Table 5 Frequencies of the Haplotype Constructed by the Polymorphisms A162C and T8733A in the Total Group and in Males

Haplotype	Overall (%)	Control (%)	MI (%)	Permutation p-value	Overall (%)	Control males (%)	MI males (%)	Permutation p-value
A162C/T8733A				<0.0001				0.043
AT	31.0	31.3	29.4	0.388	31.4	32.0	29.8	0.361
CT	25.6	25.2	27.8	0.196	26.1	25.5	27.5	0.421
AA	20.9	20.0	25.8	0.003	21.4	20.1	25.1	0.035
CA	22.6	23.6	16.9	0.001	21.1	22.3	17.6	0.03

The percentage of the haplotype constructed by the polymorphisms A162C and T8733A is indicated. Permutation p-values were calculated by 1,000 iterations of the permutation test using the SNPAlyze Pro statistical package.
The haplotypes [AT], [CT], [AA], and [CA] mean as follows: AT, A162 and T8733; CT, C162 and T8733; AA, A162 and A8733; CA, C162 and A8733, respectively.

variants and MI that has been recently reported in Caucasian populations.

Because the genetic contribution of a single gene to common disease susceptibility seems to be very low, as observed in the I/D polymorphism of the ACE gene in cardiovascular diseases,[20,21] validation studies in other populations are very important. However, some of the allele frequencies of the HapA and HapB haplotypes were too low in our study population and so we could not replicate the previous studies by DeCode.[6] However, the haplotype that was newly identified in our study population was revealed to be significantly associated with MI. Thus, the hypothesis that *ALOX5AP* contributes to the susceptibility for MI is validated and strengthened by the present study.

The precise mechanism of how variants of *ALOX5AP* confer susceptibility for atherothrombotic diseases remains to be determined. The biological significance of the haplotype defined by A162C and T8733A remains to be solved, because these 2 polymorphisms reside in intron regions. Future studies will be needed to investigate whether the haplotype influences the production of leukotrienes by neutrophils.

Identification of *ALOX5AP* as one of the genes contributing to MI may have clinical implications. Leukotriene antagonists are currently used to treat asthma and various allergic diseases.[22] It would be interesting to determine whether these clinically useful antagonists could be helpful for the secondary prevention of MI in selected subjects defined by haplotype.

Table 6 Characteristics of Subjects With the Homozygous Genotype of the [CA] Haplotype and the Others

Genotype	[CA][CA] homozygous	Others	p-value
n	113	2,115	
Sex (% male)	45.1	53.3	0.0920
Age (years)	62.3±1.06	63.7±0.24	0.2218
BMI (kg/m^2)	23.1±0.29	22.9±0.07	0.5411
C-SM (%)	44.3	47.2	0.5453
HT (%)	37.2	43.0	0.2192
HLP (%)	28.3	31.8	0.4353
DM (%)	8.9	11.4	0.3846
MI (%)	8.0	16.3	0.0107

Data are mean±standard error. Differences between the 2 groups ([CA] [CA] homozygous vs the others) were calculated by t-test or χ^2 analysis.
BMI, body mass index; C-SM, current smoking habit; HT, hypertension; HLP, hyperlipidemia; HDL-C, high-density lipoprotein cholesterol; DM, diabetes mellitus.

Acknowledgments

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Circ J 2005; **69:** 1192–1195

Assessment of MEF2A Mutations in Myocardial Infarction in Japanese Patients

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Background Recently, a mutation in the human MEF2A gene was reported to be responsible for an autosomal dominant form of coronary artery disease, so the purpose of the present study was to assess the significance of MEF2A mutations in Japanese subjects with myocardial infarction (MI).

Methods and Results The study population consisted of 589 control subjects recruited from the Suita study and 379 subjects with MI. The promoter, all the exons, and 3'-UTR regions of MEF2A were sequenced in 190 subjects with myocardial infarction. We found 2 amino acid length polymorphisms, a 7-amino acid deletion polymorphism, and a nonsense mutation (R447X) in exon 12. The length and deletion polymorphisms did not confer susceptibility to MI. Although the nonsense mutation was detected in 1 subject with MI, and in none of the control subjects, the impact of this mutation does not appear to be great; the subject had the MI while in his 70s, had 2 major risk factors, and no family history of ischemic heart disease.

Conclusion MEF2A polymorphism does not contribute appreciably to MI in the Japanese population. (*Circ J* 2005; **69:** 1192–1195)

Key Words: MEF2A; Myocardial infarction; Polymorphisms

Myocardial infarction (MI) is a multifactorial disease caused by environmental and genetic factors. There is an increasing number of studies that have identified the genes contributing to ischemic heart diseases (IHD)[1–8] and recently, a mutation in the human MEF2A gene was reported as responsible for an autosomal dominant form of coronary artery disease (CAD)[9] The 7-amino acid deletion disrupts the nuclear localization of the mature protein and reduces MEF2A-induced transcriptional activation[9] The same authors have reported MEF2A missense mutations in 4 of 207 sporadic CAD cases and estimated that MEF2A mutations contribute to approximately 2% of CAD![10] On the other hand, Weng et al recently reported a lack of MEF2A mutations in 300 CAD cases;[11] so the purpose of the present study was to assess the significance of MEF2A mutations in Japanese subjects with MI.

