Table 2. Impact of CKD on Prevalence of LMCAD

	Univariate analysis			Multivariate analysis		
	OR	95%CI	P value	OR	95%CI	P value
CKD	1.67	1.07–2.60	0.02	1.74	1.09–2.76	0.01
Age	1.01	0.99–1.04	0.12			
Male gender	1.24	0.76–2.02	0.37			
Diabetes mellitus	0.87	0.51–1.48	0.61			
Hypertension	1.44	0.87–2.38	0.14			
Dyslipidemia	1.47	0.92–2.34	0.10	1.48	0.92–2.37	0.09
Smoking	0.79	0.51–1.24	0.31			

OR, odds ratio; CI, confidence interval. Other abbreviations as in Table 1.

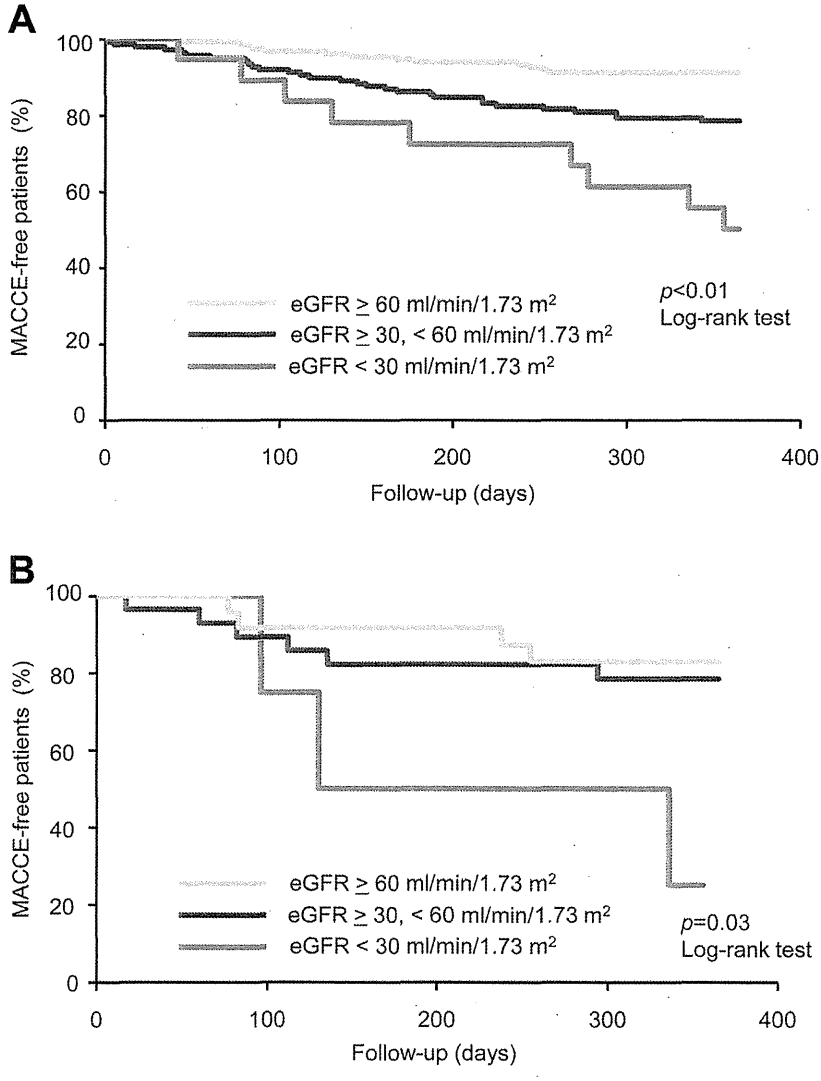

Figure. Kaplan-Meier analysis in patients with (A) stable angina pectoris or (B) left main coronary artery disease. Major adverse cardiovascular and cerebrovascular events (MACCE) were defined as one of the following conditions: revascularization due to new or recurrent fatal and non-fatal acute myocardial infarction, new or recurrent unstable angina pectoris, and de novo stable lesion and target lesion restenosis; heart failure admission; stroke and transient ischemic attack; cardiac death. eGFR, estimated glomerular filtration rate.

(10%), and 68 were treated with medication only (27%). Patients with eGFR <30 ml·min^{-1}·1.73 m^{-2} more frequently experienced MACCE. This held true for both patients with stable angina pectoris and patients with LMCAD.

Patients subsequently were reassigned to 6 groups on the basis of their LMCAD status and eGFR. The MACCE for those groups are listed in Table 3. Clinical characteristics such as age, gender, hypertension, diabetes mellitus, dyslipidemia, and medications did not differ between the groups, but treatments such as PCI and CABG did differ (Table S1). As shown in Table 4, multivariate logistic analysis indicated that the risk of MACCE in non-LMCAD patients with eGFR <30 ml·

Table 3. MACCE vs. Presence of LMCAD

	eGFR (ml·min^{-1}·1.73 m^{-2})			P value
	<30	≥30, <60	≥60	
Non-LMCAD				
n	15	111	123	
MACCE (total)	6	23	8	<0.01
Revascularization	2	10	8	NS
Hospitalization for HF	2	8	0	0.01
Cardiac death	1	3	0	NS
Cerebrovascular events	1	2	0	NS
LMCAD				
n	4	28	24	
MACCE (total)	3	6	5	0.05
Revascularization	2	2	2	0.03
Hospitalization for HF	1	4	2	NS
Cardiac death	0	0	1	NS
Cerebrovascular events	0	0	0	NS

MACCE, major adverse cardiovascular and cerebrovascular events; HF, heart failure. Other abbreviations as in Table 1.

Table 4. Effect of Renal Dysfunction on MACCE vs. Presence of LMCAD

eGFR (ml·min^{-1}·1.73 m^{-2})	No. patients	MACCE (%)	HR (95%CI)	P value
Non-LMCAD				
≥60	123	7	1.00	
≥30, <60	111	21	2.39 (1.35–4.26)	<0.01
<30	15	40	6.82 (3.21–14.52)	<0.01
LMCAD				
≥60	24	17	2.25 (0.86–5.88)	NS
≥30, <60	28	21	1.86 (0.70–4.93)	NS
<30	4	75	9.54 (3.15–28.89)	<0.01

This multivariate logistic analysis was adjusted for PCI and CABG.
HR, hazard ratio. Other abbreviations as in Tables 1–3.

min^{-1}·1.73 m^{-2} was approximately 7-fold higher than for non-LMCAD patients with eGFR ≥60 ml·min^{-1}·1.73 m^{-2}. Furthermore, the risk of MACCE in LMCAD patients with eGFR <30 ml·min^{-1}·1.73 m^{-2} was approximately 9-fold higher than for non-LMCAD patients with eGFR ≥60 ml·min^{-1}·1.73 m^{-2}. Thus, the risks of MACCE in both groups for patients with eGFR <30 ml·min^{-1}·1.73 m^{-2} were similarly high in spite of the presence or absence of LMCAD.

Discussion

In this study, we demonstrated that (1) CKD was independently associated with the presence of LMCAD in patients with stable angina pectoris, even though the frequency of traditional risk factors such as advanced age, male gender, hypertension, dyslipidemia, diabetes mellitus, and smoking did not differ between patients with and without LMCAD; and (2) the risk ratio of MACCE in patients with eGFR <30 ml·min^{-1}·1.73 m^{-2} was similar between patients with stable angina pectoris with and without LMCAD. These results suggest that CKD is an independent risk factor of LMCAD and that the impact of CKD adversely affects the outcomes of patients both with and without LMCAD treated with optimal initial treatment.

In this study, LMCAD occurred in 15% of patients with stable angina pectoris. Previous studies have reported LMCAD in approximately 3–8% of stable angina pectoris patients.[2,20,21] The high level of LMCAD in the present study may reflect the criteria for patient selection. The present subjects had significant stenosis (>50% coronary artery narrowing in at least 1 vessel, as determined on coronary angiography). As a consequence, subjects with stable angina pectoris and coronary narrowing <50% were excluded from the study. Among the 1,601 consecutive patients who underwent coronary angiography during the study period, the percentage of patients with LMCAD was 5.9%. Further, almost all of the present patients with LMCAD had significant stenosis in an additional major coronary artery. These findings support the hypothesis that LMCAD represents the most advanced stage of coronary atherosclerosis. These results also are consistent with earlier studies, which demonstrated that >90% of patients with LMCAD have significant disease in an additional coronary artery.[20,22–24]

The present results show for the first time that CKD is an independent factor associated with LMCAD. Efforts have been made in the past to identify clinical risk profiles that predict LMCAD, but those efforts have had limited success.[2,4,25] The LMCAD risk factor profile established to date is similar to that associated with diffuse and multi-vessel coronary artery disease. In agreement with previous studies, the present findings identified comparable clinical characteristics between patients with stable angina pectoris and multi-vessel disease and patients with LMCAD. The eGFR, however, was the only factor that differed between the non-LMCAD and LMCAD groups. Intriguingly, eGFR levels gradually decreased as the severity of coronary artery disease worsened. Specifically, patient

groups could be ranked on the basis of eGFR level (high to low): (1) control; (2) single-vessel disease without LMCAD; (3) multi-vessel disease without LMCAD; and (4) LMCAD. Many patients with LMCAD had the most advanced stage of coronary atherosclerosis, and the severity of renal insufficiency has been shown to correlate closely with the severity of coronary artery disease.[26] In the present study, the prevalence of dyslipidemia in the LMCAD group was shown to be higher than that in the control group and the non-LMCAD group, but logistic analysis failed to confirm dyslipidemia as an independent risk factor for LMCAD. One possible reason is that the statistical power was not sufficient due to the relatively small number of subjects. We also evaluated the relationship between LMCAD and AA/EPA ratio, which is a promising risk factor for cardiovascular events.[27] We found that the AA/EPA ratio did not correlate with the prevalence of LMCAD or with the severity of coronary artery disease. In addition, the risk factors for CKD such as advanced age, hypertension, dyslipidemia, diabetes mellitus, and smoking are, however, also risk factors of severe coronary artery disease. Therefore, it is possible that the association between CKD and the prevalence of LMCAD was simply due to residual confounding factors. In this study, CKD was found to be an increased risk for the presence of LMCAD, while the number of patients enrolled in this study was limited. A larger study is needed to clarify other potential risk factors of LMCAD.

