Cystatin C, Left Ventricular Hypertrophy, and Diastolic Dysfunction: Data From the Heart and Soul Study

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ABSTRACT

Background: Impaired kidney function, as measured by serum cystatin C, is associated with risk of incident heart failure. Whether cystatin C is associated with preclinical cardiac structural abnormalities is unknown. We evaluate whether cystatin C is associated with left ventricular hypertrophy, diastolic dysfunction, and systolic dysfunction among 818 outpatients with coronary artery disease who were free of clinical heart failure.

Methods and Results: The 818 study participants were categorized into quartiles based on serum cystatin C concentrations, with ≤0.91 mg/L constituting the lowest quartile (I) and ≥1.28 mg/L constituting the highest (IV). Left ventricular hypertrophy (left ventricular mass index >90 g/m^2 by truncated ellipsoid method), diastolic dysfunction (impaired relaxation, pseudo-normal, or restrictive filling patterns) and systolic dysfunction (left ventricular ejection fraction ≤50%) were determined by echocardiography. Left ventricular hypertrophy was present in 68% of participants in quartile IV, compared with 44% of those in quartile I (adjusted odds ratio [OR] 2.17; 95% confidence interval [CI] 1.34 to 3.52; $P = .002$). Diastolic dysfunction was present in 52% of participants in quartile IV, compared with 24% of those in quartile I (adjusted OR 1.79; 95% CI 1.04 to 3.11; $P = .04$). Systolic dysfunction was present in 12% of those in quartile IV, compared with 6% of those in quartile I (adjusted OR 1.83; 95% CI 0.75 to 4.46; $P = .15$).

Conclusion: Higher cystatin C concentrations are strongly associated with left ventricular hypertrophy and diastolic dysfunction in outpatients with coronary artery disease and without heart failure.

Key Words: Heart failure, Echocardiography, Kidney, Structure.

Cystatin C is a novel endogenous marker of kidney function that obviates many of the limitations of serum creatinine as an endogenous marker of glomerular filtration rate (GFR).[1−3] Serum concentrations of cystatin C appear to be unaffected by age, sex, or muscle mass and are more sensitive to mild decrements in GFR than serum creatinine.[1,3−8] Recently, higher cystatin C concentrations were demonstrated to be associated with incident heart failure among a community-based cohort.[9] Because cystatin C may be a more sensitive and accurate marker of kidney function than serum creatinine, creatinine based estimates of glomerular filtration (eGFR), or creatinine clearance, its application may provide opportunities to gain insight into the mechanisms responsible for the association between chronic kidney disease and heart failure and for detection of cardiac structural abnormalities earlier in the course of disease. However, whether cystatin C is associated with particular cardiac structural and functional abnormalities that precede the onset of heart failure is not known.

In the current study, we examined the associations of serum cystatin C with left ventricular hypertrophy (LVH),

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Table 1. Baseline Characteristics of Participants Without Heart Failure by Cystatin C Quartiles