Methods

Study Population

The control group consisted of 589 subjects recruited from the Suita study who were at least 60 years of age with no cardiovascular disease and no family history IHD. The selection criteria and design of the Suita Study have been described previously![12–14] We excluded young subjects from the control group, because they might develop MI in their 50s and 60s. The MI group consisted of 379 randomly selected inpatients and outpatients with documented MI who were admitted to the Division of Cardiology at the National Cardiovascular Center between May 2001 and April 2003 (MI group)![15] The characteristics of the study population are shown in Table 1. All subjects gave written informed consent and the present study was approved by the Ethics Committee of the National Cardiovascular Center and by the Committee on Genetic Analysis and Gene Therapy of the National Cardiovascular Center.

DNA Studies

A promoter region and all of the 12 exon regions were sequenced in 190 of the subjects with MI (Fig 1) and we found variations that altered the amino acid sequences in exon 12 only. Next, we sequenced exon 12 in 589 control subjects and the remaining 189 subjects with MI. The variations in exon 12 were all determined by sequencing.

Statistical Analysis

All statistical analyses were performed with the JMP

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Table 1 Characteristics of the Study Population

	Control	*MI*	*p-value*
n	*584*	*379*	
Gender (% male)	*49.3*	*85.5*	*<0.0001*
Age (years)	*70.6±0.3*	*58.0±0.4*	*<0.0001*
BMI (kg/m²)	*22.67±0.12*	*23.83±0.115*	*<0.0001*
TC (mg/dl)	*207.7±1.4*	*199.7±2.3 (n=224)*	*0.0030*
HDL-C (mg/dl)	*58.8±0.6*	*43.0±1.1 (n=194)*	*<0.0001*
Smoking			*<0.0001*
Current	*93*	*228*	
Past	*163*	*74*	
Never	*328*	*77*	
DM (%)	*7.7*	*38.7*	*<0.0001*
HT (%)	*35.5*	*52.9*	*<0.0001*

Data are mean±standard error. Differences between 2 groups (Control vs myocardial infarction (MI)) were calculated by t-test or χ^2 analysis. BMI, body mass index; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; DM, diabetes mellitus; HT, hypertension.

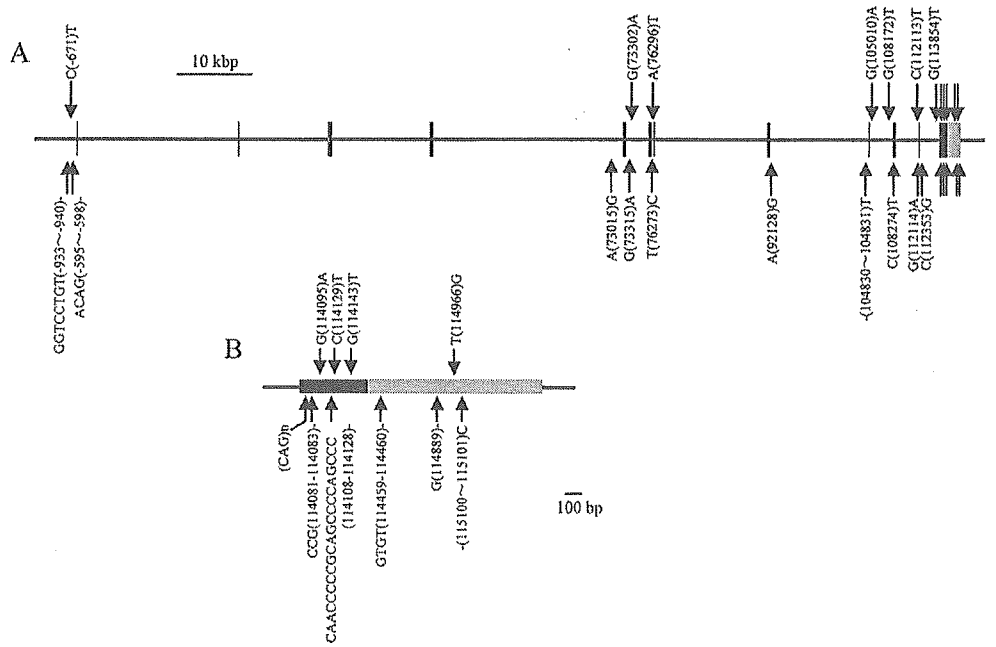

Fig 1. Scheme of the MEF2A gene. (A) Promoter region and all of the 12 exon regions are shown. (B) Expanded region of exon 12. The 5'- and 3'-UTR regions are indicated by gray boxes, and coding regions are indicated by black boxes. The 27 polymorphisms that were found are indicated by arrows.

statistical package (SAS Institute Inc, Cary, NC, USA) unless otherwise stated. Chi-squared analysis was performed to compare haplotype frequencies between the control and MI groups.

Results

We found 27 variations in MEF2A (Table 2), and 4 variations in exon 12 that altered the amino acid sequence of the MEF2A protein (Fig 2). The number of polyglutamine tandem repeats (region A) varied between 4 and 15 (genotype 1), and the number of proline tandem repeats (region B) varied between 4 and 5 (genotype 2). The 21-bp deletion (7-amino acid deletion), which was originally implicated in an autosomal dominant form of CAD,[9] was also observed in region C (genotype 3) (Fig 2). We found one nonsense mutation (R447X) in exon 12 in a MI subject, and it was localized just downstream of the 21-bp deletion site (Fig 3).

The haplotype frequencies defined by the 3 genotypes are shown in Table 3: there were no significant differences between the control and MI groups.