The mechanisms that underlie the association between renal dysfunction and coronary artery disease have not been elucidated fully. Previous studies have shown that renal dysfunction is associated with low-grade inflammation and activation of the sympathetic nervous system or the rennin-angiotensin-aldosterone system.[28–30] Other factors such as calcium-phosphate production, oxidative stress, and abnormal apolipoprotein levels also were shown to promote renal dysfunction.[31,32] As such, these factors could also contribute to the pathogenesis of atherosclerosis. To evaluate the relationship between oxidative stress and LMCAD, we measured plasma levels of malondialdehyde-modified low-density lipoprotein (MDA-LDL) in approximately half of the subjects enrolled in this study (data not shown). No association was found, however, between the presence of LMCAD and MDA-LDL levels. Further investigation is needed to identify the specific factors that link CKD and LMCAD.

The present study evaluated the impact of renal dysfunction on MACCE in patients with or without LMCAD, who were treated with only medication or PCI or CABG. In patients with severe renal dysfunction, the risk of MACCE was 7–9-fold higher than for patients with mild renal dysfunction (regardless of their LMCAD status). In contrast, as shown in Table 3, patients with eGFR $<30\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$ and LMCAD had a 2-fold greater chance of suffering MACCE than patients with eGFR $<30\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$ and non-LMCAD. These results imply that the influence of renal dysfunction on cardiovascular events after revascularization is greater than the influence of LMCAD. Recent improvements in PCI or CABG have provided a safer and more feasible treatment for LMCAD.[13] Even if PCI and CABG effectively resolve the stenosis associated with left main coronary artery, the incidence of new lesions and other complications remains high in patients with severe renal dysfunction. Medications do not adequately protect against the development of new coronary lesions in patients with severe renal dysfunction. This may explain the comparable impact of renal dysfunction on MACCE regardless of LMCAD, but the follow-up in the present study was limited to 1 year. Longer follow-up is required to evaluate cardiovascular death. There are many theories to explain the association between renal dysfunction and increased risk of MACCE. For example, patients with chronic renal failure may not have symptoms typically associated with restenosis, which could result in severe silent ischemia. Suboptimal medical therapies (eg, under-use of beta-blockers, angiotensin-converting enzyme inhibitors, and statins) also worsen health outcomes for these patients. We also found that the proportion of patients under statins was smaller in the LMCAD group than in the non-LMCAD group. In addition, recent studies showed that lower eGFR is associated with lipid-rich composition in coronary plaque, using integrated backscatter intravascular ultrasound,[33] and with PCI-related myocardial injury. Thus, plaque vulnerability associated with lower eGFR explains the relationship between renal dysfunction and increased risk of MACCE.

Study Limitations

First, only approximately half of the enrolled patients were followed up. In addition, the follow-up period was short. Therefore, we cannot deny that those lost subjects and the short-follow up period may have affected the impact of renal function on outcomes and the comparison of outcomes between patients with and without LMCAD. Second, some patients with CKD were categorized on the basis of a single eGFR measurement. This eGFR value was derived from a single serum creatinine determination done on the day of the coronary angiogram. This creatinine value may have been influenced by medication or an acute clinical status. Third, we did not have data concerning the course of renal function in these patients, either before or after the angiogram. There is a common tendency to refrain from coronary angiography, which can decrease the eGFR. As such, we could not address the influence of these factors on outcomes. Fourth, we included a few patients with end-stage renal disease who required dialysis. The data for these patients may have affected the relationships between risk factors and health outcomes. Fifth, patients underwent PCI or medication only, instead of CABG, because of either the patient's or physician's preference or the high risk associated with CABG. We cannot deny the possibility that the selection of treatment could have affected the results.

Conclusions

CKD is independently associated with LMCAD in patients with stable angina pectoris. Furthermore, severe renal dysfunction significantly affected the incidence of MACCE after optimal initial treatment of patients with and without LMCAD. Therefore, meticulous attention is required with regard to renal dysfunction when treating patients with stable angina pectoris.

Acknowledgment

There is no conflict of interest.

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Supplementary Files

Supplementary File 1

Table S1. Patient Characteristics vs. Presence of LMCAD and Renal Function

Please find supplementary file(s);
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CARDIO VASCULAR DIABETOLOGY

ORIGINAL INVESTIGATION Open Access

Elevated serum adipocyte fatty acid-binding protein concentrations are independently associated with renal dysfunction in patients with stable angina pectoris

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Abstract

Background: Chronic kidney disease (CKD) is associated with cardiovascular events. Adipocyte fatty acid-binding protein (A-FABP) plays an important role in atherosclerosis. We investigated whether plasma A-FABP is involved in renal function in patients with stable angina pectoris.

Methods: A total of 221 patients with significant coronary artery stenosis were enrolled after coronary angiography. CKD was defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2. The severity of coronary stenosis was assessed using a modified Gensini score and coronary angiography. Serum A-FABP levels were determined by enzyme-linked immunosorbent assay.

Results: Serum A-FABP levels were significantly correlated with both eGFR ($r = -0.41$, $p < 0.01$) and the severity of coronary artery stenosis ($r = 0.16$, $p = 0.02$), and these relationships remained significant after adjusting for confounding factors. The prevalence of CKD and multi-vessel disease was significantly higher among patients with serum A-FABP levels above the median value of 20.3 ng/ml than among patients with serum A-FABP levels below the median value (57% vs. 27%, $p < 0.01$ and 64% vs. 48%, $p = 0.02$, respectively). Multivariate analysis revealed that the presence of three-vessel disease in comparison with single-vessel disease was independently associated with the higher A-FABP (per doubling) (odds ratio; 2.26, 95% confidential interval; 1.28-3.98, $p < 0.01$) and tended to be associated with the lower eGFR ($p = 0.06$).

Conclusion: Serum A-FABP may have a significant role in the interplay between renal dysfunction and coronary atherosclerosis.

Keywords: Adipocyte, Fatty acid-binding protein, Renal dysfunction, Coronary artery disease

Background

Obesity and obesity-associated disorders, including insulin resistance, type 2 diabetes, dyslipidemia, and hypertension, are rapidly increasing in developed countries. In association with weight gain, the hyperplasia and hypertrophy of adipocytes influence the secretion pattern of adipocyte-derived proteins, adipokines, by adipose tissue. Recent evidence shows that adipokines contribute to the increased metabolic and cardiovascular risk among obese patients [1]. Among those adipokines, adipocyte fatty acid-binding protein (A-FABP), also known as aP2 or FABP4, is small intracellular lipid-binding protein which is expressed abundantly in adipocytes and activated macrophages [2]. Now, there are nine types of FABPs, showing tissue-specific expression patterns, and several members of the FABP family have been shown to have important roles in regulating metabolism and have links to the development of insulin resistance and

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the metabolic syndrome [3]. A-FABP was reported to play an essential regulatory role in energy metabolism and inflammation [4], and found not only in tissue, but also in blood stream [5].

The pathophysiological role of A-FABP has been investigated in murine experimental models and clinical studies. In mice, A-FABP deficiency ameliorates the development of insulin resistance in diet-induced obesity [2], type 2 diabetes [6], and atherosclerosis in models of hypercholesterolemia [7]. Clinically, A-FABP is detected in human serum [5]. Higher serum A-FABP levels are used to predict and diagnose obesity-related metabolic syndrome and type 2 diabetes [8,9]. Previous studies also showed that serum A-FABP levels are associated with carotid intima-media thickness [10], coronary artery disease [11], the number of stenotic coronary arteries [12], and coronary plaque volume, as determined by intravascular ultrasound [13]. Furthermore, the involvement of A-FABP in atherosclerosis is supported by a genetic study in humans. Carriers of the T87C polymorphism have lower serum triglyceride levels, demonstrating a reduced cardiovascular risk [14]. These findings demonstrate that A-FABP may play a critical role in the development of metabolic syndrome, type 2 diabetes, and cardiovascular disease.

Although the association between A-FABP and several metabolic parameters has been studied in detail, little is known about the relationship between this adipokine and renal function. One study showed that serum A-FABP concentrations in patients with chronic hemodialysis are higher than those in control patients without hemodialysis [15], although serum A-FABP levels in patients with a mild to moderate decrease in glomerular filtration rate (GFR) remain untested. Furthermore, the association between serum A-FABP, eGFR, and severity of coronary artery disease has not been evaluated. Therefore, we determined serum A-FABP levels in 221 patients with stable angina pectoris and assessed the correlation between serum A-FABP levels and biochemical measures of renal function, as well as the severity of coronary artery disease.

