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Pentraxin 3 Is a New Inflammatory Marker Correlated With Left Ventricular Diastolic Dysfunction and Heart Failure With Normal Ejection Fraction

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Objectives This study investigated the clinical significance of plasma pentraxin 3 (PTX3) levels in patients with heart failure with normal ejection fraction (HFNEF) and whether PTX3 is produced from coronary circulation.

Background Pentraxin 3 is a novel inflammatory marker and a member of pentraxin superfamily including C-reactive protein (CRP). The relationship between inflammatory markers and HFNEF remains unclear.

Methods We measured peripheral blood levels of PTX3, high-sensitivity CRP, tumor necrosis factor-alpha, and interleukin-6 in 323 patients comprising 82 HFNEF, 70 heart failure (HF) with reduced EF, and 171 non-HF patients. Levels of PTX3 were also measured at the aortic root and the coronary sinus in 75 patients.

Results The levels of PTX3, tumor necrosis factor-alpha, and interleukin-6, but not high-sensitivity CRP, were significantly higher in HFNEF patients than in non-HF patients. Multivariate logistic regression analysis identified only high levels of PTX3 as the independent inflammatory marker correlated with the presence of HFNEF in patients with normal left ventricular (LV) EF (odds ratio [OR]: 1.49, 95% confidence interval [CI]: 1.11 to 1.98, $p < 0.01$) and with the presence of left ventricular diastolic dysfunction (LVDD) in non-HF patients (OR: 1.23, 95% CI: 1.02 to 1.50, $p < 0.05$). Levels of PTX3 at the coronary sinus were significantly higher than at the aortic root in HFNEF patients ($p < 0.05$) and in non-HF patients with LVDD ($p < 0.01$), but not different in non-HF patients without LVDD ($p = 0.33$).

Conclusions Pentraxin 3 is significantly elevated in HFNEF patients and produced in the coronary circulation in patients with LVDD. Pentraxin 3, but not high-sensitivity CRP, is an independent inflammatory marker correlated with the presence of LVDD and HFNEF. (The Clinical Significance of Plasma Pentraxin 3 levels for Patients with Diastolic Heart Failure; UMIN000002170) (J Am Coll Cardiol 2011;57:861–9) © 2011 by the American College of Cardiology Foundation

Heart failure (HF) results from cardiac overload or injury as well as from a complex interplay among genetic, neurohormonal, and inflammatory factors. Biomarkers such as those for inflammation and neurohormones provide important information about the pathogenesis, risk stratification, diagnosis, and monitoring therapy of HF (1). Inflammatory markers are closely associated with the worst functional states, role of pathogenesis, and adverse prognoses in patients with HF. Pentraxin 3 (PTX3) is a newly identified member of the pentraxin superfamily, which includes C-reactive protein (CRP) and serum amyloid P. Pentraxin 3 is produced by various cell types following inflammatory stimuli (2). Pentraxin 3 might reflect local inflammatory status in tissues and is used as a new biomarker of inflammation (3).

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Abbreviations and Acronyms

BMI = body mass index
BNP = B-type natriuretic peptide
E/e′ = the mitral early diastolic peak flow velocity to tissue Doppler early mitral annular diastolic velocity
eGFR = estimated glomerular filtration rate
HF = heart failure
HFNEF = heart failure with normal ejection fraction
HFREF = heart failure with reduced ejection fraction
hsCRP = high-sensitivity C-reactive protein
IL = interleukin
LVDD = left ventricular diastolic dysfunction
LVEF = left ventricular ejection fraction
LVMI = left ventricular mass index
PTX3 = pentraxin 3
TNF = tumor necrosis factor

Pentraxin 3 was also implicated as a predictor of adverse clinical outcomes in patients with HF (4). Thus, there is considerable interest in PTX3 as a more useful and immediate inflammatory marker in cardiovascular medicine.

There are 2 types of HF: heart failure with reduced ejection fraction (HFREF) and heart failure with normal ejection fraction (HFNEF). However, the relationship between levels of inflammatory markers and HFNEF remains to be identified. The aims of the present study, therefore, were to determine the clinical significance of plasma PTX3 levels for HFNEF in patients with normal left ventricular ejection fraction (LVEF). We also investigated the correlation between inflammatory biomarkers and left ventricular diastolic dysfunction (LVDD) among non-HF patients. Furthermore, we investigated whether PTX3 could be produced from a heart with LVDD.

Methods

Study subjects and protocol. We screened 181 HF patients with New York Heart Association functional class II to IV who were referred to Kumamoto University Hospital, Kumamoto, Japan, from January to December 2008. In each patient, echocardiography was performed. We finally analyzed 82 HFNEF and 70 HFREF patients (Fig. 1). This study also enrolled 171 control subjects without HF (non-HF patients). Venous blood samples were obtained at stable and fasting condition to measure levels of serum high-sensitivity CRP (hsCRP), plasma PTX3, tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), B-type natriuretic peptide (BNP), and other biochemical markers. Pentraxin 3 was measured using a high-sensitivity enzyme-linked immunosorbent assay system (Perseus Proteomics, Tokyo, Japan). An expanded methods section is available in the Online Appendix.

The study was approved by the ethics review committee of our institution and a signed informed consent was obtained from each patient before participation. This study was registered at the University Hospital Medical Information Network protocol registration system.