Discussion

Wang et al reported that a mutation in the human MEF2A gene was responsible for an autosomal dominant form of CAD,[9] but Weng et al could not find any MEF2A mutations in 300 cases of CAD.[11] Thus, the association between mutations of MEF2A and CAD is controversial,[16,17] and our results favors a lack of association.

Our results indicate that length polymorphisms in MEF2A do not contribute appreciably to MI in the Japanese population. Furthermore, the 21-bp deletion in MEF2A, which was originally implicated,[9] did not seem to be associated with MI. The nonsense mutation (R447X) may affect susceptibility to MI, but the particular patient with this mutation had the MI in his 70 s, and had no family history of IHD. He also had 2 risk factors: diabetes mellitus and smoking. Thus, the impact of this mutation does not appear to be great.

We sequenced all the coding regions of MEF2A in 190 subjects with MI and found neither missense nor nonsense mutations, except for R447X. Taking all our results together, MEF2A polymorphism does not appear to contribute appreciably to MI in the Japanese population.

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Table 2 The 27 Variations Found in the MEF2A Gene

Region	*Polymorphisms*	*Sequence around polymorphisms*	*Amino acid mutation*
Promoter	*GGTCCTGT(–933~–940)–*	*AGACATTTTAATTTCACCTC[GGTCCTGT/–]GGTCCTGTGGTCCTGTGATC*	
	C(–671)T	*TGGCCGACGCTTAAGGAAAA[C/T]AGAAAAGAACCTACATGAAT*	
	ACAG(–595~–598)–	*TTTATTAATGTGAATCATAG[ACAG/–]CCATCAGTCTTCTATTCATT*	
Intron 4	*A(73015)G*	*CCTGTAAGTACTTTTACTTT[A/G]CCTCTACTTTTTATTTGTTG*	
Intron 5	*G(73302)A*	*GGTGATGACAACAATAAGTA[G/A]AAGGGAAGAAATGCATTTTA*	
	G(73315)A	*ATAAGTAGAAGGGAAGAAAT[G/A]CATTTTATTAGTATTTTTTA*	
Intron 6	*T(76273)C*	*CTTTGATGAGCAAGAATCAC[T/C]GATACATAATTGGCCTCATT*	
	A(76296)T	*TACATAATTGGCCTCATTTT[A/T]AAGTATTTTTTTGAAAATCA*	
Intron 8	*A(92128)G*	*GTATTTGAAGAGACAAGTCT[A/G]TTTCAAATACACAAAAATCA*	
	–(104830~104831)T	*TAGTGTCCAAATATGTTTTT[T/–]CTAAAGAAATATTTTGTTTG*	
Intron 9	*G(105010)A*	*CGTGTTGTTATCTAACCAAT[G/A]TTCCCTTTGTTACACAAATT*	
	G(108172)T	*CAGTGCTTCAGAAAATGACA[T/G]TCATATGAAACTGTGAAAAA*	
Exon 10	*C(108274)T*	*TCTTTTTTGATCTCACAGAA[T/C]ACCCAGAGGATCAGTAGTTC*	*N297N*
Intron 10	*C(112113)T*	*AGGAACTTTTGCAGTAGCTA[C/T]GTAAAAAATAGATTCCGTA*	
	G(112114)A	*GGAACTTTTGCAGTAGCTAC[G/A]TAAAAAATAGATTCCGTATG*	
Intron 11	*C(112353)G*	*TTACTCCTGGCCTACACACT[C/G]TCTTTTCCTATCAGTGACAG*	
	G(113854)T	*CTCTGGGCCCTTTTCCATCA[G/T]GCAGTGTCTCTACTGTATCA*	
Exon 12	*(CAG)n(n=4–15)(114048–114080)*	*GTATGACCCCATCGGGCTTC[(CAG)n]CCGCCGCCACCACCGCAGCC*	*(Q)n (n=4–15)*
	CCG(114081–114083)–	*AGCAGCAGCAGCAGCAG[CCG/–]CCGCCACCACCGCAGCCCA*	*(P)n (n=4 or 5)*
	G(114095)A	*CAGCAGCCGCCGCCACCACC[G/A]CAGCCCCAGCCACAACCCCC*	*P435P*
	CAACCCCCGCAGCCCCAGCCC(114108–114128)–	*CACCACCGCAGCCCCAGCCA[CAACCCCCGCAGCCCCAGCCC/–]CGACAGGAAATGGGGCGCTC*	*7 amino acid deletion*
Exon 12	*C(114129)T*	*AACCCCCGCAGCCCCAGCCC[C/T]GACAGGAAATGGGGCGCTCC*	*R447X*
	G(114143)T	*CAGCCCCGACAGGAAATGGG[G/T]CGCTCCCCTGTGGACAGTCT*	*G451G*
3'-UTR	*GTGT(114459–114460)-*	*ATATATGTATGTGGGTGTGA[-/GTGT]GTGTGTATGTGTGGGTGTGT*	
	G(114889)-	*AAAACAAACAAAACAAAAAA[G/-]CCCCACACATAACTGTTTTG*	
	T(114966)G	*TAGCTAATAAAGAAAGAGAA[T/G]AGAAAACACGCATGAGATAT*	
	-(115100~115101)C	*TCATATCTTAAAAATTAAAG[-/C]AAACTGATTTTAGCTCATGT*	

In the polymorphisms found in the exons, mutations of the amino acid sequence are also indicated.