Methods

Study group

This study included 221 patients with stable angina pectoris who underwent coronary angiography between April 2008 and September 2009 at Kagawa Prefectural Central Hospital, Japan. Patients who had 75% or greater organic stenosis of at least one major coronary artery or who had previously undergone percutaneous transluminal coronary angioplasty were included. Patients with chronic hemodialysis, acute coronary syndrome, recent (within 4 weeks) myocardial infarction, or malignancies were excluded. The study protocol complied with the Declaration of Helsinki and was approved by the Ethics Committees of the institute. Written informed consent was obtained from all patients before study enrollment.

Clinical and biochemical assessments

Blood samples were taken after overnight fasting. The serum was separated and stored at -80°C, and serum levels of A-FABP (Biovendor Laboratory Medicine, Modrice, Czech Republic) and high-sensitivity C-reactive protein (hs-CRP; R&D Systems, Minneapolis, MN, USA) were measured by enzyme-linked immunosorbent assay [13]. The performance characteristics of these assays were < 7% and < 8% intra-assay coefficient of variation (CV), and < 5% and < 7% inter-assay CV for A-FABP and hs-CRP, respectively.

Risk factors were defined as follows. Diabetes was confirmed using the criteria of the American Diabetes Association [16] or by a history of treatment for diabetes mellitus. Dyslipidemia was defined as one or more of the following criteria: (1) serum triglyceride ≥ 150 mg/dl; (2) high-density lipoprotein (HDL)-cholesterol < 40 mg/dl; (3) low-density lipoprotein (LDL)-cholesterol ≥ 140 mg/dl; and (4) current use of lipid-lowering medication. Hypertension was defined as a sitting blood pressure ≥ 140/90 mmHg or current use of antihypertensive medication. Smoking status was determined and classified as current smoker or not. The estimated GFR (eGFR) was calculated using the equation put forth by the Modification of Diet in Renal Disease (MDRD) Study Group [17], with coefficients modified for Japanese patients [18]: eGFR (ml/min/1.73 m^2) = 194 × (serum creatinine)$^{-1.094}$ × (age)$^{-0.287}$ (x0.739 if female). The distribution of the eGFR was divided into three categories: less than 60 (moderately decreased eGFR, n = 93), 60-89 (mildly decreased eGFR, n = 106) and at least 90 ml/min/1.73 m^2 (normal eGFR, n = 22). Patients with end stage renal disease were not included. Chronic kidney disease (CKD) was defined as eGFR < 60 ml/min/1.73 m^2.

Coronary angiography

Coronary angiography was performed according to standard methods. After intracoronary injection of isosorbide dinitrate, angiograms were obtained in two or more views. The coronary angiogram was scored by two independent investigators. The stenosis score is a modified Gensini score [19]. Briefly, the most severe stenosis in each of eight segments was graded according to severity, from 1 to 4. The scores in each of the eight segments were added to provide a total stenosis score out of a maximum of 32.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range [(IQR]) values, and differences between groups were analyzed using an unpaired Student's *t* test. Data that were not normally distributed, as determined using the Kolmogorov-Smirnov test, were logarithmically transformed before linear regression analysis. Categorical variables are presented as frequency counts and corresponding percentages, and intergroup comparisons were analyzed using the chi-square test. Associations between serum A-FABP and other parameters were first analyzed by simple linear regression analysis and then by multivariate logistic regression analysis. To assess the association between serum A-FABP level and the presence of CKD or three-vessel coronary artery disease, logistic regression analyses were performed. In those analyses, factors that were associated with the dependent variable at $p < 0.05$ in the univariate analysis were entered into the multivariate model. In multivariate model, diabetes was selected as a covariate because fasting glucose levels, hemoglobinA1c, the homeostasis model assessment ratio are confounding factors of diabetes. Statistical significance was defined as $p < 0.05$. Statistical analyses were performed using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

The clinical characteristics of the study population are shown in Table 1. Patients with eGFR levels < 60, 60-89, or > 90 ml/min/1.73 m^2 differed in age, the presence of hypertension, smoking status, serum triglycerides levels, uric acid levels, fasting glucose levels, hemoglobinA1c, the homeostasis model assessment ratio (HOMA-R), and serum A-FABP levels but not in the number of diseased vessels or the stenosis score. The eGFR value was significantly lower among patients with hypertension than among patients without hypertension (mean ± SD, 66.3 ± 18.1 ml/min/1.73 m^2 vs. 73.1 ± 18.6 ml/min/1.73 m^2, $p < 0.01$ by Student's *t* test). The eGFR value was significantly higher among smokers than among non-smokers (76.1 ± 17.3 ml/min/1.73 m^2 vs. 63.9 ± 18.5 ml/min/1.73 m^2, $p < 0.01$). The eGFR value did not vary by the presence or absence of diabetes mellitus or dyslipidemia, gender, or the use of specific medications (data not shown). The stenosis score was significantly higher among patients with diabetes mellitus than among patients without diabetes mellitus (1.9 ± 0.8 vs. 1.6 ± 0.7, $p < 0.01$). The stenosis score did not vary by the presence or absence of hypertension or dyslipidemia, smoking status, gender, or the use of specific medications (data not shown). The prevalence of CKD and multi-vessel disease based on the median value of serum A-FABP (20.7 ng/ml) were shown in Figures 1A and 1B. The prevalence of CKD and multi-coronary vessel disease was significantly higher among patients with serum A-FABP levels over the median value than among patients with serum A-FABP levels less than the median value (57% vs. 27%, $p < 0.01$ and 64% vs. 48%, $p = 0.02$, respectively).

Table 1 Patient characteristics in this study

		eGFR (ml/min/1.73 m^2)			
	ALL (n = 221)	< 60 (n = 93)	60-89 (n = 106)	≥ 90 (n = 22)	p
Age (years)	71 ± 10	76 ± 8	68 ± 10	62 ± 11	< 0.01
Male, n (%)	185(84)	74(80)	92(87)	19(86)	0.36
Body mass index (kg/m^2)	24.7 ± 3.6	24.5 ± 3.7	25.0 ± 3.4	24.0 ± 4.5	0.29
Hypertension, n (%)	157(71)	77(83)	77(73)	12(55)	0.02
Dyslipidemia, n (%)	183(83)	75(81)	89(84)	19(86)	0.72
Diabetes Mellitus, n (%)	96(43)	31(33)	53(50)	12(54)	0.03
Smoking (Yes)	28(13)	5(5)	18(16)	5(23)	0.02
LDL-Cholesterol (mg/dl)	102 ± 28	100 ± 28	103 ± 29	10.4 ± 26	0.77
HDL-Cholesterol (mg/dl)	43 ± 12	42 ± 11	44 ± 12	44 ± 11	0.59
Triglycerides (mg/dl)	163(79)	155 (107)	169(61)	167(68)	< 0.01
Uric acid (mg/dl)	5.8 ± 1.6	6.4 ± 1.6	5.5 ± 1.4	4.9 ± 1.6	< 0.01
Fasting blood glucose (mg/dl)	100(25)	96(18)	102(34)	104(28)	< 0.01
HOMA-R	1.7(1.5)	1.7(1.3)	1.8(1.7)	1.3(1.1)	< 0.01
HemoglobinA1c (%)	5.6(1.2)	5.4(0.8)	5.7(1.2)	5.9(1.0)	0.04
hs-CRP(mg/l)	0.97 (2.35)	1.25 (3.27)	0.82 (1.79)	1.59 (2.72)	0.10
Serum A-FABP (ng/ml)	20.3 (13.6)	26.9 (19.5)	19.6 (11.1)	16.1(4.7)	< 0.01
Number of diseased vessels	1.8 ± 0.8	1.9 ± 0.8	1.7 ± 0.8	1.5 ± 0.7	0.12
Stenosis score	9.9 ± 4.9	9.3 ± 4.5	9.5 ± 5.8	10.2 ± 5.1	0.71
Medications	28(13)	5(5)	18(16)	5(23)	0.02
ACEI/ARB, n (%)	119(54)	39(43)	66(62)	14(64)	0.18
CCBs, n (%)	120(54)	48(52)	57(38)	15(68)	0.39
β-blockers, n (%)	73(33)	27(29)	40(38)	6(27)	0.36
Statins, n (%)	126(57)	49(52)	63(59)	14(63)	0.50

Data are presented as the mean ± SD, median (IQR), or frequency counts (percentages), as appropriate. LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FBS, fasting blood glucose; HOMA-R, homeostasis model assessment ratio; hs-CRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; A-FABP, adipocyte fatty acid-binding protein: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCBs, calcium channel blockers

Serum A-FABP levels and other biochemical parameters

Serum A-FABP levels were significantly higher among females than among males (median (IQR), 30.9 (26.7)