		Cystatin C Quartiles				
Cut points (mg/L)	Study Sample	I ≤0.91	II 0.92−1.05	III 1.06−1.27	IV ≥1.28	
Number	818	211	203	203	201	*P* Value
Demographics						
Age (years) ± SD	67 ± 11	61 ± 10	65 ± 9	69 ± 10	72 ± 11	<.001
Male (%)	666 (82)	149 (71)	167 (83)	179 (89)	171 (85)	<.001
Race						.02
Caucasian (%)	490 (60)	108 (51)	125 (62)	126 (63)	131 (65)	
African American (%)	125 (15)	47 (22)	31 (15)	27 (13)	20 (10)	
Other (%)	199 (25)	56 (27)	45 (22)	48 (24)	50 (25)	
Medical history						
Myocardial infarction (%)	408 (51)	94 (45)	104 (52)	92 (46)	118 (59)	.02
Stroke (%)	98 (12)	22 (11)	24 (12)	23 (12)	29 (14)	.66
Diabetes mellitus (%)	194 (24)	47 (22)	47 (24)	38 (19)	62 (31)	.04
Measurements						
Estimated glomerular filtration rate (mL·min·1.73m^2) ± SD	77 ± 23	95 ± 18	84 ± 17	75 ± 15	55 ± 17	<.001
Systolic blood pressure (mm Hg) ± SD	133 ± 21	131 ± 18	130 ± 20	135 ± 22	138 ± 23	.20
Diastolic blood pressure (mm Hg) ± SD	75 ± 11	77 ± 10	74 ± 11	74 ± 12	75 ± 12	.72
Anemia (Hg ≤12 g/dL) (%)	81 (10)	13 (6)	10 (5)	16 (8)	42 (21)	<.001
C-reactive protein (mg/dL)*	2.1 (0.8−4.5)	1.4 (0.5−3.6)	1.7 (0.6−3.5)	2.4 (1.0−5.5)	2.9 (1.5−6.3)	<.001
Medications						
Aspirin (%)	633 (78)	153 (77)	171 (80)	151 (75)	158 (79)	.66
β-blocker (%)	453 (56)	93 (47)	120 (56)	113 (56)	127 (63)	.01
Angiotensin-converting enzyme inhibitor (%)	385 (47)	68 (34)	100 (47)	101 (50)	116 (58)	<.001
Echocardiographic measures						
End-systolic volume (mL)*	91 (75−112)	85 (71−105)	94 (76−115)	92 (76−113)	92 (73−114)	.12
End-diastolic volume (mL)*	32 (25−43)	30 (23−40)	33 (25−45)	32 (26−45)	35 (26−45)	.02
Left ventricular mass (g) ± SD	187 ± 54	176 ± 51	180 ± 48	191 ± 57	201 ± 58	<.001
LV mass/end-diastolic volume (g/mL)*	1.9 (1.6−2.4)	1.9 (1.7−2.2)	1.8 (1.5−2.2)	1.9 (1.6−2.4)	2.1 (1.7−2.6)	<.001
Septal wall thickness (mm) ± SD	1.20 ± 0.24	1.17 ± 0.18	1.16 ± 0.20	1.23 ± 0.28	1.25 ± 0.26	<.001
Posterior wall thickness (mm) ± SD	1.16 ± 0.28	1.10 ± 0.15	1.13 ± 0.17	1.19 ± 0.46	1.20 ± 0.22	.001
Stroke volume (mL) ± SD	58 ± 27	57 ± 24	59 ± 27	60 ± 17	55 ± 35	.22
Mitral early velocity (E) (cm/s) ± SD	77 ± 22	76 ± 20	77 ± 21	76 ± 21	77 ± 25	.80
Mitral atrial velocity (A) (cm/s) ± SD	78 ± 25	76 ± 25	76 ± 25	80 ± 24	81 ± 25	0.16
Early/atrial ratio ± SD	1.1 ± 0.4	1.1 ± 0.4	1.1 ± 0.4	1.0 ± 0.4	1.0 ± 0.6	0.44

*Median (interquartile range).

diastolic dysfunction, and systolic dysfunction, in a cross-sectional study among 818 outpatients with coronary artery disease who were free of clinical heart failure. We hypothesized that elevated cystatin C would be associated with LVH, diastolic dysfunction, and systolic dysfunction.

Methods

Participants

The Heart and Soul Study is a prospective cohort designed to investigate the influence of psychosocial factors on coronary artery disease progression. Methods have been described previously.[10−12] Briefly, participants were recruited from several outpatient clinics in the San Francisco Bay Area if they met one of the following inclusion criteria: (1) history of myocardial infarction; (2) angiographic evidence of >50% stenosis in 1 or more coronary vessels; (3) evidence of exercise-induced ischemia by treadmill or nuclear testing; (4) history of coronary revascularization; or (5) documented diagnosis of coronary artery disease by an internist or cardiologist. Participants were excluded if they were not able to walk 1 block, had a myocardial infarction within the prior 6 months, or were likely to move out of the area within 3 years. The study protocol was approved by the appropriate Institutional Review Boards and all participants provided written informed consent.