Statistical analysis. Normally distributed results were expressed as mean ± SD. The values of PTX3, hsCRP, TNF-alpha, IL-6, BNP, the mitral early diastolic peak flow velocity to tissue Doppler early mitral annular diastolic velocity (E/e′), and left ventricular mass index (LVMI) were not normally distributed and expressed as the median value (interquartile range). Statistical analyses are detailed in the Online Appendix.

Results

Study sample characteristics. Table 1 details the clinical characteristics of all study subjects. The patients with HFNEF were older on average than non-HF and HFREF patients. The levels of estimated glomerular filtration rate (eGFR) were significantly lower in patients with HFNEF than in non-HF patients, although the levels of LVEF were not significantly different between these 2 groups. The levels of PTX3, TNF-alpha, IL-6, and BNP were significantly elevated in patients with HFNEF and HFREF compared with those in non-HF patients. However, hsCRP levels were significantly elevated only in patients with HFREF, but not in patients with HFNEF ($p = 0.14$), compared with non-HF patients.

The levels of PTX3 and BNP increased significantly as New York Heart Association functional class increased. Although the levels of hsCRP were significantly higher in severe HF patients, they were not significantly different in New York Heart Association functional classes (Online Fig. 1). Simple linear regression analysis revealed a significant positive correlation between levels of ln(PTX3) and ln(BNP) ($r = 0.472$, $p < 0.001$) and significant positive correlation between levels of ln(PTX3) and ln(hsCRP) ($r = 0.230$, $p < 0.001$).

Clinical markers correlating with the presence of HFNEF in patients with normal LVEF. Multivariate linear regression analysis revealed that the levels of ln(PTX3) independently correlated with values of ln(E/e′) among inflammatory markers (beta = 0.297, $p < 0.05$, model $R^2 = 0.213$) and adjusted age, sex, body mass index (BMI), eGFR, hypertension, and diabetes (beta = 0.157, $p < 0.05$, model $R^2 = 0.289$) in patients with normal LVEF. However, the levels of ln(PTX3) did not significantly correlate with LVEF, the parameter of LV systolic dysfunction ($r = 0.05$, $p = 0.43$). Table 2 details the univariate and multivariate logistic regression analyses to identify clinical markers for the presence of HFNEF among patients with normal LVEF, excluding the parameters in diagnostic criteria: BNP, E/e′, and LVMI. The levels of PTX3, hsCRP, and TNF-alpha, as well as age and eGFR were significantly correlated with the presence of HFNEF by the univariate logistic regression analysis. In the multivariate logistic regression analysis, PTX3 significantly and independently correlated with the presence of HFNEF (odds ratio [OR]: 1.49, 95% confidence interval [CI]: 1.11 to 1.98, $p < 0.01$). This model was reliable ($p = 0.23$ by the Hosmer-Lemeshow test). In the forced entry models, PTX3, but not hsCRP, was significantly correlated with the presence of HFNEF among patients with normal LVEF (OR: 1.47, 95% CI: 1.25 to 1.73,