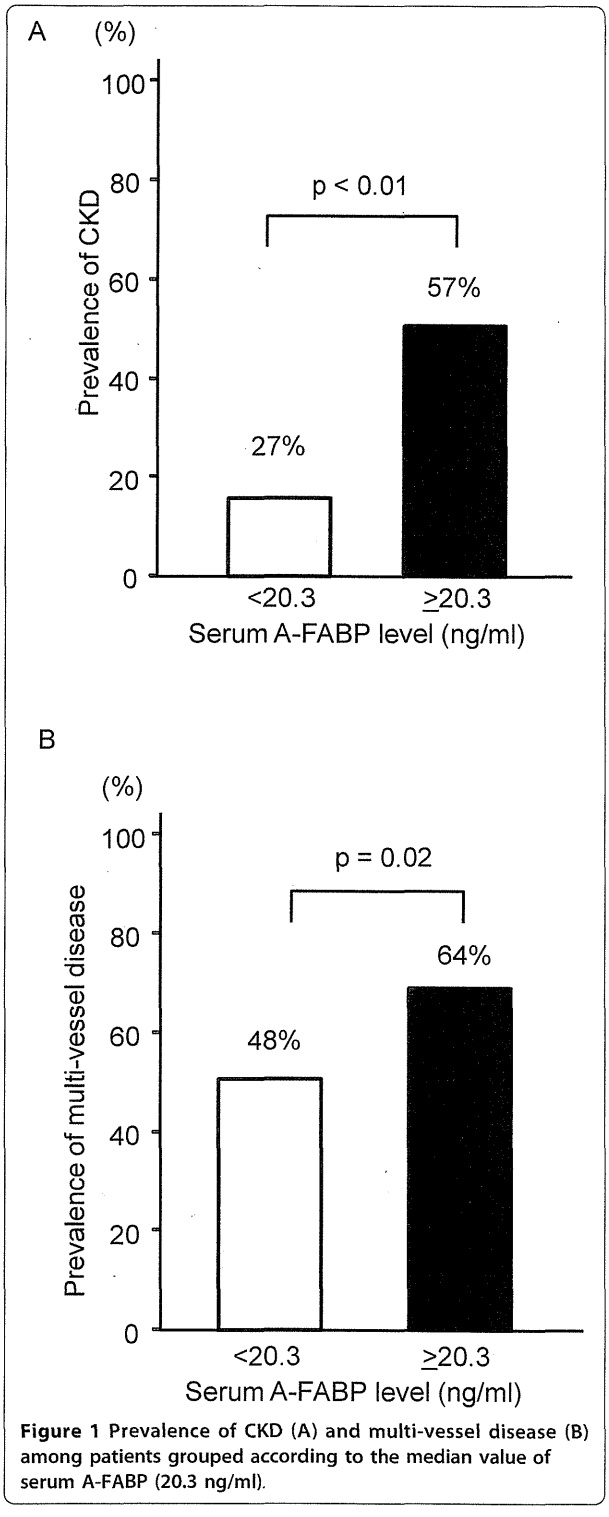

Figure 1 Prevalence of CKD (A) and multi-vessel disease (B) among patients grouped according to the median value of serum A-FABP (20.3 ng/ml).

ng/ml vs. 19.79(11.5) ng/ml, p < 0.01). Serum A-FABP levels were also significantly higher in patients with hypertension than those without hypertension (21.4 (14.9) ng/ml vs. 18.5(13.3) ng/ml, p = 0.02). Serum A-FABP levels did not vary by the presence or absence of diabetes mellitus, dyslipidemia, smoking status, or the use of specific medications (data not shown). As shown in Table 2 and Figure 2, serum A-FABP levels correlated significantly with gender, eGFR levels (Figure 2A), body mass index, hs-CRP levels, and stenosis scores (Figure 2B). Multiple linear regression analysis revealed that the serum A-FABP level was independently associated with the eGFR value and the stenosis score along with gender or body mass index. Next, the associations between CKD and other biochemical parameters were assessed (Table 3). Multiple logistic regression analysis revealed that the serum-A-FABP level (per doubling) was independently associated with CKD, with an odds ratio of 3.7 (95% confidential interval; 2.14-6.461, p < 0.01). Finally, the associations of the severity coronary artery disease with the levels of eGFR and serum A-FABP were analyzed by logistic regression analysis (Table 4). Multivariate analysis revealed that the presence of three-vessel disease in comparison with single-vessel disease was independently associated with the higher A-FABP level(per doubling) (odds ratio; 2.26, 95% confidential interval; 1.28-3.98, p < 0.01) and tended to be involved in the lower eGFR value (per ml/min/1.73 m^2)(odds ratio; 0.98, 95% confidential interval; 0.96-1.00, p < 0.06).

Discussion

We demonstrated that the serum A-FABP level was independently correlated with the eGFR value in patients with stable angina pectoris without hemodialysis. Serum A-FABP may be a novel marker of renal function as well as the severity of coronary artery

Table 2 Relationship between serum A-FABP and other parameters

	Univariate		Multivariate	
	r	p	β	p
Age	0.09	0.14		
Gender (male = 1)	-0.33	< 0.01	-0.31	< 0.01
Body mass index	0.35	< 0.01	0.35	< 0.01
Uric acid	0.12	0.08		
LDL-cholesterol	0.06	0.37		
HDL-cholesterol	-0.12	0.09		
Triglycerides*	-0.05	0.50		
HbA1c*	0.06	0.46		
HOMA-R*	0.11	0.10		
hs-CRP*	0.15	0.03	0.05	0.32
eGFR	-0.41	< 0.01	-0.40	< 0.01
Stenosis score	0.16	0.02	0.15	< 0.01

Values indicated with * were included in the model after log-transformation.
In the model, $R^2 = 0.42$

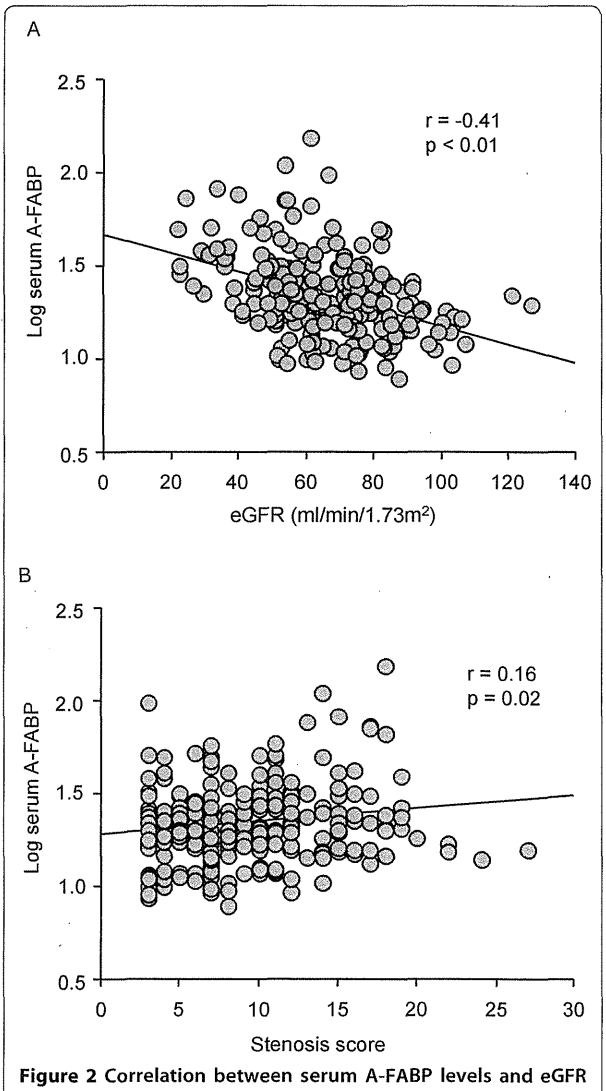

Figure 2 Correlation between serum A-FABP levels and eGFR (A) and coronary stenosis score (B) (n = 221).

disease in patients with a mild to moderate decrease in eGFR. Our findings suggest that circulating A-FABP may have an important role in the interplay between renal dysfunction and the development of coronary atherosclerosis.

The mechanism underlying the relationship between A-FABP and eGFR has not been fully clarified. Sommer et al. reported that serum A-FABP levels are more than 10-fold higher among patients with chronic hemodialysis than among controls [15]. In addition to A-FABP, circulating levels of adiponectin, leptin, and retinol-binding protein 4 have been reported to be higher among patients with chronic hemodialysis than among controls [20-22]. These results suggest that renal elimination plays an important role in determining the serum concentration of various adipocyte-derived proteins, including adiponectin, leptin, retinol-binding protein 4, and A-FABP, although the causal relationship between the elevated circulating A-FABP and renal dysfunction remains unclear. More mechanistic studies involving animal experiments are necessary to prove the concept that A-FABP is not only secreted from adipose tissue but also is cleared by the kidneys. Furthermore, markers of renal function should be included in future studies as potential confounders when examining the physiology and regulation of A-FABP in humans.

The finding that serum A-FABP was independently associated with the severity of coronary atherosclerosis is in agreement with our previous findings [11]. In human, recent study showed that circulating A-FABP levels were shown to be associated with vascular inflammation, as measured using (18)F-fluorodeoxyglucose positron emission tomography [23]. Peeters et al. reported that serum A-FABP levels and A-FABP concentrations in human carotid tissue were associated with the vulnerability of carotid plaques [24]. On the other hand, experimental studies showed that A-FABP plays a critical role in the development of atherosclerosis by coordinating the cholesterol-trafficking and inflammatory activity of macrophages [25]. A-FABP deficiency reduces foam cell formation in response to oxidized LDL and increases the cholesterol efflux pathway [25]. A-FABP-deficient mice also show a significant decrease in vascular atherosclerosis in the absence of differences in serum lipid levels or insulin sensitivity in a model of hyperlipidemia, and this effect is due OR has been attributed to the effects of A-FABP on macrophages [7]. In addition, A-FABP can activate several key inflammatory pathways. In A-FABP-deficient macrophages, the activity of the peroxisome proliferator-activated receptor γ and the liver X receptor α is enhanced, leading to suppressed transcription of several inflammatory genes [26,27]. In addition, the NF-κB pathway is impaired, resulting in suppression of inflammatory function [25].