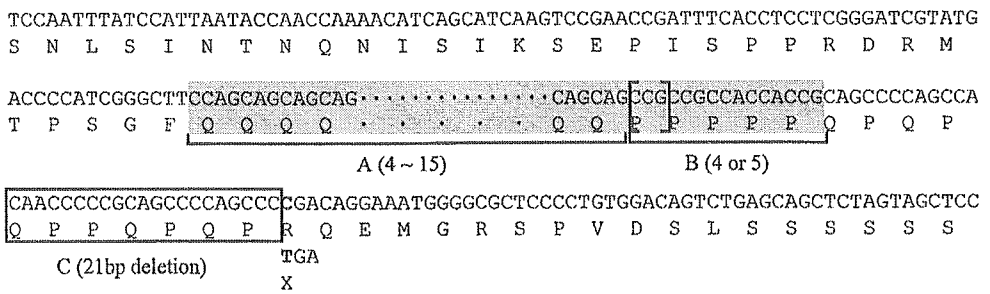

Fig 2. Nucleotide and amino acid sequences of the region containing the 4 variations in exon 12 of MEF2A. The gray box marks the polyglutamine and proline tandem repeats: the number of polyglutamine tandem repeats varies between 4 and 15, the number of proline tandem repeats varies between 4 and 5. The 21-bp deletion site is indicated by a box. The nonsense mutation (R447X) site is localized just downstream to the 21-bp deletion site.

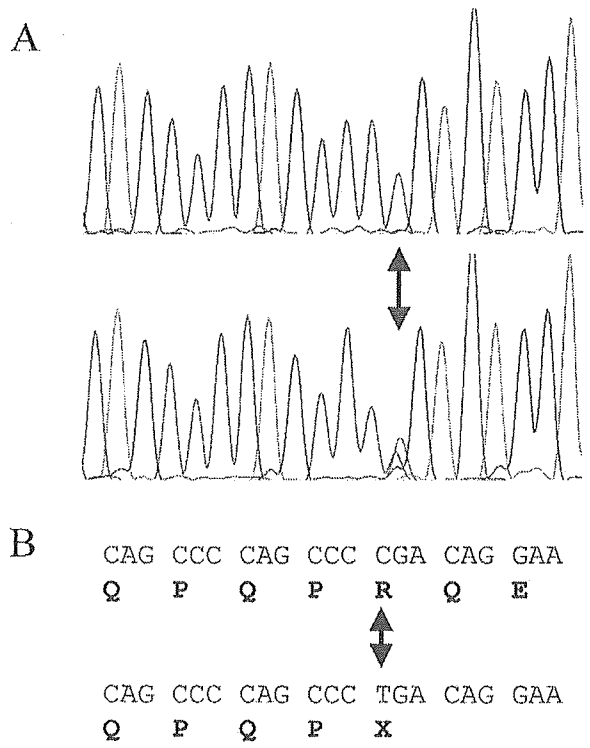

Fig 3. MEF2A nonsense mutation R447X in exon 12 in the subject with myocardial infarction (MI). (A) Sequence analysis of the control and MI subject indicated a C to T substitution at codon 447 in exon 12 of MEF2A. This mutation changes the amino acid residue arginine to stop codon (B).

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Table 3 Frequencies of Haplotypes Defined by the 3 Genotypes

Haplotype	*C (numbers)*	*% (row)*	*MI (numbers)*	*% (row)*
A4B5C+	*26*	*2.23*	*10*	*1.32*
A5B5C+	*2*	*0.17*	*5*	*0.66*
A5B4C+	*1*	*0.09*	*0*	*0.00*
A6B5C+	*2*	*0.17*	*2*	*0.26*
A7B5C+	*5*	*0.43*	*2*	*0.26*
A8B5C+	*3*	*0.26*	*8*	*1.05*
A9B5C+	*396*	*33.90*	*263*	*34.61*
A9B5C–	*3*	*0.26*	*3*	*0.39*
A9B4C+	*78*	*6.68*	*50*	*6.58*
A10B5C+	*140*	*11.99*	*96*	*12.63*
A10B4C+	*0*	*0.00*	*2*	*0.26*
A11B5C+	*475*	*40.67*	*298*	*39.21*
A11B4C+	*6*	*0.51*	*1*	*0.13*
A12B5C+	*5*	*0.43*	*6*	*0.79*
A12B4C+	*0*	*0.00*	*1*	*0.13*
A14B5C+	*22*	*1.88*	*11*	*1.45*
A15B5C+	*4*	*0.34*	*2*	*0.26*
	1,168		*760*	

The frequencies of haplotypes defined by genotypes 1–3 in the control (C) or myocardial infarction (MI) groups are shown. The haplotypes are defined as follows: A represents the number of polyglutamine tandem repeats between 4 and 15 (region A in Fig 2); B represents the number of proline tandem repeats between 4 and 5 (region B); and C+ or – represents the existence or deletion of the 21-bp nucleotide (region C).

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Circ J 2005; **69:** 1315–1319

Angiotensin-Converting Enzyme Genotype is Not Associated With Exercise Capacity or the Training Effect of Cardiac Rehabilitation in Patients After Acute Myocardial Infarction

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Background The relationship of the genotype for the angiotensin-converting enzyme (ACE) with exercise capacity or training effects has been studied in athletes or healthy persons, but recently the ACE DD genotype was reported to be associated with decreased exercise capacity in patients with congestive heart failure. Therefore, in the present study the association between the ACE genotype and exercise capacity was investigated in patients with acute myocardial infarction (AMI) participating in cardiac rehabilitation (CR) for 3 months.