Between September 2000 and December 2002, a total of 1024 individuals enrolled and underwent a day-long baseline study appointment that included a medical history interview, a physical examination, an exercise treadmill test with rest and stress echocardiography, and a comprehensive health status questionnaire. Fasting (12-hour) venous samples were drawn and serum was frozen at −70°C. Subjects for whom frozen serum was not available (n = 32) or who reported a history of heart failure (n = 174) were excluded, resulting in a final study sample of 818 participants for the present analysis. Because the determination of diastolic function requires accurate assessment of systolic and diastolic pulmonary venous flow, participants who were not in sinus rhythm, had moderate or severe mitral regurgitation, or for whom the presence of diastolic dysfunction could not be determined for other reasons were also excluded from the diastolic function analysis (n for diastolic function = 693).

Measurements

Kidney Function. Serum cystatin C was measured from frozen samples collected at the study visit using a BNII nephelometer (Dade Behring, Inc., Deerfield, IL) with a particle-enhanced

Table 2. Associations of Cystatin C Quartiles with Left Ventricular Hypertrophy, Diastolic Dysfunction, and Systolic Dysfunction

	Cystatin C Quartiles								
	I ≤0.91		II 0.92−1.05		III 1.06−1.27		IV ≥1.28		
Range (mg/L)	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	*P* for Trend
Left ventricular hypertrophy									
Unadjusted	1.00	Reference	0.95	0.64−1.40	1.56	1.06−2.31	2.72	1.82−4.06	<.001
Adjusted[†]	1.00	Reference	0.78	0.51−1.19	1.20	0.78−1.87	2.17	1.34−3.52	<.001
Diastolic dysfunction[*]									
Unadjusted	1.00	Reference	1.35	0.84−2.16	2.00	1.28−3.21	3.56	2.23−5.68	<.001
Adjusted[‡]	1.00	Reference	1.04	0.62−1.75	1.26	0.75−2.13	1.79	1.04−3.11	.02
Systolic dysfunction									
Unadjusted	1.00	Reference	1.04	0.47−2.31	1.41	0.67−2.98	2.16	1.07−4.36	.02
Adjusted[‖]	1.00	Reference	0.74	0.31−1.80	1.00	0.41−2.44	1.83	0.75−4.46	.15

*Excludes participants not in sinus rhythm or with moderate or greater mitral regurgitation. n = 693.
[†]Adjusted for age, sex, race/ethnicity, tobacco use, alcohol use, history of myocardial infarction, serum albumin, and diuretic use.
[‡]Adjusted for age, sex, race/ethnicity, tobacco use; history of myocardial infarction, coronary bypass, or diabetes mellitus; systolic blood pressure, anemia, low-density lipoprotein cholesterol, and C-reactive protein.
[‖]Adjusted for age, sex, race/ethnicity; history of myocardial infarction, tobacco use, and physical activity; systolic blood pressure, diastolic blood pressure; serum albumin; total, high-density lipoprotein and low-density lipoprotein cholesterol; and aspirin use.

immunonephelometric assay (N Latex Cystatin C, Dade Behring, Inc.).[13] Monoclonal antibodies to cystatin C were coated on polystyrene particles, which agglutinate to increase the intensity of scattered light in proportion to the concentration of cystatin C. The assay range is 0.195 to 7.330 mg/L; the reference range for young healthy persons ranges from 0.53 to 0.95 mg/L. The intra-assay coefficient of variation ranges from 2.0% to 2.8%, and the interassay coefficient of variation ranges from 2.3% to 3.1%.

Estimated GFR was determined by the modified (4 variable) Modification of Diet and Renal Disease study formula:

$$\text{eGFR} = 186 \times \left(\text{serum creatinine}^{-1.154}\right) \times \left(\text{age}^{-0.203}\right) \times (0.742 \text{ if female}) \times (1.21 \text{ if black}).^{14}$$

Cardiac Structure and Function. All participants underwent transthoracic echocardiography at rest on the same day as their serum cystatin C was measured. An Acuson Sequoia ultrasound system (Mountain View, CA) using a 3.5-MHz transducer was used to perform a complete 2-dimensional echocardiogram, including Doppler imaging in all standard views and subcostal imaging of the inferior vena cava. We obtained standard 2-dimensional parasternal short axis and apical 2- and 4-chamber views during suspended inspiration. An expert cardiologist (NBS) who was blinded to all clinical information including cystatin C concentrations interpreted the echocardiograms.