The physiological significance of increased serum A-FABP in renal failure remains to be elucidated. CKD is strongly associated with the development of atherosclerotic lesions and mortality from cardiovascular disease [28]. Because A-FABP has been reported to induce dyslipidemia and atherosclerosis in animal models [7], A-FABP may contribute to the significantly increased cardiovascular mortality among patients with CKD. Recently, Furuhashi et al. reported that the circulating A-FABP level is a predictor of cardiovascular events in end-stage renal disease [29]. Peeters et al. also reported that the serum A-FABP levels in human carotid athermanous plaques were associated with adverse cardiovascular events [30]. Regarding a circulating FABP, recent studies showed heart -FABP may represent a marker for

Table 3 Relationship between CKD and other parameters

	Crude		Adjusted	
Factors	OR (95%CI)	p	OR (95%CI)	p
Age (per year)	1.11(1.08-1.16)	< 0.01	1.11(1.07-1.17)	< 0.01
Male	0.59(0.29-1.22)	0.16		
Smoking (yes)	0.28(0.10-0.76)	0.01	0.44(0.13-1.49)	0.18
Hypertension (yes)	2.19(1.13-4.29)	0.03	1.25(0.54-2.914)	0.56
Diabetes (yes)	0.53(0.31-0.93)	0.03	0.62(0.29-1.33)	0.22
Fasting blood glucose (per doubling)	0.16 (0.05-0.46)	< 0.01		
HOMA-R* (per doubling)	0.99(0.78-1.27)	0.97		
HbA1c (per doubling)	0.192(0.05-0.74)	0.02		
Dyslipidemia	0.77(0.38-1.56)	0.47		
HDL (per mg/dl)	0.99(0.97-1.01)	0.31		
LDL (per mg/dl)	0.99(0.98-1.00)	0.49		
Triglycerides (per doubling)	0.44(0.27-0..71)	< 0.01	0.49(0.26-0.93)	0.03
Uric acid (per mg/dl)	1.59(1.29-1.94)	< 0.01	1.70 (1.02-2.22)	< 0.01
A-FABP (per doubling)	3.03(1.94-4.72)	< 0.01	3.14(1.89-5.31)	0.01

In the model, $R^2 = 0.34$

early atherosclerosis [31]. Thus, the roles of FABPs as a predictor of cardiovascular events are promising. Taken together with our findings, the elevated serum A-FABP in patients with CKD may be involved in plaque vulnerability in atherosclerotic lesions and may predict a future cardiovascular event.

The role of circulating A-FABP as an atherogenic factor remains unknown. A recent study reported that A-FABP directly and acutely depresses the contraction of cardiomyocytes by decreasing intracellular Ca^{2+} levels [32], suggesting that a direct bioactive role for A-FABP may exist in cells. It is well established that A-FABP is expressed by adipocytes, which may be major contributors to circulating A-FABP levels. Therefore, A-FABP secreted from adipose tissue may contribute to the development of atherosclerosis. Future studies should address whether circulating A-FABP induces atherosclerosis by activating macrophages and vascular cells.

Table 4 Relationship between severe coronary artery disease and other parameters

	Crude		Adjusted	
Factors	OR (95%CI)	p	OR (95%CI)	p
Age (per year)	1.01(0.98-1.04)	0.55		
Male	1.39(0.51-3.79)	0.51		
Smoking (yes)	1.16(0.39-3.40)	0.79		
Hypertension (yes)	1.63(0.69-3.84)	0.26		
Diabetes (yes)	2.63(1.29-5.36)	< 0.01	3.20(1.43-7.17)	< 0.01
FBS (per doubling)	3.6(1.26-10.53)	0.02		
HOMA-R (per doubling)	1.31(0.95-1.80)	0.10		
HbA1c (per doubling)	5.95(1.21-29.14)	0.03		
Dyslipidemia	1.72(0.64-4.66)	0.28		
Triglycerides (per doubling)	1.11(0.63-1.95)	0.72		
HDL (per mg/dl)	0.97(0.94-1.00)	0.05		
LDL (per mg/dl)	0.99(0.98-1.00)	0.16		
Uric acid (per mg/dl)	1.02(0.82-1.27)	0.87		
eGFR (per ml/min/1.73m2)	0.97(0.95-0.99)	< 0.01	0.98(0.95-1.00)	0.06
A-FABP (per doubling)	2.97(1.77-4.98)	< 0.01	2.26(1.28-3.98)	0.01

In the model, $R^2 = 0.16$

Limitations

This study has several limitations that should be considered when interpreting the results. First, the sample size was not large. Second, our study was cross-sectional, which does not allow us to determine if a causal relationship exists between A-FABP and renal dysfunction or between A-FABP and the development of coronary artery disease. Prospective population-based studies are needed to address whether serum A-FABP is a risk factor for CKD or coronary artery disease. Finally, we enrolled patients who were admitted to the hospital for coronary angiography in order to obtain more accurate data on coronary stenosis. Most of our patients had established risk factors for coronary artery disease, and so, the generalizability of our findings to other patient populations is unclear.

Conclusions

We demonstrated that the serum A-FABP level was independently associated with CKD. Serum A-FABP may be a marker of renal dysfunction and may be associated with the severity of coronary artery disease in patients with a mild to moderate decrease in eGFR.

Thus, circulating A-FABP may have an important role in the interplay between renal dysfunction and the development of coronary atherosclerosis. Further studies with larger cohorts derived from the general population are necessary to evaluate whether circulating A-FABP levels can be used to predict the risk of renal dysfunction and the development of coronary artery disease.

Abbreviations

A-FABP: Adipocyte fatty acid-binding protein; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; CCBs: Calcium channel blockers.; CKD: Chronic kidney disease; CV: intra-assay coefficient of variation; eGFR: estimated glomerular filtration rate; FBS: fasting blood glucose; HDL-C: high-density lipoprotein cholesterol; HOMA-R: homeostasis model assessment ratio; hs-CRP: high-sensitivity C-reactive protein; IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol.

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Authors' contributions

MI, TM, MD, KT, MK, KN, SK and RN conceived the study, participated in study design and coordination, and assisted with the preparation of this manuscript. SU conducted the immunoassays. SH, SK, KN, and HI assisted with the preparation or critical review of this manuscript. All authors read and approved the submitted manuscript.

Competing interests

The authors declare that they have no competing interests.

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ORIGINAL ARTICLE

Evaluation of exercise capacity using wave intensity in chronic heart failure with normal ejection fraction

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Abstract Impaired exercise capacity has been found in patients with diastolic dysfunction with preserved systolic function. Although conventional transthoracic echocardiography (TTE) provides useful clinical information about systolic and diastolic cardiac function, its capability to evaluate exercise capacity has been controversial. The inertia force of late systolic aortic flow is known to have a tight relationship with left ventricular (LV) performance during the period from near end-systole to isovolumic relaxation. The inertia force and the time constant of LV pressure decay during isovolumic relaxation can be estimated noninvasively using the second peak (W_2) of wave intensity (WI), which is measured with an echo-Doppler system. We sought to determine whether W_2 is associated with exercise capacity in patients with chronic heart failure with normal ejection fraction (HFNEF) and to compare its ability to predict exercise capacity with parameters obtained by conventional TTE including tissue Doppler imaging. Sixteen consecutive patients with chronic HFNEF were enrolled in this study. Wave intensity was obtained with a color Doppler system for measurement of blood velocity combined with an echo-tracking system for detecting changes in vessel diameter. Concerning conventional TTE, we measured LV ejection fraction (EF), peak velocities of early (*E*) and late (*A*) mitral inflow using pulse-wave Doppler, and early (Ea) and late (Aa) diastolic velocities using tissue Doppler imaging. Left ventricular EF, *E*/*A* ratio, Ea, and *E*/Ea ratio did not correlate with exercise capacity, whereas W_2 significantly correlated with peak VO_2 ($r = 0.54$, $p = 0.03$), VE/VCO_2 slope ($r = -0.53$, $p = 0.03$), and $\Delta VO_2/\Delta WR$ ($r = 0.56$, $p = 0.02$). W_2 was associated with exercise capacity in patients with chronic HFNEF. In conclusion, W_2 is considered to be clinically more useful than conventional TTE indices for evaluating exercise capacity in patients with chronic HFNEF.

Keywords Wave intensity · Second peak · Exercise capacity · Echocardiography · Heart failure

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Introduction

Left ventricular (LV) diastolic abnormalities with preserved systolic function contribute to symptoms of heart failure [1, 2]. Cardiopulmonary exercise testing provides an objective means of assessing exercise capacity, and has become an important clinical tool with which to predict outcome in chronic heart failure patients [3–5]. Most investigators have focused on cardiac factors that predict exercise capacity, and it has been suggested that LV diastolic function is useful for determining exercise capacity, because an excessive rise in pulmonary capillary wedge pressure is the main cardiac cause of exertional dyspnea [6, 7].