Methods and Results The study population comprised 168 patients stratified as II (n=75), ID (n=67), and DD (n=26) according to ACE genotype. Baseline left ventricular ejection fraction (LVEF) was similar among the genotype groups. In all patients, exercise capacity (peak work rate (PWR) and peak oxygen uptake ($P\dot{V}O_2$)) significantly increased after CR. However, no differences were observed in PWR and $P\dot{V}O_2$ among the genotype groups at baseline or after CR. The results were similar even when analyzed in 60 patients with left ventricular (LV) dysfunction (LVEF <45%).

Conclusion The present study suggests that there is no association between ACE I/D polymorphism and exercise capacity in patients after AMI, even with LV dysfunction. Furthermore, ACE genotype may have no influence on the effects of CR after AMI. (*Circ J* 2005; **69:** 1315–1319)

Key Words: ACE genotype; Cardiac rehabilitation; Left ventricular dysfunction; Myocardial infarction

Exercise-based cardiac rehabilitation (CR) improves functional capacity and reduces mortality in patients with acute myocardial infarction (AMI).[1–3] Although the exact mechanisms by which exercise reduces mortality are unclear, one of the definite effects is improving exercise tolerance.[4,5] Exercise tolerance itself is a multifactorial phenotype influenced by several genetic and environmental factors and the training benefits may be attributed predominantly to adaptations in the peripheral circulation and skeletal muscles rather than to adaptations in cardiac performance.[6] However, the precise mechanism is not fully understood.

Over the past decade, the insertion/deletion (I/D) polymorphism of a 287-bpAlu element in intron 16 of the angiotensin-converting enzyme (ACE) gene has been extensively investigated in a spectrum of cardiovascular phenotypes, because of its correlation with serum ACE activity.[7] Many of the previous studies have shown a positive association between the DD genotype and an increased risk of MI, and recent reports suggested a potential pharmacogenetic interaction between the ACE genotype and therapy with β-blockers in chronic heart failure (CHF) patients.[8] However, results in hypertension, left ventricular (LV) hypertrophy, cardiomyopathy and restenosis after percutaneous transluminal coronary angioplasty remain quite controversial.

Several studies have shown that the ACE I allele is associated with enhanced physical performance. An increased frequency of the ACE I allele has been reported in army recruits, rowers, and high altitude mountaineers.[9,10] The ACE I allele has been associated with higher peak oxygen consumption ($P\dot{V}O_2$) levels in postmenopausal women.[11] Moreover, a recent study has demonstrated an association of the ACE DD genotype with decreased exercise tolerance in 57 patients with CHF.[12] However, the association between ACE genotype and exercise capacity or the effect of exercise training in patients after AMI with or without LV dysfunction remains unknown. Accordingly, in the current study, we examined exercise capacity in relation to ACE polymorphism in patients with AMI participating in CR for 3 months.

Methods

Study Population

One hundred sixty-eight consecutive patients who were admitted to the National Cardiovascular Center with a diagnosis of AMI and participated in the 3-month CR program with exercise training between January 2001 and September 2002 were recruited. The CR program started approximately 2 weeks after the onset of AMI and continued for 3 months. Patients exercised for 60 min 4–5 times a

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Table 1 Characteristics of the Patients With AMI According to Their ACE Genotype

	II	ID	DD	p value
N	75	67	26	
F, %	14	14	19	0.851
Age, years	59±1	56±1	60±2	0.139
BW, kg	61.3±1.2	65.4±1.4	61.7±2.1	0.068
BMI, kg/m^2	23.1±0.4	24.1±0.4	23.0±0.6	0.160
DM, %	55	40	59	0.102
HLP, %	60	61	59	0.970
HT, %	61	54	50	0.540
Smoking, %	64	63	81	0.164
LVEF, %	45±1	48±1	47±2	0.129
Heart rate, beats/min	72±2	76±2	74±3	0.336
ACE inhibitor, %	58	51	59	0.679
β-blocker, %	32	27	11	0.078

AMI, acute myocardial infarction; BW, body weight; BMI, body mass index; DM, diabetes mellitus; HLP, hyperlipidemia; HT, hypertension; LVEF, left ventricular ejection fraction; ACE, angiotensin converting enzyme. Values are mean±SE.

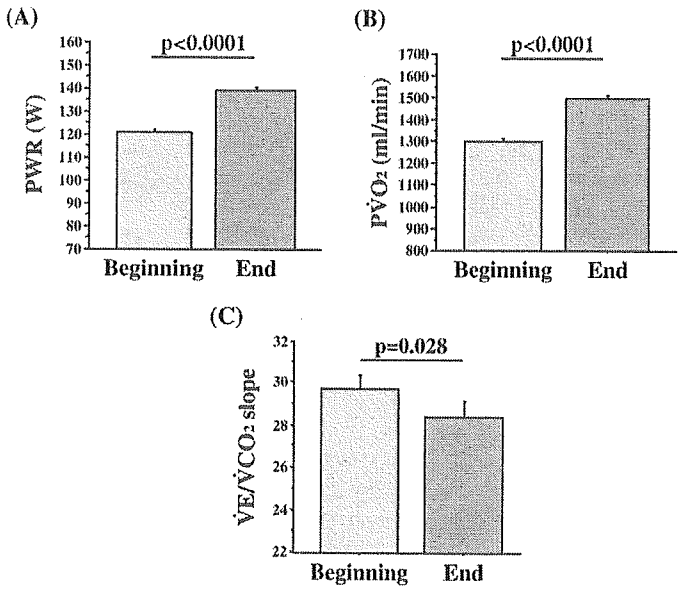

Fig 1. Changes in the cardiopulmonary exercise parameters after 3-month cardiac rehabilitation in 168 patients. (A) peak work rate (PWR), (B) peak oxygen consumption ($P\dot{V}O_2$), and (C) the slope of minute ventilation–carbon dioxide production relationship ($\dot{V}E/\dot{V}CO_2$ slope). Bars represent mean±SE.

