/dL)	50.6 ± 14.5	51.1 ± 15.0	.76
Urine albumin/creatinine (mg/g)	12.5 ± 20.4	16.3 ± 46.2	.40
CRP* (mg/L)	2.4 (1.0-5.4)	1.6 (0.8-3.5)	.005
Presence of coronary calcium, n (%)	65 (58)	346 (51)	.19
LV ejection fraction (%)	70.3 ± 7.0	69.1 ± 7.5	.12
LV mass index (g/m^2)	80.0 ± 16.6	77.6 ± 16.4	.17

LDL, low-density lipoprotein; HDL, high-density lipoprotein.
* Median (interquartile range).

smoking status (never, former, current), body mass index, current medication use (antihypertensive therapy, aspirin, and statins), and glomerular filtration rate in addition to model 1 covariates, higher CRP was also related to Ecc deterioration (B = 0.10, 0.05-0.14, P < .001). In model 3, we included indices of subclinical cardiovascular disease (LV mass, presence of coronary calcium) as well as interim myocardial infarction and coronary revascularization in addition to model 2 covariates. Higher CRP remained related to Ecc deterioration (B = 0.09, 0.05-0.14, P < .001). Moreover, the relationship remained statistically significant after adjustment for baseline Ecc in model 4 (B = 0.06, 0.02-0.10, P = .002). Even after systolic blood pressure was replaced by diastolic blood pressure, relation between CRP and Ecc change remained significant. Finally, in a sensitivity analysis, after exclusion of participants with interim myocardial infarction or coronary revascularization, higher CRP was still significantly related to Ecc deterioration. Importantly also, in logistic regression analysis, higher CRP was significantly correlated with definite myocardial deterioration using the same models (Table IV).

Discussion

In this study, we found that elevated levels of CRP were significantly associated with future regional myocardial functional deterioration in asymptomatic individuals independent of coronary artery disease and its clinical consequences. To the best of our knowledge, the present study is the first longitudinal population study to demonstrate the relationship between inflammation and progressive myocardial dysfunction. Our results might provide mechanistic support to the well-established association of elevated CRP with incident HF, suggesting, therefore, that inflammation may have an active role in the pathogenesis of HF.

Age-related changes in circumferential shortening

Myocardial Ecc is a sensitive indicator of ventricular function and is more reliable than indices of global ventricular function for the assessment of myocardial mechanics.[7] Detection of subclinical myocardial dysfunction could potentially identify asymptomatic individuals at high risk for the development of HF, which could be systolic or diastolic.[13] We found that a subset of MESA participants with heightened inflammation as surrogated by increased baseline CRP had experienced subsequence deterioration of circumferential mid–myocardial function during the 5 years of this study, despite the absence of interim myocardial infarction or other clinical manifestations of coronary artery disease. Such deterioration could have been caused by microvascular dysfunction, age-related subclinical interstitial fibrosis, or worsening of calcium-ATP metabolism accompanied by adverse ventricular remodeling, among other potential mechanisms.[14] Meanwhile, many participants exhibited an increase in circumferential shortening during the 5 years of follow-up. This might be explained by different loading conditions between the baseline and follow-up examinations, measurement error or true functional improvement due to therapy, lifestyle changes, and compensatory hypertrophy to maintain ejection fraction in the face of increased blood pressure and vascular stiffness.[15,16] In our results, hypertensive people, especially angiotensin-converting enzyme inhibitor users, were significantly related to Ecc improvement, which supports the presence of compensatory mechanism in preclinical hypertensive population.[15] To reduce the effects of different loading conditions as well as other sources of variability at each examination, we considered definite regional myocardial functional deterioration as Ecc deterioration greater than 1 SD in average myocardial Ecc at the mid-LV cross-sectional level. In addition, we also analyzed change in myocardial strain as a continuous variable using linear regression analysis.

Inflammation and regional myocardial dysfunction

In our study, the group with the highest CRP quartile exhibited a significantly higher prevalence of current smoking, hypertension, higher body mass index, and LV mass. This finding might suggest that CRP would simply be a mediator of other risk factors thought to be associated with myocardial functional deterioration.

Table III. Predictors of definite myocardial functional deterioration and ΔEcc after adjustment for baseline Ecc

	Definite deterioration group			ΔEcc		
Variables	**OR**	**95% CI**	***P***	***B***	**95% CI**	***P***
Age, per year	1.01	0.10-1.03	.38	0.005	−0.02 to 0.03	.65
Male	1.63	1.06-2.52	.03	0.70	0.32-1.08	<.001
Body mass index, per kg/m^2	1.02	0.97-1.06	.52	0.003	−0.04 to 0.04	.90
Systolic blood pressure, per mm Hg	1.01	0.99-1.02	.12	0.002	−0.008 to 0.01	.74
Diastolic blood pressure, per mm Hg	1.02	0.99-1.04	.18	0.02	0.005-0.04	.01
Hypertension	1.30	0.84-2.00	.24	0.04	−0.34 to 0.42	.84
Diabetes	1.41	0.73-2.72	.30	0.31	−0.27 to 0.89	.29
Current smoking	2.11	1.52-2.91	<.001	1.35	0.73-1.97	<.001
Statin use	1.32	0.77-2.26	.32	0.20	−0.29 to 0.69	.42
Aspirin use	1.42	0.86-2.35	.17	0.07	−0.38 to 0.51	.77
β-Blocker use	1.52	0.79-2.93	.21	0.26	−0.38 to 0.89	.43
ACE inhibitor use	0.76	0.45-1.80	.76	−0.25	−0.81 to 0.31	.38
ARB use	1.54	0.66-3.62	.32	0.21	−0.60 to 1.03	.61
Urine albumin/ creatinine, per mg/g	1.00	0.99-1.01	.51	−0.001	−0.006 to 0.003	.57
LV mass index, per 1 g/m^2	1.02	1.01-1.04	.002	0.03	−0.87 to −0.72	<.001
LV ejection fraction, per 1%	1.00	0.95-1.02	.46	−0.05	−0.08 to −0.03	<.001
Presence of coronary calcium	1.32	0.86-2.03	.21	0.21	−0.17 to 0.58	.28
CRP, per 1 mg/dL	1.07	1.04-1.11	<.001	0.06	0.03-0.097	.001

ACE, Angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker.