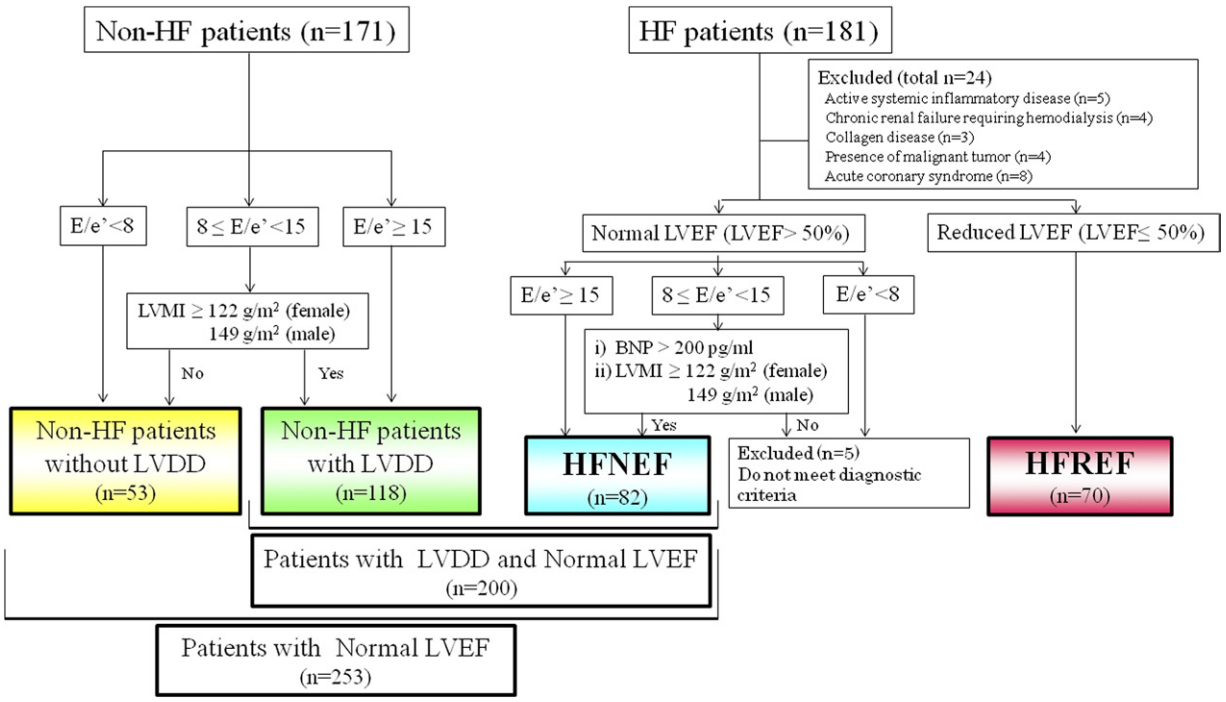

Figure 1 **Flow Chart Showing the Enrollment Protocol**

Flow chart showing the protocol used for enrollment of heart failure (HF) patients with normal ejection fraction and reduced ejection fraction and non–HF patients with or without left ventricular diastolic dysfunction (LVDD). BNP = B-type natriuretic peptide; E/e′ = the mitral early diastolic peak flow velocity to tissue Doppler early mitral annular diastolic velocity; HFNEF = heart failure with normal ejection fraction; HFREF = heart failure with reduced ejection fraction; LV = left ventricular; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index.

$p < 0.001$) independent of age, sex, eGFR, hypertension, and diabetes. This model was reliable ($p = 0.63$ by the Hosmer-Lemeshow test).

Relationship between PTX3 and LVDD in non-HF patients. Table 3 details the clinical characteristics of non-HF patients with or without LVDD. The non-HF patients with LVDD were older on average than non-HF patients without LVDD. The levels of PTX3, BMI, and waist circumference were significantly higher and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use and hypertension were significantly dominant, whereas eGFR was significantly lower in non-HF patients with LVDD than those without LVDD. However, the levels of hsCRP, TNF-alpha, IL-6, BNP, and LVEF were not significantly different between the 2 groups. In the non-HF population, multivariate linear regression analysis revealed that the levels of ln(PTX3) independently correlated with values of ln(E/e′) among inflammatory markers (beta = 0.291, $p < 0.05$, model $R^2 = 0.148$) and adjusted age, sex, BMI, eGFR, hypertension, diabetes, and BNP (beta = 0.147, $p < 0.05$, model $R^2 = 0.289$). However, the levels of ln(PTX3) did not significantly correlate with values of LVEF ($r = 0.110$, $p = 0.14$). We investigated logistic regression analysis of markers to correlate with the presence of LVDD in non-HF patients, excluding the parameters in diagnostic criteria, E/e′, and LVMI. The univariate logistic regression analysis identified levels of PTX3, age, BMI, waist circumference, eGFR, and hypertension, but not hsCRP ($p = 0.62$), TNF-alpha ($p = 0.44$), IL-6 ($p = 0.62$), and BNP ($p = 0.55$), as significant markers of the presence of LVDD. In the multivariate logistic regression analysis, PTX3 was the independent marker correlated with the presence of LVDD among non-HF patients (OR: 1.23, 95% CI: 1.02 to 1.50, $p < 0.05$), independent of age, sex, BMI, eGFR, and hypertension. This model was reliable ($p = 0.70$ by the Hosmer-Lemeshow test).

The presence of HFNEF in patients with LVDD and normal LVEF. Among patients with LVDD and normal LVEF (Fig. 1), the levels of PTX3, BNP, TNF-alpha, IL-6, E/e′, and LVMI were significantly higher, and beta-blockers and diuretics were significantly more used, whereas eGFR was significantly lower in patients with HFNEF than in non-HF patients with LVDD. However, hsCRP levels ($p = 0.20$), LVEF ($p = 0.26$), and age ($p = 0.19$) were not significantly different between the 2 groups. Table 4 presents the univariate and multivariate logistic regression analyses of markers to correlate with the presence of HFNEF in patients with LVDD and normal LVEF, excluding BNP as the diagnostic criteria of HF. In the multivariate logistic regression analysis, PTX3 was the significant and independent marker cor-

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Table 1 Clinical Characteristics