We measured left ventricular mass on echocardiography according to the truncated ellipsoid method.[15] We considered participants who had left ventricular mass index >90 g/m^2 to have LVH.[16,17] For categorization of diastolic function, we evaluated whether the velocity-time integral in the pulmonary veins was greater during systole (systolic dominant) or during diastole (diastolic dominant). Participants with systolic dominant velocity-time integrals were further subdivided into patterns of normal relaxation (E/A wave ratio >1) and impaired relaxation (E/A wave ratio ≤1). Similarly, participants with diastolic dominant velocity-time integrals were subcategorized into pseudo-normal patterns (E/A wave ratio >1 but ≤2) and restrictive patterns (E/A wave ratio >2). Participants who had impaired relaxation, pseudo-normal, or restrictive patterns were considered to have diastolic dysfunction.[18,19] Left ventricular ejection fraction was determined by the American Society of Echocardiography recommended biplane method of disks.[20] We defined systolic dysfunction as left ventricular ejection fraction ≤50%.[21]

Other Measurements. Baseline demographics and medical history were determined by self-reported questionnaire. Age, sex, and race or ethnicity were obtained by questionnaire. Participants were instructed to bring their medication bottles to the study appointment, and study personnel recorded all current medications. We considered participants users of β-blockers, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, calcium channel blockers, or diuretics if they reported taking these medications daily. We considered participants users of aspirin if they took it weekly or more.

Statistical Analysis

As age-, sex-, and race-specific ranges for serum cystatin-C have not been established, we categorized cystatin C into quartile groups. Differences in baseline characteristics were compared using analysis of variance or the Kruskal-Wallis test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate. We used multivariable logistic regression analyses to evaluate the association between the primary predictor variable (cystatin C quartiles) and each of the 3 dichotomous outcomes (LVH, diastolic dysfunction, and systolic dysfunction). Covariates for adjustment were selected with use of a model that included cystatin C as a continuous predictor of each of the 3 outcomes. Candidate covariates included all variables in Table 1, except for the echocardiographic measures. Additional candidate covariates included a history of hypertension, coronary revascularization, body mass index, regular alcohol use, physical activity scale, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol cholesterol, triglycerides, serum albumin, diuretic use, and statin use. Covariates were then individually removed from the model beginning

with the least significant. Covariates for which deletion resulted in a change in the beta coefficient between cystatin C and the outcome by more than 5% were retained in the final adjusted model. For each outcome, the same covariates were entered into models for categories of cystatin C and estimated GFR. We calculated odds ratios and 95% confidence intervals from model parameter coefficients and standard errors, respectively. Two-tailed *P* values $<.05$ were considered statistically significant. Analyses were performed using the Stata statistical software (version 9, College Station, TX).

Results

Among the 818 participants, the mean age was 67 years, 82% were male and 40% were non-white. The median concentration of cystatin C was 1.05 mg/L (interquartile range 0.91 to 1.28 mg/L). Baseline characteristics of the study sample by cystatin C quartile groups are shown in Table 1. Compared with those in the lowest cystatin C quartile ($\leq$0.91 mg/L), participants in the high cystatin C quartile ($>$1.28 mg/L) were older and more often male and Caucasian. Additionally, they more often had a history of myocardial infarction and diabetes mellitus. Blood pressures were similar among groups, whereas higher cystatin C was associated with anemia, increased C-reactive protein concentrations, and use of β-blockers and angiotensin-converting enzyme inhibitors. As anticipated, estimated GFR was lower among persons with higher cystatin C. As compared with the lowest cystatin C quartile, participants with higher cystatin C quartiles had higher end-diastolic volumes, increased left ventricular mass, increased left ventricular mass to volume ratio, and higher septal and posterior wall thicknesses.