week: 2–3 times in hospital under supervision and the remaining 2–3 times at home. Exercise consisted of aerobic dance and stationary bicycle riding in hospital and brisk walking at home. The training heart rate (HR) was determined according to the HR reserve method or Karvonen's equation (k=0.5–0.6): training HR=(peak HR−rest HR)×k+rest HR, where peak and rest HR were obtained in a symptom-limited exercise test at the beginning of the program.[13] Six patients failed to complete the 3-month CR program and so the total number of subjects was 162.

Cardiopulmonary Exercise Testing (CPX)

All patients underwent symptom-limited incremental CPX on a bicycle ergometer at the beginning and end of the 3-month CR program. Breath-by-breath respiratory gas exchange measurements were performed using a computerized metabolic cart (Minato Products, Japan). Details of the test protocol have been published elsewhere![14]

Assessment of LV Systolic Function

LV ejection fraction (LVEF) was determined as an index of LV systolic function by contrast left ventriculography at the beginning of the CR program (approximately 3 weeks after AMI onset). LVEF <45% was considered as LV dysfunction.

Blood Tests

Genomic DNA was isolated from peripheral leukocytes as previously reported![15] The ACE genotypes were determined by polymerase chain reaction as previously reported![15]

The institutional ethics committee approved the study and written informed consent was obtained from each patient before participation.

Statistics

The ANOVA method was used to assess the statistical significance of differences in means across genotype groups. All data are expressed as the mean value±SD. A p-value <0.05 was considered significant. All statistical analyses were performed with the JMP statistical package (SAS Institute Inc, Cary, NC, USA).

Results

Patient Characteristics

The 168 patients were divided into 3 groups according to

Table 2 Exercise Capacity at the Beginning and End of Cardiac Rehabilitation of the Patients With AMI According to Their ACE Genotype

	II (n=74)	ID (n=62)	DD (n=26)	p value
Beginning				
PWR	118±3	125±4	119±6	0.285
PV̇O2	1,262±42	1,370±46	1,292±71	0.218
V̇E/V̇CO2	30.1±0.9	27.9±1.1	30.1±1.6	0.243
End				
PWR	136±4	141±4	133±6	0.452
PV̇O2	1,465±49	1,562±53	1,414±82	0.229
V̇E/V̇CO2	27.7±0.7	27.5±0.8	27.8±1.2	0.960
Increase rate				
%PWR	13.6±1.5	12.9±1.6	12.0±2.5	0.863
%PV̇O2	14.5±1.9	14.3±2.0	10.4±3.2	0.507
%V̇E/V̇CO2	−4.4±2.4	−1.7±2.8	−5.1±4.3	0.704

AMI, acute myocardial infarction; ACE, angiotensin converting enzyme; PWR, peak work rate; PV̇O2, peak oxygen consumption; V̇E/V̇CO2, minute ventilation carbon dioxide production relationship. Values are mean±SE.

Table 3 Exercise Capacity at the Beginning and End of Cardiac Rehabilitation of the Patients With AMI and LV Dysfunction (LVEF <45%) According to Their ACE Genotype

	II (n=31)	ID (n=21)	DD (n=8)	p value
Beginning				
PWR	113±5	124±6	105±10	0.192
PV̇O2	1,210±60	1,331±73	1,123±119	0.259
V̇E/V̇CO2	30.9±1.2	28.3±1.7	28.7±3.2	0.428
End				
PWR	127±6	136±7	114±11	0.225
PV̇O2	1,354±73	1,501±90	1,202±141	0.170
V̇E/V̇CO2	29.9±1.1	27.4±1.4	25.8±2.4	0.228
Increase rate				
%PWR	7.7±1.9	11.2±2.3	9.2±3.5	0.509
%PV̇O2	8.5±3.1	12.4±3.7	7.8±5.8	0.681
%V̇E/V̇CO2	2.0±3.6	0.1±4.8	−10.1±8.8	0.453

AMI, acute myocardial infarction; LV, left ventricular; LVEF, LV ejection fraction; ACE, angiotensin converting enzyme; PWR, peak work rate; PV̇O2, peak oxygen consumption; V̇E/V̇CO2, minute ventilation carbon dioxide production relationship. Values are mean±SE.

their ACE genotype, the frequencies of which were in a Hardy-Weinberg equilibrium in this population. Baseline characteristics of the 3 groups are summarized in Table 1. Sex, mean age, body weight, body mass index and risk factors did not differ significantly among the genotypes. No significant difference in either resting LVEF or HR was detected. Although the subjects with the DD genotype had a trend toward a lower percentage of β-blocker treatment, no significant difference was observed.

Effects of CR on Exercise Capacity

Fig 1 shows the effects of 3-month CR on the CPX parameters in all subjects. The peak work rate (PWR), PV̇O2 and the slope of the minute ventilation–carbon dioxide production relationship (V̇E/V̇CO2 slope) improved significantly after 3 months of CR (12.1%, 13.3%, −3.9% from baseline, respectively).