	Non-HF Patients (n = 171)	All Patients With HF (n = 152)	HFNEF (n = 82)	HFREF (n = 70)
Age, yrs	66.5 ± 11.2	68.6 ± 12.2	71.2 ± 10.2*†	65.5 ± 13.6
Sex, male/female	97/74	97/55	59/33	48/22
NYHA functional class (II/III/IV)		78/50/24	52/23/7 †	26/27/17
Body mass index, kg/m^2	24.4 ± 6.2	23.8 ± 3.9	24.0 ± 3.7	23.5 ± 4.1
Metabolic syndrome	80 (46.8%)	65 (44.8%)	39 (50.6%)	26 (38.2%)
Waist circumference, cm	87.7 ± 9.1	87.9 ± 10.7	89.9 ± 10.0‡	85.6 ± 11.1
Current smoking	32 (18.7%)	21 (13.8%)	11 (13.4%)	10 (14.3%)
Hypertension	116 (67.8%)	97 (63.8%)	59 (72.0%)‡	38 (54.3%)
Diabetes mellitus	64 (37.4%)	57 (37.5%)	37 (45.1%)‡	20 (28.6%)
Glucose, mg/dl	100.4 ± 26.1	100.2 ± 28.2	102.7 ± 28.5	97.2 ± 27.8
Hemoglobin A1c, %	5.9 ± 1.1	5.9 ± 1.0	5.8 ± 1.0	5.9 ± 1.0
CAD	94 (55.0%)	76 (50.0%)	44 (53.7%)	32 (45.7%)
Atrial fibrillation	9 (5.3%)	17 (11.2%)	8 (9.8%)	9 (12.9%)
Biochemical markers, mg/dl				
Total cholesterol	178.5 ± 27.9	174.2 ± 31.7	173.7 ± 27.9	174.9 ± 35.9
HDL cholesterol	54.8 ± 15.0	49.7 ± 13.1§	51.8 ± 13.9‡	47.3 ± 11.8§
Triglycerides	117.6 ± 60.7	115.5 ± 54.3	114.1 ± 51.8	117.1 ± 57.3
LDL cholesterol	103.6 ± 24.9	102.9 ± 25.1	99.9 ± 22.0	106.4 ± 27.9
Estimated GFR, ml/min/1.73 m^2	69.5 ± 17.8	59.1 ± 21.6§	61.6 ± 21.2*	56.3 ± 21.9§
Inflammatory markers				
PTX3, ng/ml	2.18 (1.51–2.90)	3.28 (2.20–4.55)§	3.26 (2.36–4.35)‡§	3.56 (2.20–6.28)§
hsCRP, mg/l	0.70 (0.30–1.33)	1.00 (0.50–2.25)§	0.90 (0.40–1.60)‡	1.15 (0.60–3.30)§
TNF-alpha, pg/ml	1.01 (0.05–2.25)	1.66 (0.82–3.21)‖	1.64 (0.68–2.88)‖	1.73 (0.95–3.64) ‖
IL-6, pg/ml	1.24 (0.65–2.39)	3.80 (1.93–7.92)§	2.45 (1.15–3.96)*†	5.55(2.65–9.41)§
BNP, pg/ml	26.9 (13.2–50.4)	149.8 (49.0–371.2)§	94.5 (34.8–232.2)†§	286.5 (98.4–760.2)§
Echocardiography				
LVEF, %	65.7 ± 5.1	51.0 ± 17.0§	64.6 ± 7.2†	35.1 ± 9.8§
E/e′	11.0 (9.0–13.8)	13.9 (11.2–17.8)§	13.9 (10.9–16.1)§	13.9 (11.5–19.7)§
LV mass index, g/m^2	143.7 (124.4–160.2)	192.8 (153.2–265.2)§	158.7 (139.6–194.8)†§	249.9 (203.5–322.2)§
Medications				
Beta-blockers	33 (19.4%)	75 (49.3%)*	35 (45.5%)‖	40 (61.5%)§
ACE-Is or ARBs	72 (42.4%)	98 (64.5%)§	45 (54.9%)‡	53 (75.7%)§
Calcium-channel blockers	108 (63.5%)	69 (45.4%)*	51 (62.2%)†	18 (25.7%)§
Statins	71 (41.8%)	61 (40.1%)	40 (48.7%)‡	21 (30.0%)
Aspirin	90 (52.9%)	79 (52.0%)	48 (58.5%)	31 (44.3%)
Diuretics	7 (4.1%)	71 (46.7%)§	19 (23.2%)†‖	52 (74.3%)§

Data are mean ± SD, n (%), or median and (interquartile range). *$p < 0.01$ versus non-HF; †$p < 0.001$ versus HFREF; ‡$p < 0.05$ versus HFREF; §$p < 0.001$ versus non-HF; ‖$p < 0.05$ vs. non-HF.
ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BNP = B-type natriuretic peptide; CAD = coronary artery disease; E/e′ = mitral early diastolic peak flow velocity to tissue Doppler early mitral annular diastolic velocity; GFR = glomerular filtration rate; HDL = high-density lipoprotein; HF = heart failure; HFNEF = heart failure with normal ejection fraction; HFREF = heart failure reduced ejection fraction; hsCRP = high-sensitivity C-reactive protein; IL = interleukin; LDL = low-density lipoprotein; LV = left ventricular; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PTX3 = pentraxin 3; TNF = tumor necrosis factor.

related with the presence of HFNEF among patients with LVDD and normal LVEF (OR: 1.54, 95% CI: 1.08 to 2.18, $p < 0.05$). This model was reliable ($p = 0.54$ by the Hosmer-Lemeshow test). In the forced entry models, PTX3, but not hsCRP, was significantly correlated with the presence of HFNEF among patients with LVDD and normal LVEF (OR: 1.40, 95% CI: 1.19 to 1.65, $p < 0.001$) independent of age, sex, eGFR, hypertension, and diabetes. This model was reliable ($p = 0.67$ by the Hosmer-Lemeshow test).

Production of PTX3 in the coronary circulation. In 75 consecutive patients who received coronary angiography, we examined the levels of PTX3 at the coronary sinus and the aortic root. Levels of PTX3 at the coronary sinus were significantly elevated compared with those at the aortic root in non-HF patients with LVDD, but were not different in those without LVDD (Figs. 2A and 2B). In HF patients, the levels of PTX3 at the coronary sinus were significantly elevated compared with those at the aortic root in HFNEF or HFREF patients (Figs. 2C and 2D). The transcardiac gradient of PTX3 (ΔPTX3 = coronary sinus − aortic root) in patients with HFNEF and HFREF, and non-HF patients with LVDD were significantly higher than in non-HF patients without LVDD (Fig. 3A). Furthermore, the simple linear regression analysis revealed a significant positive correlation between the peripheral levels of ln(PTX3) and the amount of PTX3 production in coronary circulation ($r = 0.288$, $p < 0.01$) (Fig. 3B).