Left Ventricular Hypertrophy

As compared with participants in the lowest cystatin C quartile (I), those in the highest quartile (IV) were significantly more likely to have LVH; an association that remained significant after multivariable adjustment (Table 2, Fig. 1). For comparison, we also evaluated the association of quartiles of estimated GFR with LVH. Participants in the lowest estimated GFR quartile were more likely to have LVH than individuals in the highest quartile in crude analysis. After multivariable adjustment for identical covariates as in the cystatin C model, this association remained statistically significant, albeit with weaker associations as compared with the cystatin C model (Table 3, Fig. 1).

Diastolic Dysfunction

Compared with participants in the lowest cystatin C quartile, those in the highest quartile were more likely to have diastolic dysfunction, an association that remained significant after multivariable adjustment (Table 2, Fig. 1). This association persisted despite further adjustment for left ventricular mass index (adjusted OR comparing quartile IV versus I 1.72; 95% CI 0.98 to 3.01; P = 0.06; *P* for trend = .05).

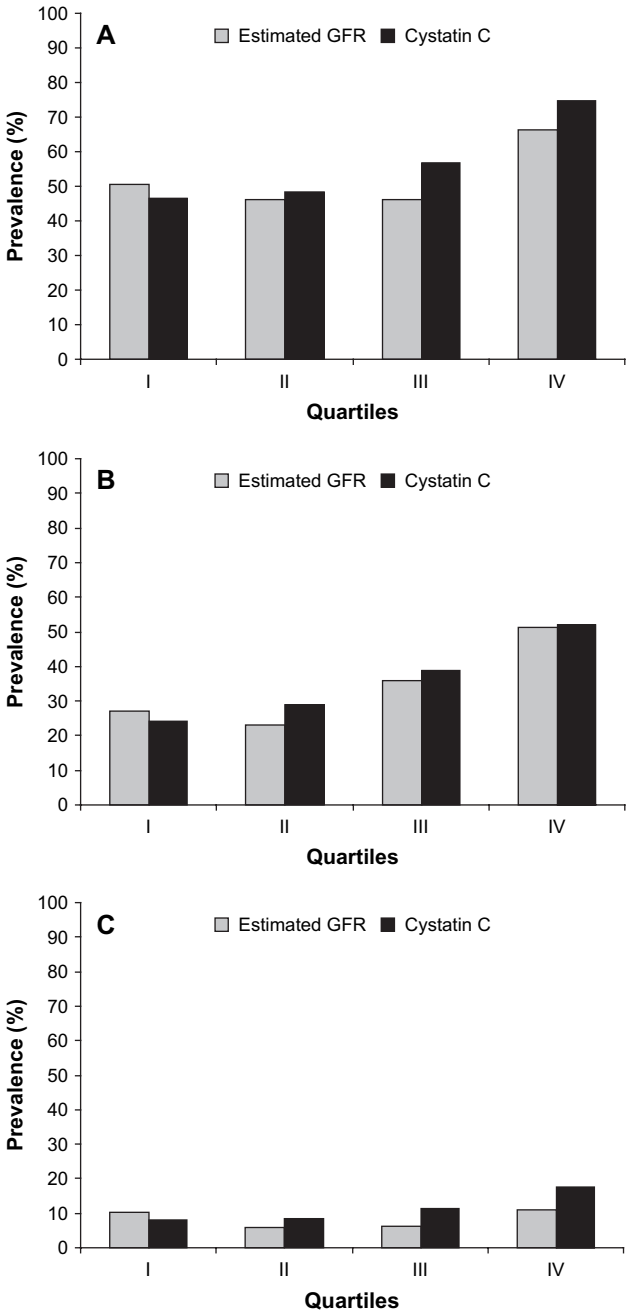

Fig. 1. Proportion with ventricular dysfunction by kidney function quartile groups among persons without heart failure. (A) Left ventricular hypertrophy. (B) Diastolic dysfunction. (C) Systolic dysfunction.

Although we had limited statistical power to determine associations of cystatin C quartiles with impaired, pseudo-normal, and restrictive diastolic function as individual outcomes, we observed increased prevalence all three abnormalities with increasing cystatin C quartiles (Table 4).