In the previous study, Sugawara et al. [8] proposed the concept that the inertia force of aortic flow near end-ejection, which is generated by the ability of the left ventricle to actively stop blood flow, causes a rapid decrease in LV pressure, i.e., swift end-systolic unloading, producing a much smaller LV end-systolic volume. The resulting greater elastic recoil force brings faster LV relaxation. Thus, the inertia force may be linked with exercise capacity because it has a tight relationship with LV performance during the period from near end-systole to isovolumic relaxation. In the clinical setting, the inertia force can be estimated by the concept of wave intensity (WI), which is obtained noninvasively using an echo-Doppler system. Wave intensity is a hemodynamic index, which can evaluate the working condition of the heart interacting with the arterial system [9–11], and carotid arterial WI has two positive peaks. The first peak (W_1) of WI occurs in the early phase of LV ejection, and the second peak (W_2) occurs near end-ejection. During the period of W_2, the left ventricle actively stops aortic blood flow by generating forward traveling expansion (suction) waves. Therefore, we considered that W_2 obtained noninvasively may be useful for predicting exercise capacity.

Recent studies have emphasized that tissue Doppler imaging, which provided an estimate of LV diastolic function, i.e., the ratio of early transmitral velocity to tissue Doppler mitral annular early diastolic velocity (*E*/Ea), correlated with exercise capacity [12, 13]. However, several studies reported the limitations of current Doppler echocardiography for estimating LV diastolic function [14–16].

Therefore, we hypothesized that W_2 may be more strongly linked with exercise capacity compared with conventional transthoracic echocardiography (TTE) including tissue Doppler imaging. In the present study, we sought to determine whether W_2 is associated with exercise capacity in patients with chronic heart failure with normal ejection fraction (HFNEF), and to assess its ability to predict exercise capacity in comparison with parameters obtained by conventional TTE including tissue Doppler imaging.

Patients and methods

Study population

The study population consisted of 16 consecutive patients with chronic HFNEF (LV ejection fraction ≧45%) [17]. There were 10 males and 6 females with a mean age of 59 ± 13 years (range 39–73 years). The causes of heart failure were ischemia in 4 patients (25%) and nonischemia in 12 patients (75%). Current medication included β-blockers (44%), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (56%), digitalis (31%), and diuretics (31%). Patients were excluded if they had uncontrolled heart failure, angina, severe native valvular disease, or chronic lung disease. Patients were also excluded if the symptom-limited exercise test was not possible because of other non-cardiac conditions. All patients gave written informed consent.

Definition of time-normalized wave intensity

Wave intensity was originally defined as the product of ΔP and ΔU, where ΔP and ΔU are the changes in blood pressure P and velocity U, during constant short time intervals [9, 10]. This original wave intensity depends on the sampling interval, Δt, which makes it difficult to compare data taken at different sampling rates. Therefore, we normalized WI as the product of the derivatives of P and U with respect to time, dP/dt and dU/dt [11, 18]. Thus, the time-normalized WI is introduced:

$$\mathrm{WI} = (dP/dt) \cdot (dU/dt),$$

where dP/dt and dU/dt are the derivatives of P and U with respect to time. This time-normalized WI has the same property as the original wave intensity: if WI >0, the changes in pressure and velocity caused by the forward wave are greater than those caused by the backward wave, and vice versa [9, 10].

Measurements of wave intensity

Blood pressure waveforms are needed to calculate WI. Previous studies have demonstrated that arterial pressure waveforms and diameter-change waveforms are similar [19–21]. The similarity between carotid arterial pressure waveforms measured with a catheter-tipped micromanometer and carotid arterial diameter-change waveforms measured by echo tracking in humans has been reported [21] (Fig. 1). Therefore, using systolic and diastolic pressure measured with a cuff-type manometer applied to the upper arm, we calibrated the maximum and minimum values of a diameter-change waveform and used it as a surrogate for a blood pressure waveform. We used the system consisting of a color Doppler system (Prosound α10; Aloka, Tokyo, Japan) with a 7.5-MHz linear array probe, an echo-tracking subsystem, which is installed in the color Doppler system, and a personal computer [22, 23]. The echo-tracking subsystem automatically measures arterial diameter change with a precision of one-sixteenth of the ultrasound wavelength. The blood flow velocity averaged along the Doppler beam crossing the artery is measured by using range-gated color Doppler signals. This system uses different ultrasound beams for diameter change and for blood flow velocity measurements that can be manipulated independently. The two beams intersect so

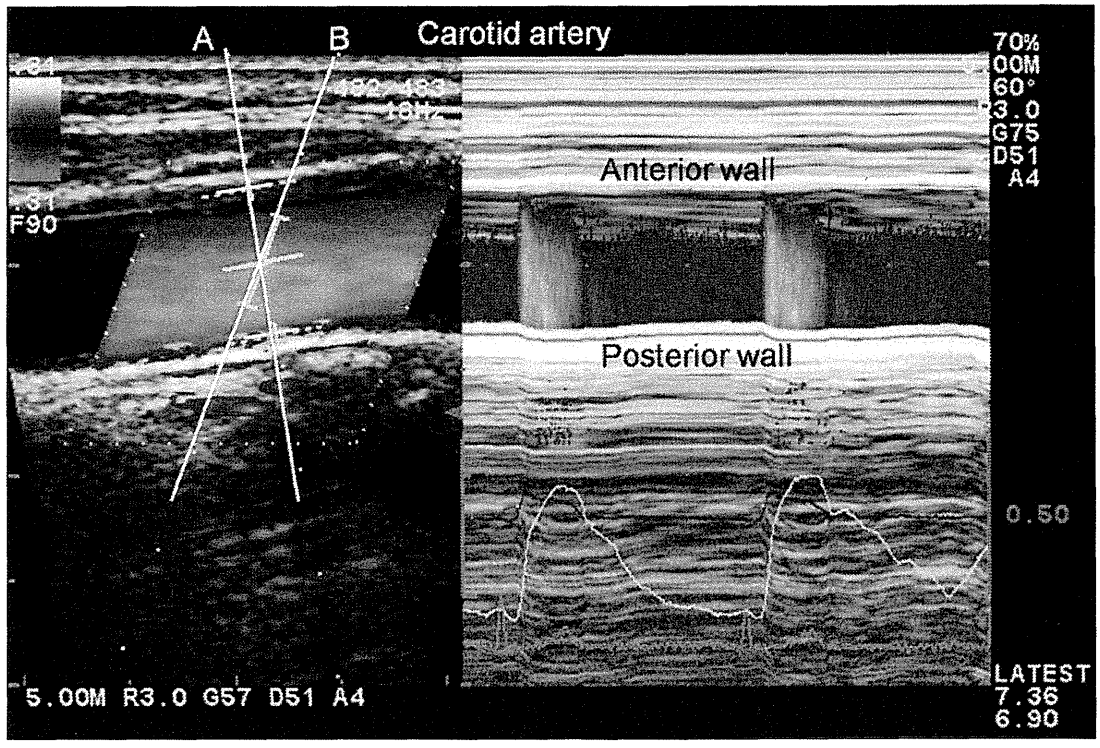

Fig. 1 Simultaneous measurements of diameter-change waveform and blood flow velocity. View on the monitor during the measurements **Left** color Doppler/B-mode long-axis view of the common carotid artery. *Line A* and *B* indicate the ultrasonic beam for echo-tracking and for blood flow velocity measurement, respectively. By setting the tracking positions displayed as small orange bars on the echo tracking beam (*line A*) to arterial walls, echo tracking automatically starts. The blood flow velocity averaged along the Doppler beam (*line B*) crossing the artery was measured using range-gated color Doppler signals (color of the blood flow velocity is removed to indicate the tracking bars clearly). **Right** the diameter-change waveform, which is calculated by subtracting the distance to the near wall from that to the far wall, and the velocity waveform are displayed on the M-mode view

that the center of the two tracking lines on the diameter-measuring beam and the center of the range gate of the velocity-measuring beam are superimposed. The diameter-change waveform, which is calculated by subtracting the distance to the anterior wall from that to the posterior wall, and the blood flow velocity waveform are displayed on the M-mode view. The sphygmomanometer-measured blood pressure data are entered for calibration. Five consecutive beats are ensemble-averaged to obtain a representative waveform. The maximum and minimum values of the diameter-change waveform are calibrated by systolic and diastolic blood pressure, and WI indices, W_1 and W_2, are calculated automatically. A stiffness parameter β is also calculated from the measured data.

In this study, the measurements of WI were made with the patients in the supine position after 15 min rest. Data were acquired from the right common carotid artery at about 2 cm proximal to the bifurcation to avoid any influence of the complex flow in the carotid sinus. In the long-axis scanning, optimal images were best achieved by positioning and orienting the probe so that clear and parallel delineation of the intima-media complex at both the anterior and posterior walls could be seen. The echo-tracking beam was steered so that it was orthogonal (90°) to the arterial walls. Echo tracking was performed just outside of the intima-media complex where stable echo tracking was possible. The color Doppler beam was steered so that the angle between the beam and flow direction was less than 60°. Recording of diameter, velocity, and WI were made.

The reproducibility of the present WI measurement system has been reported, but the variability of W_2 is higher than those of other WI indices [23]. Therefore, WI was measured more than six times just before cardiopulmonary exercise testing, and the mean value in each patient was calculated. The analysis was performed by two independent experienced investigators who were blinded to the data of cardiopulmonary exercise testing.