Table 2 Logistic Regression Analysis of Clinical Factors for the Presence of HFNEF Among Patients With Normal LVEF

	Univariate		Multivariate		Forced Models					
					Model 1		Model 2		Model 3	
Factor	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Age, yrs	1.04 (1.01–1.07)	<0.01	0.99 (0.94–1.06)	0.98	1.02 (0.99–1.05)	0.25	1.03 (1.00–1.06)	<0.05	1.02 (0.99–1.05)	0.21
Sex, male	1.15 (0.67–1.96)	0.62	Not selected		1.11 (0.60–2.03)	0.74	1.11 (0.62–1.97)	0.72	1.10 (0.60–2.02)	0.76
Body mass index, kg/m^2	0.98 (0.93–1.04)	0.55	Not selected							
Metabolic syndrome, yes	1.12 (0.65–1.92)	0.69	Not selected							
Waist circumference, cm	1.02 (0.99–1.05)	0.11	Not selected							
Current smoking	0.67 (0.32–1.40)	0.29	Not selected							
Hypertension, yes	1.23 (0.69–2.19)	0.49	Not selected		1.19 (0.63–2.27)	0.59	1.02 (0.55–1.89)	0.96	1.14 (0.59–2.17)	0.70
Diabetes mellitus, yes	1.36 (0.80–2.33)	0.26	Not selected		1.16 (0.63–2.15)	0.63	1.13 (0.63–2.02)	0.69	1.12 (0.61–2.08)	0.72
Glucose, mg/dl	1.00 (0.99–1.01)	0.53	Not selected							
Hemoglobin A1c, %	0.99 (0.77–1.28)	0.93	Not selected							
CAD, yes	0.94 (0.55–1.59)	0.81	Not selected							
Atrial fibrillation, yes	1.93 (0.72–5.21)	0.19	Not selected							
Total cholesterol, mg/dl	0.99 (0.98–1.01)	0.21	Not selected							
HDL cholesterol, mg/dl	0.99 (0.97–1.00)	0.13	Not selected							
Triglycerides, mg/dl	1.00 (0.99–1.01)	0.66	Not selected							
LDL cholesterol, mg/dl	0.99 (0.98–1.01)	0.25	Not selected							
Estimated GFR, ml/min/1.73 m^2	0.98 (0.96–0.99)	<0.01	0.99 (0.95–1.02)	0.42	0.99 (0.97–1.01)	0.19	0.99 (0.97–1.01)	0.13	0.99 (0.97–1.01)	0.26
ln(PTX 3), 0.1	1.54 (1.32–1.80)	<0.001	1.49 (1.11–1.98)	<0.01	1.49 (1.27–1.76)	<0.001			1.47 (1.25–1.73)	<0.001
ln(hsCRP), 0.1	1.06 (1.01–1.12)	<0.05	1.08 (0.97–1.20)	0.17			1.05 (0.99–1.12)	0.09	1.04 (0.97–1.10)	0.28
ln(TNF-alpha), 0.1	1.11 (1.02–1.21)	<0.05	1.09 (0.98–1.20)	0.10						
ln(IL-6), 0.1	1.06 (0.96–1.13)	0.26	Not selected							
LVEF, %	0.97 (0.92–1.01)	0.15	Not selected							

CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

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Table 3 Clinical Characteristics of Non-HF Patients With or Without LVDD

	Non-HF Patients (n = 171)		
	With LVDD (n = 118)	Without LVDD (n = 53)	p Value
Age, yrs	68.7 ± 10.6	61.7 ± 10.9	<0.001
Sex, male/female	67/51	30/23	0.99
Body mass index, kg/m^2	25.4 ± 3.1	23.2 ± 3.2	<0.05
Metabolic syndrome	60 (50.8%)	20 (38.5%)	0.13
Waist circumference, cm	88.8 ± 8.6	85.2 ± 9.5	<0.05
Current smoking	19 (16.1%)	13 (24.5%)	0.21
Hypertension	90 (76.3%)	26 (49.1%)	<0.001
Diabetes mellitus	48 (40.7%)	16 (30.2%)	0.23
Glucose, mg/dl	101.8 ± 28.5	97.1 ± 20.0	0.27
Hemoglobin A1c, %	6.0 ± 1.1	5.6 ± 0.8	0.07
CAD	69 (59.0%)	25 (47.2%)	0.18
Atrial fibrillation	5 (4.2%)	4 (7.5%)	0.46
Biochemical markers, mg/dl			
Total cholesterol	177.4 ± 28.4	180.8 ± 26.7	0.45
HDL cholesterol	54.5 ± 14.5	55.4 ± 16.2	0.72
Triglycerides	113.7 ± 56.5	123.6 ± 77.5	0.17
LDL cholesterol	103.3 ± 24.9	104.2 ± 25.0	0.83
eGFR, ml/min/1.73 m^2	67.4 ± 17.0	74.2 ± 18.7	<0.05
Inflammatory markers			
PTX3, ng/ml	2.28 (1.63–3.00)	1.99 (1.35–2.65)	<0.05
hsCRP, mg/l	0.65 (0.30–1.45)	0.70 (0.30–1.10)	0.50
TNF-alpha, pg/ml	1.05 (0.14–2.24)	0.98 (0.01–1.70)	0.27
IL-6, pg/ml	1.26 (0.67–2.95)	1.18 (0.89–1.84)	0.56
BNP, pg/ml	28.6 (12.7–51.8)	26.3 (14.3–41.1)	0.50
Echocardiography			
LVEF, %	65.2 ± 5.2	66.7 ± 5.3	0.18
E/e′	12.3 (10.0–14.7)	9.0 (6.7–10.7)	<0.001
LV mass index, g/m^2	151.7 (139.7–172.7)	121.1 (110.7–135.4)	<0.001
Medications			
Beta-blockers	24 (20.3%)	9 (17.0%)	0.68
ACE-Is or ARBs	58 (49.2%)	14 (26.4%)	<0.01
Calcium-channel blockers	78 (66.1%)	30 (56.6%)	0.23
Statins	51 (43.2%)	20 (37.7%)	0.51
Aspirin	66 (56.0%)	24 (45.3%)	0.19
Diuretics	6 (5.1%)	1 (1.9%)	0.44