For comparison, in unadjusted analysis, the lowest quartile of estimated GFR was also associated with diastolic dysfunction when compared with the highest quartile in

Table 3. Associations of Estimated GFR Quartiles with Left Ventricular Hypertrophy, Diastolic Dysfunction, and Systolic Dysfunction

	Estimated GFR Quartiles								
	I >90		II 77−90		III 63−76		IV ≤62		
Range (mL·min·1.73m^2)	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	*P* for Trend
Left ventricular hypertrophy									
Unadjusted	1.00	Reference	0.84	0.57−1.24	0.84	0.57−1.24	1.91	1.28−2.86	.003
Adjusted[†]	1.00	Reference	0.76	0.49−1.17	0.76	0.49−1.18	1.65	1.03−2.64	.05
Diastolic dysfunction*									
Unadjusted	1.00	Reference	0.90	0.56−1.46	1.65	1.05−2.60	3.05	1.93−4.81	<.001
Adjusted[‡]	1.00	Reference	0.52	0.30−0.90	1.08	.065−1.81	1.36	0.79−2.37	.06
Systolic dysfunction									
Unadjusted	1.00	Reference	0.55	0.26−1.15	0.59	0.29−1.22	1.08	0.57−2.02	.79
Adjusted[‖]	1.00	Reference	0.74	0.32−1.72	0.78	0.33−1.85	1.26	0.55−2.89	.58

*Excludes participants not in sinus rhythm or with moderate or greater mitral regurgitation. n = 693.
[†]Adjusted for age, sex, race/ethnicity, tobacco use, alcohol use, history of myocardial infarction, serum albumin, and diuretic use.
[‡]Adjusted for age, sex, race/ethnicity, tobacco use; history of myocardial infarction, coronary bypass, or diabetes mellitus; systolic blood pressure, anemia, low-density lipoprotein cholesterol, and C-reactive protein.
[‖]Adjusted for age, sex, race/ethnicity; history of myocardial infarction, tobacco use, and physical activity; systolic blood pressure, diastolic blood pressure; serum albumin; total, high-density lipoprotein and low-density lipoprotein cholesterol; and aspirin use.

crude analysis. However, this association was attenuated and no longer statistically significant after multivariable adjustment for identical covariates as in the cystatin C model (Table 3).

Systolic Dysfunction

The prevalence of systolic dysfunction was 12% in the highest cystatin quartile group, compared with 6% in those within the lowest quartile (Fig. 1). Although significant in unadjusted analysis, the association of cystatin C quartiles with systolic dysfunction was attenuated and no longer statistically significant after multivariable adjustment (Table 2). When evaluating the mean left ventricular ejection fraction by cystatin C quartiles, there was a significant inverse correlation in crude analyses (higher cystatin C was associated with lower left ventricular ejection fraction, *P* for trend = .002), but after multivariable adjustment, the association was attenuated and of marginal statistical significance (adjusted mean left ventricular ejection fraction 63% [95% CI; 62% to 65%] in quartile I and 61% [95% CI; 60% to 62%] in quartile IV, *P* for trend = 0.06). We observed no statistically significant association of estimated GFR with either systolic dysfunction (Table 3) or with left ventricular ejection fraction (unadjusted and adjusted *P* values were .21 and .17, respectively).

Discussion

We found that elevated serum concentrations of cystatin C were strongly associated with LVH and diastolic dysfunction among outpatients with coronary artery disease and without clinical heart failure. These results may help explain the high rates of incident heart failure among persons with elevated serum cystatin C previously observed in community based cohorts.[9]

These observations have several important implications. First, the associations of cystatin C with diastolic dysfunction were strong in comparison to the associations with systolic dysfunction. Previous longitudinal studies have shown that presence of diastolic dysfunction predicts subsequent development of diastolic heart failure.[22] Therefore, our results would support the hypothesis that elevated concentrations of cystatin C may disproportionately predict development of diastolic heart failure as compared with systolic heart failure. In this study, we observed stronger associations of cystatin C with each outcome as compared