Measurements of conventional transthoracic echocardiography

All patients underwent TTE just before cardiopulmonary exercise testing. All measurements were averaged from

three consecutive cycles. Left ventricular end-diastolic and end-systolic volumes were calculated by the modified Simpson rule, and the standard formula was applied to give LV ejection fraction (EF). Mitral inflow was analyzed for peak early diastolic (*E*) and late diastolic (*A*) velocities, *E*/*A* ratio, and deceleration time of *E* velocity by pulse-wave Doppler. The early (Ea) and late (Aa) diastolic velocities were measured by tissue Doppler imaging, obtained from the apical four-chamber view. Ea septal mitral annulus velocities were measured, and the dimensionless mitral *E*/Ea ratio was calculated.

Cardiopulmonary exercise testing

All patients underwent symptom-limited exercise tests on an upright bicycle ergometer using a ramp protocol (15 W/min) with simultaneous respirator gas analysis. Patients were encouraged to exercise to exhaustion or to a respiratory exchange ratio ≧1.09. Blood pressure and heart rate were measured every minute. A 12-lead electrocardiogram was continuously monitored during exercise testing. Breathed gas was continuously collected by a gas analyzer to analyze oxygen uptake (VO_2), carbon dioxide production (VCO_2), and minute ventilation (VE). Exercise duration was defined as the time from the start of exercise until its cessation from dyspnea or leg fatigue. Peak VO_2 was defined as the highest VO_2 value achieved at peak exercise after reaching the respiratory compensation point. The gradient of the VE–VCO_2 relationship (VE/VCO_2 slope) and the oxygen uptake to work rate ($\Delta VO_2/\Delta WR$) were also determined.

Statistical analysis

Continuous data are presented as mean ± standard deviation (SD). Discrete data are presented as numbers or frequencies of occurrence. Pearson's correlation coefficients were used to evaluate the correlation between WI or conventional TTE and exercise capacity. A probability value (p) of less than 0.05 was considered statistically significant.

Results

Clinical characteristics of the 16 patients are summarized in Table 1. The measurements of conventional TTE, WI, and cardiopulmonary exercise testing are summarized in Table 2. The mean value of LVEF was 59 ± 10%. The mean value of *E*/Ea ratio was 9.9 ± 2.5, and 13 (81%) of the patients had a value of *E*/Ea ranging from 8 to 15. The mean values of W_1 and W_2 were 7170 ± 4180 mmHg m/s^3 and 1550 ± 590 mmHg m/s^3. Regarding cardiopulmonary exercise testing, the mean exercise time was 9.0 ± 2.1 min. The peak VO_2 averaged 19.0 ± 4.3 ml/min/kg, which corresponded to 62 ± 14% of the maximal age- and sex-predicted peak VO_2. Dyspnea, rather than leg fatigue, was the most frequent cause of exercise cessation. No patients had angina, significant ischemic ST abnormalities in the electrocardiogram, or severe arrhythmia during cardiopulmonary exercise testing.

The correlations of conventional TTE and WI with exercise capacity are summarized in Table 3. Left ventricular EF did not correlate with the parameters of exercise capacity (exercise time, peak load, peak VO_2, VE/VCO_2 slope, or $\Delta VO_2/\Delta WR$) (Fig. 2a–c). There were also no correlations between *E*/*A* ratio, Ea (Fig. 2d–f) or *E*/Ea ratio (Fig. 2g–i) and the parameters of exercise capacity. Regarding WI, there were no correlations between W_1 and the parameters of exercise capacity. However, W_2 was significantly correlated with exercise time ($r = 0.63$, $p = 0.009$), peak load ($r = 0.58$, $p = 0.02$), peak VO_2 ($r = 0.54$, $p = 0.03$), VE/VCO_2 slope ($r = -0.53$, $p = 0.03$), and $\Delta VO_2/\Delta WR$ ($r = 0.56$, $p = 0.02$) (Fig. 2j–l). W_2 was associated with exercise capacity in patients with chronic HFNEF.

Discussion

In the present study, LVEF, *E*/*A* ratio, Ea and *E*/Ea ratio did not correlate with the parameters of exercise capacity, while W_2, which is connected to the inertia force, significantly correlated with peak VO_2, VE/VCO_2 slope, and $\Delta VO_2/\Delta WR$. We found that W_2 more strongly correlated

Table 1 Patient characteristics

Variables	
Age (years)	59 ± 13
Male	10 (63)
Body mass index (kg/m^2)	24.8 ± 5.9
Clinical diagnosis	
Ischemia	4 (25)
Nonischemia	12 (75)
Systolic blood pressure (mmHg)	125 ± 17
Diastolic blood pressure (mmHg)	77 ± 13
Heart rate (beats/min)	68 ± 10
Medical treatment	
β-Blockers	7 (71)
ACE inhibitors or ARBs	9 (56)
Digitalis	5 (31)
Diuretics	5 (31)

Data are presented as mean ± SD or numbers (percentage)

ACE angiotensin-converting enzyme, *ARB* angiotensin receptor blocker

Table 2 Measurements of transthoracic echocardiography, wave intensity, and cardiopulmonary exercise testing

Variables	
Transthoracic echocardiography	
LVEF (%)	59 ± 10
LVDd (mm)	51 ± 7
LVDs (mm)	35 ± 8
E (m/s)	0.64 ± 0.19
A (m/s)	0.68 ± 0.14
E/*A* ratio	1.0 ± 0.3
Deceleration time (ms)	246 ± 59
Ea (cm/s)	6.6 ± 1.7
E/Ea ratio	9.9 ± 2.5
Wave intensity	
W_1 (mmHg m/s^3)	7170 ± 4180
W_2 (mmHg m/s^3)	1550 ± 590
Stiffness parameter β	9.3 ± 3.8
Cardiopulmonary exercise testing	
Exercise time (min)	9.0 ± 2.1
Peak load (W)	101 ± 42
Peak VO_2 (ml/min/kg)	19.0 ± 4.3
VE/VCO_2 slope	26.4 ± 5.4
$\Delta VO_2/\Delta$WR	7.5 ± 1.4

Data are presented as mean ± SD

LVEF left ventricular ejection fraction, *LVDd* left ventricular diastolic dimension, *LVDs* left ventricular systolic dimension, *E* peak early transmitral diastolic velocity, *A* peak late transmitral diastolic velocity, *Ea* peak early diastolic velocity of medial mitral annulus, W_1 first peak of wave intensity, W_2 second peak of wave intensity, VO_2 oxygen uptake, *VE/*VCO_2 *slope* gradient of the ventilation to carbon dioxide production, $\Delta VO_2/\Delta WR$ oxygen uptake to work rate

with exercise capacity than with conventional TTE. This suggests the potential of W_2 in the clinical setting for predicting exercise capacity in patients with chronic HFNEF.

It has been established that patients with heart failure have impaired exercise tolerance, which is the predictor of mortality [24]. Although the mechanisms of exercise intolerance are multifactorial, they depend at least in part on the pump function of the heart, i.e., the response of cardiac output to exercise. The increase in cardiac output during exercise is the primary determinant of exercise tolerance in patients with heart failure [25, 26]. Several studies have shown that more than 50% of elderly patients who present with symptoms of heart failure have preserved LV systolic function [27–29]. Recently, LV diastolic dysfunction has been considered to be a major factor in limiting exercise capacity by raising diastolic pressures and compromising LV filling [6, 7]. In the clinical setting, Doppler echocardiography can characterize LV diastolic function through a combination of measurements, which show evidence of slowed LV relaxation, increased LV stiffness, or abnormality of LV filling pressure. In particular, *E*/Ea ratio measured by tissue Doppler echocardiography has been shown to be useful in estimating LV filling pressure, one component of diastolic function that reflects pulmonary capillary wedge pressure [30]. However, it remains controversial whether parameters of resting conventional TTE, including tissue Doppler echocardiography, can predict exercise capacity [12, 13, 31]. There are several limitations in estimating LV diastolic function with tissue Doppler echocardiography [14–16]. The patients with a value of *E*/Ea >15 are considered to have diagnostic evidence for elevated LV filling pressure [15], whereas the patients with a wide range of *E*/Ea values ($8 < E/\text{Ea} < 15$) are required to obtain an LV filling pressure estimate from additional investigations, including left atrial size, mitral filling time, deceleration time of *E* velocity, pulmonary venous flow velocity, and pulmonary artery systolic pressure. No single parameter of Doppler echocardiography has yielded a robust criterion for LV diastolic function. Furthermore, there are technical limitations including angle dependency, signal noise, signal drifting, spatial resolution, sample volume, and tethering artifacts. In the present study, patients with *E*/Ea values ranging from 8 to 15 were included. This may have brought about our result that *E*/Ea ratio did not associate with exercise capacity.