Data are mean ± SD, n (%), or median and (interquartile range).
LVDD = left ventricular diastolic dysfunction; other abbreviations as in Table 1.

In contrast, the levels of hsCRP were not significantly different between levels of the coronary sinus and the aortic root in all groups (data not shown).

Discussion

In this study, we identified the presence of significantly elevated levels of PTX3, but not hsCRP, in HFNEF patients compared with non-HF patients. The levels of PTX3, but not hsCRP, TNF-alpha, and IL-6, significantly correlated with values of E/e′, which reflected LVDD. The elevated levels of PTX3, but not hsCRP, TNF-alpha, and IL-6, were significantly and independently correlated with the presence of HFNEF among patients with normal LVEF and even among patients with LVDD and normal LVEF.

Inflammatory activation is important in the pathogenesis of HF and in adverse prognoses in these patients. The established inflammatory marker, hsCRP, is an independent predictor of morbidity and mortality in patients with HF (5). The novel inflammatory marker, PTX3, was recently implicated as a predictor of adverse clinical outcomes in patients with HF (4). However, in these studies, LVEF in patients with HF was generally lower than 50%. Previous studies also identified elevated N-terminal proBNP and BNP as strong independent predictors of clinical events in patients with HFNEF (6), and BNP was found to distinguish patients with HFNEF from those with LVDD (7). However, the relationship between inflammatory markers and HFNEF remained unclear. Williams et al. (8) showed that elevated CRP levels predicted hospitalization for HF patients, although this association between CRP and HF events was no longer significant after adjustment for the presence of LVDD. The present study similarly revealed

Table 4 Logistic Regression Analysis of the Factors for the Presence of HFNEF Among Patients With LVDD and Normal LVEF

	Univariate		Multivariate		Forced Models					
					Model 1		Model 2		Model 3	
Factor	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Age, yrs	1.02 (0.99–1.05)	0.19	Not selected		1.01 (0.97–1.04)	0.88	1.01 (0.98–1.05)	0.37	1.01 (0.97–1.04)	0.82
Sex, male	1.21 (0.68–2.14)	0.52	Not selected		1.17 (0.62–2.18)	0.64	1.14 (0.62–2.08)	0.67	1.16 (0.62–2.19)	0.64
Body mass index, kg/m^2	0.95 (0.89–1.03)	0.25	Not selected							
Metabolic syndrome, yes	0.75 (0.42–1.34)	0.33	Not selected							
Waist circumference, cm	1.01 (0.98–1.04)	0.63	Not selected							
Current smoking	0.81 (0.36–1.80)	0.60	Not selected							
Hypertension, yes	0.88 (0.46–1.65)	0.68	Not selected		0.85 (0.42–1.71)	0.65	0.73 (0.37–1.43)	0.35	0.81 (0.40–1.64)	0.56
Diabetes mellitus, yes	1.12 (0.63–1.97)	0.70	Not selected		1.06 (0.55–2.01)	0.87	1.02 (0.55–1.90)	0.94	1.01 (0.53–1.94)	0.97
Glucose, mg/dl	1.00 (0.99–1.01)	0.97	Not selected							
Hemoglobin A1c, %	0.91 (0.69–1.21)	0.52	Not selected							
CAD, yes	0.67 (0.35–1.10)	0.10	Not selected							
Atrial fibrillation, yes	2.44 (0.77–7.75)	0.13	Not selected							
Total cholesterol, mg/dl	0.99 (0.99–1.01)	0.67	Not selected							
HDL cholesterol, mg/dl	0.99 (0.97–1.01)	0.42	Not selected							
Triglycerides, mg/dl	1.00 (0.99–1.01)	0.81	Not selected							
LDL cholesterol, mg/dl	0.99 (0.98–1.01)	0.63	Not selected							
Estimated GFR, ml/min/1.73 m^2	0.98 (0.97–0.99)	<0.05	0.98 (0.94–1.02)	0.31	0.99 (0.97–1.01)	0.28	0.99 (0.97–1.01)	0.23	0.99 (0.97–1.01)	0.39
ln(PTX3), 0.1	1.45 (1.23–1.70)	<0.001	1.54 (1.08–2.18)	<0.05	1.42 (1.21–1.68)	<0.001			1.40 (1.19–1.65)	<0.001
ln(hsCRP), 0.1	1.05 (0.99–1.12)	0.10	Not selected				1.05 (0.98–1.11)	0.15	1.03 (0.97–1.10)	0.34
ln(TNF-alpha), 0.1	1.12 (1.01–1.23)	<0.05	1.07 (0.96–1.19)	0.24						
ln(IL-6), 0.1	1.07 (0.96–1.19)	0.22	Not selected							
LVEF, %	0.97 (0.93–1.02)	0.25	Not selected							
ln(E/e′), 0.1	1.23 (1.02–1.62)	<0.05	1.56 (0.91–2.66)	0.11						
ln(LV mass index), 0.1	1.51 (1.09–2.09)	<0.05	1.06 (0.56–2.02)	0.85						