Table IV. Multivariable analysis for the ΔEcc and definite myocardial functional deterioration with CRP

	Linear regression			Logistic regression			Linear regression (after excluding subjects with interim events)		
	B*	**95% CI**	***P***	**OR**	**95% CI**	***P***	***B****	**95% CI**	***P***
Model 1	0.081	0.036-0.126	<.001	1.074	1.035-1.114	<.001	0.084	0.039-0.129	<.001
Model 2	0.099	0.052-0.145	<.001	1.092	1.046-1.139	<.001	0.100	0.054-0.147	<.001
Model 3	0.098	0.049-0.147	<.001	1.102	1.051-1.156	<.001	0.102	0.053-0.152	<.001
Model 4	0.061	0.022-0.099	.002	1.078	1.026-1.132	.003	0.061	0.023-0.100	.002

Model 1: age, gender, and ethnicity as covariates; model 2: model 1 + systolic blood pressure, heart rate, diabetes, smoking status, body mass index, current medications, and estimated glomerular filtration rate; model 3: model 2 + LV mass, presence of coronary calcium, interim myocardial infarction, or coronary revascularization; model 4: model 3 + baseline Ecc.

*The differences in ΔEcc (%) per 1-mg/L change in CRP.

However, in multivariable analyses, elevated CRP was correlated with future Ecc deterioration after adjustment for these CRP-influencing conditions. Therefore, it is possible that, regardless of the origin of elevated CRP, long-standing exposure to chronic inflammation might actively contribute to progressive myocardial dysfunction through activation of the complement system, promotion of endothelial dysfunction, or direct myocyte injury.[6,17]

In univariate analyses, male gender, current smoking, and higher LV mass index, all of which are related to the development of silent myocardial infarction, exhibited significant direct relationships with myocardial functional deterioration. On the other hand, higher CRP remained significantly associated with myocardial functional deterioration after adjustment for coronary risk factors and coronary calcification as well as interim symptomatic

myocardial infarction and coronary revascularization. Although it is still possible that asymptomatic micro-infarcts contribute to progressive myocardial dysfunction among asymptomatic individuals, we did not assess the presence of myocardial scar with contrast MRI in this study. Nevertheless, if significant in magnitude, such contribution appears to be, at least in part, mediated by inflammation.

There are controversies regarding beneficial effects of anti-inflammatory agent on HF. Tumor necrosis factor α inhibitors failed to achieve beneficial effects on HF.[18] However, statin therapy achieved some beneficial effects on higher CRP subgroup by actively reducing CRP level in patients with advanced HF in CORONA study.[19] This finding raised the question about in which stage inflammation can contribute to HF or whether there is any difference among anti-inflammatory agents. Our study could approach neither which inflammatory stage can affect myocardial functional change nor the effects of anti-inflammatory agents. However, based on our results, CRP, a downstream inflammatory biomarker, is at least related to progressive myocardial function in subclinical stage, suggesting that elevated CRP is not just redundant of HF. Our results support the concept that, even among asymptomatic subjects, risk stratification based on CRP might be useful for assessing the risk and progression of cardiovascular disease in general and of myocardial dysfunction.[5] Our study results provide a link between observed cross-sectional relationships and the development of HF.

Methodological consideration and study limitations

This study has some limitations. First, we analyzed high-sensitive CRP values assessed only at baseline examination. C-reactive protein values can vary according to conditions such as systemic or local inflammation; however, CRP has been shown to be relatively stable in the absence of active inflammation, and less than 5% of the participants in the present study had levels higher than 10 mg/L, suggesting active systemic inflammation.[20] Second, the myocardial region of interest in which we measured myocardial strain may not exactly match between the 2 MRI tagging examinations from a single individual. In this regard, specific efforts were taken during the follow-up examination by using the baseline study for guiding the same anatomical location. Third, participants in this study have a lower body mass index and a lower CRP compared with the whole MESA population possibly from selection bias for MRI and higher prevalence of Chinese in this study compared with the whole MESA population (18% vs 12%). However, these limitations might not affect much on the results because we used both categorical and continuous endpoints, number of Chinese population was still lower than other ethnicity, and possible exclusion of highly obese participants who were not to fit in scanner was unavoidable and infrequent.

Conclusion

We found that elevated high-sensitive CRP is an independent predictor of myocardial functional deterioration among asymptomatic adult individuals without history of heart disease. This finding may, in part, explain the previously documented association of CRP with incident HF in population-based studies including the MESA cohort. They also support continued research on the impact of anti-inflammatory therapies,[19] for prophylaxis of myocardial functional deterioration.

Disclosures

The authors are solely responsible for the design and conduct of this study, all study analyses, and drafting and editing of the manuscript.

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