Exercise Capacity and Effects According to ACE Genotype

Table 2 shows the CPX data at the beginning and end of the 3-month CR stratified by the ACE genotype. It also shows the increase rate ((end−beginning)/beginning×100; %). No significant differences in PWR, PV̇O2 or V̇E/V̇CO2 slope were observed among the 3 genotype groups at either time point. All parameters improved by a similar magnitude across the genotypes after 3-month CR as demonstrated by the increase rate.

Subanalysis was performed in patients with LV dysfunction (LVEF <45%, n=60), which is shown in Table 3. The pattern of the genotype distributions did not differ significantly between the patients with or without LV dysfunction (chi-square test, p=0.269). No significant differences in the 3 exercise parameters were observed among the 3 genotype groups at either the beginning or the end. Also, there were no significant differences in the increase rate of the 3 parameters among the 3 groups. Similar results were obtained in the subanalysis of male patients (63II/54ID/22DD) (data not shown).

Discussion

In the present study, based upon the hypothesis that the ACE genotype may have an association with the exercise capacity, we investigated this association in patients with AMI participating in CR for 3 months. However, we found no association between ACE I/D polymorphism and exercise capacity in this patient group, even in those with LV dysfunction. Furthermore, the ACE genotype may have no influence on the training effects of CR after AMI. Although many studies have explored the relationship of ACE geno-

type with the exercise capacity or training effects in athletes or healthy persons, this is the first study to examine the association between them in patients after AMI. In particular, because CR obviously provides improved exercise tolerance and quality of life and decreased mortality in patients with CHF or after AMI, it is important to clarify whether it is genetic factors, such as the ACE genotype, that are causing the training effects of CR.

The ACE genotype affects both serum and tissue ACE levels and many studies have investigated the associations with various cardiovascular diseases. As ACE is involved in the metabolism of substances that affect vascular and cardiac remodeling, it may account for the cardiopulmonary fitness of individuals and for the differences among individuals in response to physical training. Recent studies have shown higher frequencies of the ACE I allele among endurance athletes compared with non-athlete controls[9,10] Moreover, Hangberg et al reported an association between the ACE I allele and higher $P\dot{V}O_2$ levels in postmenopausal women![11] However, there also have been conflicting reports about this association. Some studies failed to find an association between the ACE I allele and exercise capacity and did not support the hypothesis that ACE I/D polymorphism plays a major role in cardiopulmonary endurance![6] Others reported that the ACE DD allele is associated with higher levels of $P\dot{V}O_2$ and that a greater strength gain in cardiac and skeletal muscles in response to resistance training program is found in the D allele carriers![7,18]

The present study demonstrated that in post-AMI patients, the ACE genotype did not affect either the baseline exercise capacity or the training effects of a 3-month CR program, and there are several possible explanations. The subjects investigated were not healthy and the intensity of the exercise training was much less than that of endurance training in athletes. It is also well known that ethnic differences can affect genetic associations. However, at present, a physiological explanation for any association between the cardiorespiratory phenotype and ACE polymorphism has not been found and requires further investigation.

Recently, Abraham et al reported an association of the ACE DD genotype with decreased exercise tolerance 57 patients with CHF![12] They observed that those with the ACE DD genotype had more restrictive pulmonary changes and a reduced lung diffusing capacity, and they attributed this to the poorer exercise capacity in the patients with CHF. Huwang et al reported that the ACE DD genotype might be a marker of a more severe condition in Chinese Han patients with CHF![19] However, it remains controversial whether ACE polymorphism is associated with CHF?[20] In a subanalysis of the present study, we demonstrated no impact of ACE I/D polymorphism on exercise capacity in patients with LV dysfunction after AMI. As we did not assess the pulmonary function, we could not confirm Abraham's observations precisely in the current study. Also, we defined LV dysfunction as LVEF <45% and Abraham et al used LVEF <35%, which might explain the different results between the 2 studies. Exercise tolerance is a multifactorial phenotype and training benefits may be attributed to adaptations in cardiac and pulmonary performances, as well as those in the peripheral circulation and skeletal muscles. Although ACE I/D polymorphism does not appear to bean important modulator of the exercise capacity of patients with LV dysfunction after AMI, further studies are necessary to clarify the contribution of other important genetic factors in the decreased exercise capacity of CHF/LV dysfunction patients.

Study Limitations

We did not assess the effect of genotype on circulating markers of the renin–angiotensin system. However, because the association of the ACE D allele with increased plasma ACE activity has been consistently demonstrated in many previous studies, our observation suggests there is no relationship between plasma ACE activity and exercise capacity. In addition, the analysis and findings of this study are limited by the retrospective design. Finally, the study population was relatively small, especially in the subanalysis of patients with LV dysfunction. Any negative finding could thus be caused by a low statistical power. A larger study will be required if associations of the ACE genotype are to be investigated further.

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Assessment of Quality of Life With 5 Different Scales in Patients Participating in Comprehensive Cardiac Rehabilitation After Acute Myocardial Infarction

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Background Measures assessing quality of life (QOL) in patients participating in comprehensive cardiac rehabilitation (CCR) have not been established in Japan.