Abbreviations as in Tables 1 and 2.

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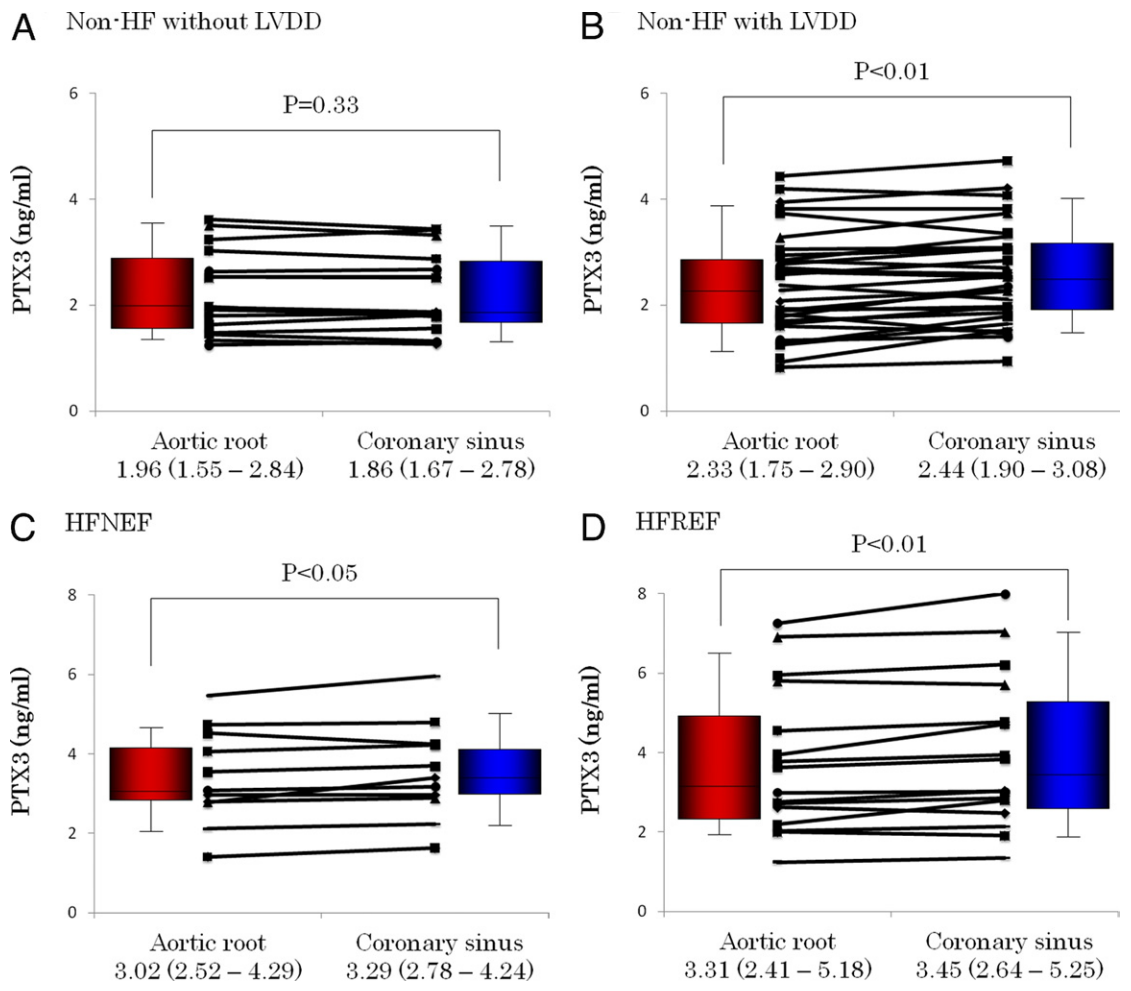

Figure 2 **PTX3 Levels at the Coronary Sinus and the Aortic Root**

The levels of pentraxin 3 at the coronary sinus were significantly elevated compared with those at the aortic root in non-HF patients with LVDD (n = 32) **(B)**, but not in those without LVDD (n = 16) **(A)**. In HFNEF (n = 11) **(C)** and HFREF patients (n = 16) **(D)**, the levels of pentraxin 3 (PTX3) at the coronary sinus were significantly elevated compared with those at the aortic root. Abbreviations as in Figure 1.

that hsCRP was not significantly correlated with the presence of HFNEF. In contrast, PTX3 was shown to be a significantly independent inflammatory marker of the presence of HFNEF.