Wave intensity is a hemodynamic index, which can evaluate the working condition of the heart interacting with the arterial system [9–11]. Several studies have indicated clinical usefulness of WI [23, 32–36]. Wave intensity is obtained in the carotid artery using an echo-Doppler system, and it has two positive peaks. W_1, which occurs in the early phase of LV ejection, correlates with the maximum rate of LV pressure rise (max. d*P*/d*t*) and reflects LV contractile function [32], whereas W_2 occurs near end-ejection. During the period of W_2, both aortic pressure and velocity are decreasing; therefore, the forward-traveling waves during this period are expansion (suction) waves. In the previous study, Sugawara et al. [8] proposed the concept that the inertia force of blood flowing out of the left ventricle toward the aorta, which must be decelerated to a standstill, causes a rapid decrease in LV pressure and generates suction waves in the left ventricle near end-ejection. The inertia force causes swift end-systolic unloading of the left ventricle, producing a much smaller LV end-systolic volume and greater elastic recoil force. Thus, the inertia force contributes to the deceleration of aortic flow and produces a greater W_2. In the clinical setting, Ohte et al. [32] reported that W_2 was significantly higher in patients with the inertia force than in those without the inertia force. From these findings, W_2 is connected to the inertia force and should have a close

Table 3 Correlations of transthoracic echocardiography and wave intensity with exercise capacity

	Exercise time	Peak load	Peak VO_2	VE/VCO_2 slope	$\Delta VO_2/\Delta WR$
Systolic blood pressure	0.06	−0.05	−0.05	−0.20	−0.02
Diastolic blood pressure	0.25	0.13	−0.28	−0.49	−0.20
Heart rate	−0.02	0.06	−0.28	0.05	0.09
Transthoracic echocardiography					
LVEF	−0.07	−0.09	−0.06	0.07	−0.02
LVDd	0.26	0.25	0.18	−0.14	0.25
LVDs	0.27	0.28	0.16	−0.16	0.12
E	0.01	0.04	0.14	0.14	−0.01
A	−0.35	−0.48	-0.45	0.36	−0.33
E/A ratio	0.12	0.28	0.29	−0.20	−0.13
Deceleration time	−0.15	−0.28	-0.44	−0.15	−0.30
Ea	0.25	0.34	0.41	−0.06	0.17
E/Ea ratio	−0.26	−0.38	−0.23	0.20	−0.21
Wave intensity					
W_1	0.21	0.20	0.15	−0.38	0.24
W_2	0.63**	0.58*	0.54*	−0.53*	0.56*
Stiffness parameter β	−0.27	−0.25	−0.35	0.08	0.05

r value is shown. $*p < 0.05$, $**p < 0.01$

LVEF left ventricular ejection fraction, *LVDd* left ventricular diastolic dimension, *LVDs* left ventricular systolic dimension, *E* peak early transmitral diastolic velocity, *A* peak late transmitral diastolic velocity, *Ea* peak early diastolic velocity of medial mitral annulus, W_1 first peak of wave intensity, W_2 second peak of wave intensity, VO_2 oxygen uptake, *VE/*VCO_2 *slope* gradient of the ventilation to carbon dioxide production, $\Delta VO_2/\Delta WR$ oxygen uptake to work rate

relationship with LV performance during the period from near end-systole to isovolumic relaxation.

Several mechanisms by which W_2 can influence exercise capacity in patients with chronic HFNEF have been proposed. LV diastolic function is a main factor limiting exercise capacity by an excessive rise in pulmonary capillary wedge pressure [6, 7]. In late systole, LV pressure rapidly declines until left atrial pressure exceeds that of the left ventricle, leading to the onset of early filling [37]. W_2 itself is closely correlated with the indices of LV relaxation calculated invasively, such as the maximum rate of LV pressure decay and the time constant of LV pressure decay during isovolumic relaxation [32]. Moreover, early diastolic relaxation is quantified by the rate of pressure decay and is also influenced by late systolic arterial loading [38, 39]. The inertia force causes rapid end-systolic unloading of the left ventricle, tending to reduce LV end-systolic volume and increase elastic recoil force [8]. Furthermore, LV contraction and ejection dynamics are intimately linked to LV relaxation from the viewpoint of cardiac mechanics [40–42]. The inertia force is a crucial parameter whereby LV systolic function delivers its effect on left ventricle early diastolic performance. The greater inertia force is produced from better LV systolic function [8, 43]. Thus, the concept of hemodynamically induced inertia force may contribute to the further understanding of LV contraction–relaxation coupling. Indeed, the previous study indicated that a higher inertia force in a resting condition was associated with greater exercise capacity [8]. The inertia force was enhanced during exercise in patients who had a relatively large inertia force in a resting condition [8] because sympathetic stimulation and tachycardia produced a downward shift of the early diastolic portion of the LV pressure–volume loop [44]. A good heart enhances its function by generating and then utilizing the inertia force more effectively during exercise. These findings support our results that W_2, which corresponds to the inertia force, correlated with exercise capacity in patients with chronic HFNEF.

Our study had several limitations. First, only 16 patients from a single center were involved. Study of large patient populations from various centers is needed to confirm our data. Second, we enrolled patients who received medical treatments. In particular, the effects of vasodilators on the vascular system are known. Niki et al. [45] evaluated the effects of nitroglycerin on the cardiovascular system using WI, and indicated that W_1 and stiffness parameter β increased after nitroglycerin administration, but W_2 did not change significantly. However, it is possible that these medical treatments cause different results of the association between W_2 and exercise capacity. Finally, exercise capacity is also influenced by noncardiac factors, such as

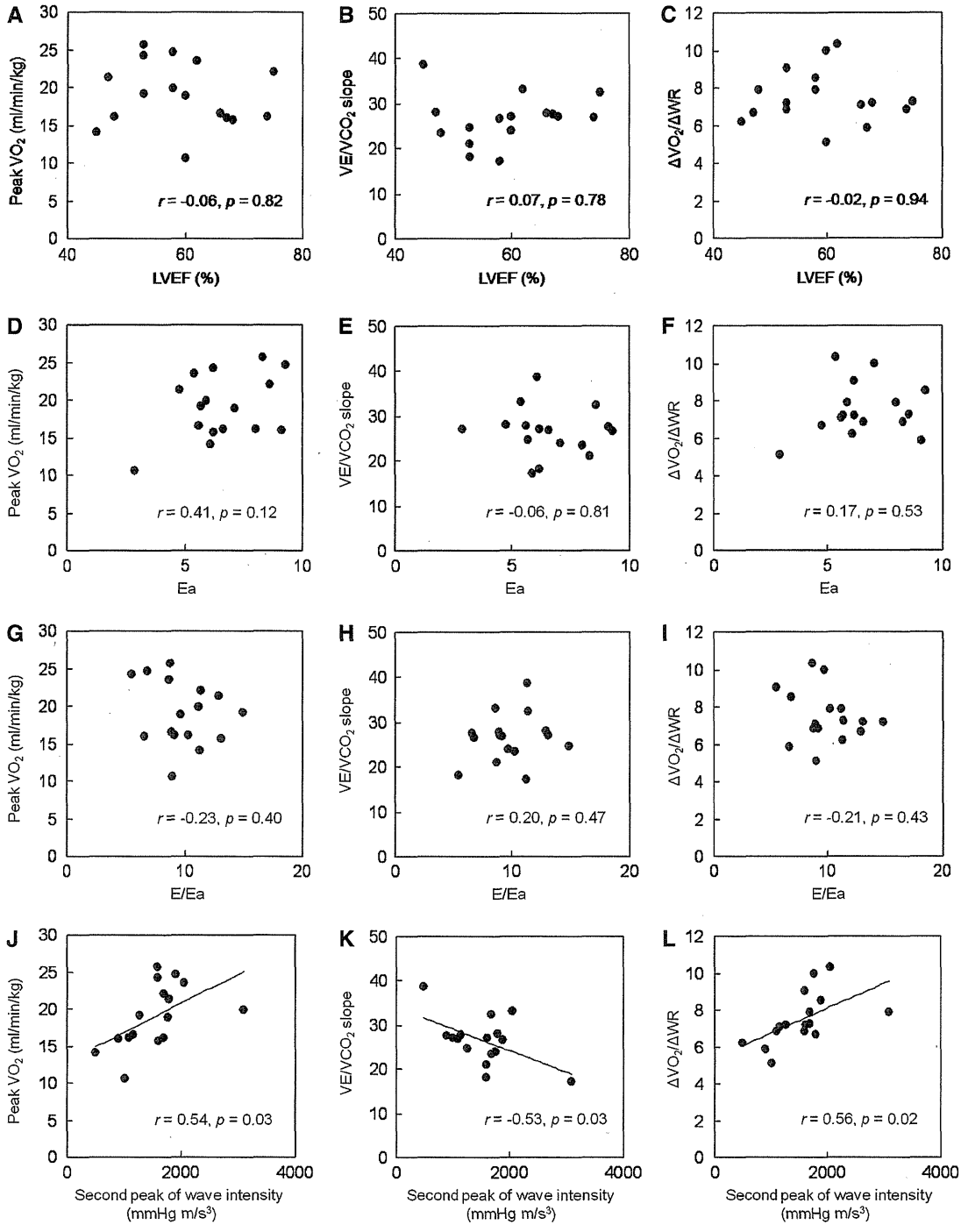

Fig. 2 Correlations of LVEF (**a–c**), Ea (**d–f**), *E*/Ea ratio (**g–i**), and the second peak of wave intensity (**j–l**) with exercise capacity. Significant correlations between the second peak of wave intensity and peak VO_2 (**j**), VE/VCO_2 slope (**k**), and $\Delta VO_2/\Delta WR$ (**l**) are observed. *LVEF* left ventricular ejection fraction, *E* peak early transmitral diastolic velocity. *Ea* peak early diastolic velocity of medial mitral annulus, VO_2 oxygen uptake, *VE*/VCO_2 *slope* gradient of the ventilation to carbon dioxide production; $\Delta VO_2/\Delta WR$ oxygen uptake to work rate

age, gender, pulmonary function, hemoglobin content, and skeletal muscle. These factors might have influenced exercise capacity in this study.

In conclusion, W_2 can be noninvasively obtained using an echo Doppler and echo-tracking system in the clinical setting, and may be more useful to predict exercise

capacity in comparison with conventional TTE in patients with chronic HFNEF.

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