Table 4. Distribution of Diastolic Function by Cystatin C Quartile Groups*

	Cystatin C Quartile Group			
Diastolic Function	I	II	III	IV
Normal (%)	136 (77)	134 (72)	110 (63)	75 (50)
Impaired relaxation (%)	31 (18)	31 (17)	51 (29)	58 (38)
Pseudo-normal (%)	7 (4)	14 (8)	8 (6)	11 (7)
Restrictive (%)	3 (2)	7 (4)	7 (4)	10 (7)

P value (chi^2) <.001.
*Includes the subset evaluated for diastolic dysfunction (n = 693).

with estimated GFR. This observation is consistent with prior studies demonstrating that cystatin C more accurately predicts risk of incident heart failure compared with serum creatinine among adult ambulatory cohorts,[9] and prior studies among pediatric populations demonstrating associations of cystatin C with diastolic dysfunction that were not observed with serum creatinine.[23] Finally, because serum cystatin C concentrations increase with age,[24] and serum creatinine is particularly insensitive to decrements of kidney function among the elderly,[25] our findings raise the possibility that previously unrecognized age associated declines in kidney function may explain the increased prevalence of diastolic heart failure in the elderly.[26,27]

These findings may also provide new insights to the pathophysiology of diastolic dysfunction. In most cases, the presence of LVH is thought to be of primary importance in the development of diastolic heart failure,[28,29] though causes of diastolic heart failure in the absence of LVH (cardiac fibrosis, ischemia, and constrictive pericarditis) are recognized. The physical properties of a thickened left ventricular wall are generally believed to contribute to an increase in the passive stiffness and to a steep diastolic pressure-volume relationship leading to diastolic dysfunction. However, the association between cystatin C and diastolic dysfunction shown here was evident even after statistical adjustment for left ventricular mass index. Kitzman and colleagues have previously reported that advanced age was associated with diastolic dysfunction independent of left ventricular mass or loading conditions.[30] Our findings suggest that mild decrements in kidney function, as detected by elevated cystatin C concentrations, may also predispose persons to diastolic heart failure through mechanisms that do not require an increased left ventricular mass.

Several limitations should be considered when interpreting our results. First, we had hypothesized that elevated serum cystatin C concentrations would be associated with systolic dysfunction. Although we observed such an association in bivariate analysis, the association was markedly attenuated and no longer statistically significant after multivariable adjustment. The association of increasing quartiles of cystatin C with adjusted mean left ventricular ejection fraction—a more powerful statistical test—was of marginal statistical significance ($P = .06$). Because the prevalence of systolic dysfunction was relatively low among our study sample (8%), the absence of a statistically significant association may reflect limited power and should be confirmed in future studies. Next, because of the cross-sectional design, our study cannot address the causal direction of the association between cystatin C and diastolic dysfunction and LVH. With regard to diastolic dysfunction, elevated cystatin C could theoretically be a result of decreased renal perfusion from reduced cardiac output. To minimize this possibility, we excluded participants who reported a history of heart failure, though self-reported history may be imperfect. Third, higher cystatin C concentrations may reflect longer duration or increased severity of established risk factors for LVH and diastolic dysfunction that may not have been adequately controlled for in our analyses, such as the duration and severity of hypertension. Further, we hypothesize that the association between serum concentrations of cystatin C and diastolic dysfunction shown here may predict disproportionately higher rates of diastolic heart failure in similar patient populations, which will need to be evaluated in cohorts with longitudinal outcomes data. Last, our study participants were mostly elderly men, and all had coronary artery disease. We are therefore not able to generalize our results to younger people, women, or to individuals without coronary disease. However, the range of cystatin C concentrations in our study is similar to that of other ambulatory cohorts in which cystatin C predicted cardiovascular risk.[9,31,32]

In summary, we found that serum cystatin C was strongly associated with LVH and diastolic dysfunction among outpatients with coronary artery disease, but without clinical heart failure. Cystatin C was more strongly associated with each outcome as compared with estimated GFR. The mechanisms underlying these associations and their potential clinical implications warrant future investigation.

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