Importantly, this study also identified that PTX3 was an independent marker correlated with the presence of LVDD among non-HF patients, independent of age, sex, BMI, eGFR, and hypertension, and was produced in the coronary circulation in not only HFNEF patients but also non-HF patients with LVDD. The amount of PTX3 production in coronary circulation indicated significant positive correlation with the peripheral levels of PTX3. Small but significant differences in PTX3 levels between the aortic root and the coronary sinus might in part contribute to the increased levels of PTX3 in peripheral circulation in patients with LVDD. However, the pathogenetic role of the elevated PTX3 in LVDD and HF, either as an inducer, suppressor, or mere marker, remains unclear. PTX3 was recently implicated in a cardioprotective role in mice models of acute myocardial infarction (9) and has an atheroprotective effect in apolipoprotein E-knockout mice (10). These studies suggested that PTX3 might exert its protective properties on the cardiovascular system through modulating the immunoinflammatory balance. Therefore, the elevated PTX3 would possibly play a compensatory cardioprotective role at the activated inflammatory condition. However, we only found that PTX3 levels were significantly correlated with the presence of HFNEF and that PTX3 is a useful inflammatory marker, but not an inducer or suppressor, in patients with HFNEF in the present study. Further studies might be required to determine the detailed pathological roles of PTX3 in HFNEF and LVDD.

Study limitations. The present study has certain limitations. The non-HF patients were not randomly selected from the general population and the values of certain parameters such as blood pressure and lipid profile were

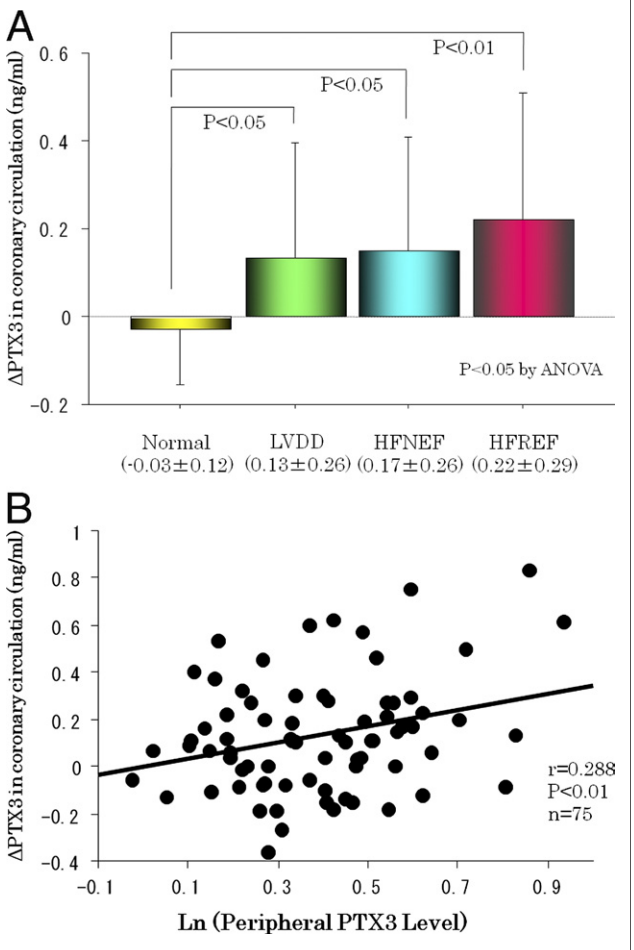

Figure 3 Production of PTX3 in Coronary Circulation

(A) The transcardiac gradient of PTX3 (coronary sinus – aortic root) in patients with HFREF and HFNEF, as well as non-HF patients with LVDD were significantly higher than in non-HF patients without LVDD ($p < 0.05$). **(B)** The simple linear regression analysis revealed a positive correlation between the peripheral levels of ln(PTX3) and the amount of PTX3 production in coronary circulation ($n = 75$, $r = 0.288$, $p < 0.01$). ΔPTX3 = transcardiac gradient of pentraxin 3; other abbreviations as in Figures 1 and 2.

probably influenced to an extent by medications. In addition, the study investigated only a relatively small number of patients in a single center. Despite these limitations, however, this study provided the first evidence for a role of PTX3 in HFNEF and LVDD. Further in vivo and in vitro experiments will be needed to determine the mechanisms of increased PTX3 production in HFNEF and LVDD. A multicenter trial with a large-scale study population is now warranted to further examine the role and clinical significance of PTX3 in HFNEF and LVDD.

Conclusions

PTX3 is produced in the coronary circulation in HFNEF patients and in non-HF patients with LVDD and is significantly elevated in patients with HFNEF. PTX3 could be a significant inflammatory marker in patients with HFNEF.

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Key Words: coronary circulation ■ heart failure with normal ejection fraction ■ left ventricular diastolic dysfunction ■ pentraxin 3.

APPENDIX

For the expanded methods section, please see the online version of this article.