Methods and Results To compare different types of QOL scales and to determine the impact of CCR on QOL in Japanese cardiac patients, 5 different types of questionnaires were assessed in 44 patients participating in CCR after acute myocardial infarction (AMI). After 3-month CCR, peak oxygen uptake ($P\dot{V}O_2$, $p<0.01$), Sickness Impact Profile (SIP) total score ($p<0.05$) and physical function-related QOL scores (Specific Activity Scale (SAS), $p<0.01$; SIP physical score, $p<0.01$) significantly improved, whereas psychosocial/mental aspect-related QOL scores (Ministry of Health and Welfare (MHW)-QOL score, SIP psychosocial score, State-Trait Anxiety Inventory, Self-rating Depression Scale) did not change on the average. However, patients with low $P\dot{V}O_2$ ($<21.7\,ml\cdot min^{-1}\cdot kg^{-1}$) showed significant improvements in all scores after CCR, whereas patients with preserved exercise capacity showed improvements only in physical function-related scores (SAS and physical SIP). Furthermore, patients with anxiety and depression showed significant improvements in these respective measures after CCR.

Conclusion In patients with AMI, physical function-related QOL scores improve after a 3-month CCR program, but psychosocial/mental aspect-related QOL scores improve only in those with impaired exercise tolerance or anxiety/depression. Thus, changes in QOL after CCR depend on type of QOL scale used and the baseline status of the patient. In addition, in Japanese cardiac patients MHW-QOL mainly reflects psychosocial/mental aspect-related QOL, as well as overall QOL. (*Circ J* 2005; **69:** 1527–1534)

Key Words: Acute myocardial infarction; Cardiac rehabilitation; Depression; Psychological wellbeing; Quality of life

Comprehensive cardiac rehabilitation (CCR) improves psychological well-being or quality of life (QOL) in patients after acute myocardial infarction (AMI),[1–4] but because the various QOL scales assess the physical and psychological aspects of QOL differently, it is not fully understood which aspect of QOL is improved by CCR. In addition, it remains unclear which patient group benefits most from CCR in terms of QOL. Furthermore, because most QOL instruments, except for the QOL score of the Ministry of Health and Welfare in Japan (MHW-QOL),[5,6] were devised in Western countries, their features have not been comparably determined in Japanese cardiac patients. In fact, conflicting results have been reported on the effect of CCR on the MHW-QOL score in Japanese patients after AMI; Yoshida et al reported a significant improvement in the MHW-QOL score[6] whereas Fujiwara et al reported no significant change.[7]

The effect of CCR on the different aspects of QOL in Japanese patients after AMI using multiple QOL instruments has not been intensively assessed. Accordingly, the purpose of the present study was to use multiple QOL instruments to assess Japanese patients after AMI, to determine the comparative features of the various QOL scales, including the MHW-QOL score, and to clarify the characteristics of the patients who are likely to benefit most from CCR in terms of QOL.

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Methods

Subjects

We studied 44 patients who had experienced an AMI (mean age: 58±9 years, range 45–78, male/female: 37/7) and who participated in CCR with exercise training program. All patients gave written informed consent.

The diagnosis of AMI was confirmed by electrocardiographic changes and serum creatine kinase (CK) elevation. Peak serum CK was 3,255±2,588 U/L. Seven patients (16%) had had a prior myocardial infarction and 2 patients (5%) had congestive heart failure (Killip's class ≥2) on admission. All patients underwent cardiac catheterization: 38 patients (86%) had successful percutaneous coronary intervention (PCI), 2 patients (5%) underwent coronary artery bypass grafting (CABG) and 5 patients (11%) with residual myocardial ischemia were medically controlled. Mean left ventricular ejection fraction (LVEF) was 45±8%

by left ventriculography 3–4 weeks after the onset of AMI.

Cardiac Rehabilitation Program

The CCR program consisted of exercise training of moderate intensity and education for 3 months, as previously described[8–10] Patients who did not have angina or ischemic changes on ECG at a low level of exercise (200–500 m walking test) were enrolled in the exercise training approximately 10–15 days after AMI. Patients with uncontrolled heart failure and/or angina, multiple organ disorders such as serum creatinine ≥2.0 mg/ml, serum transaminase ≥40 IU/ml, inflammatory disease or embolic disorders were excluded. The exercise program consisted of walking, bicycling on an ergometer, and aerobic dance sessions of 50–80 min, 3–5 times each week for 3 months. Exercise intensity was determined individually at 50–60% of heart rate reserve (Karvonen's equation, k=0.5–0.6)[11,12] obtained by maximal symptom-limited cardiopulmonary exercise testing (CPX) or at level 13 ("a little hard") of the 6–20 scale perceived rating of exercise (original Borg's score)[13] The exercise program started with supervised sessions for 2 weeks, followed by home exercise combined with once or twice weekly supervised sessions for the remaining 10 weeks. Home exercise consisted mainly of brisk walking at a prescribed heart rate for 30–60 min 3–5 times per week. There were no adverse cardiac events such as death, AMI, unplanned PCI or CABG, or worsening of heart failure during the 3-month CCR.

Patients were encouraged to attend the education classes, which were held 3 times each week with lectures on coronary artery disease, secondary prevention, diet, smoking cessation, medication, and home exercise given by physicians, nurses, dieticians, pharmacists and exercise instructors. In addition, all patients received individual counseling on exercise prescription, secondary prevention, and daily life activities by a physician and a CCR nurse at the time of hospital discharge and at the end of the CCR program.

CPX

A symptom-limited CPX was performed at the beginning and end of the 3-month CCR[14] After a 2 min rest on the bicycle ergometer (Examiner, Lode B.V. Groningen-Holland), patients started pedaling at an intensity of 0 W for 1 min (warm-up), then performed an incremental exercise test with a ramp protocol (15 W/min) until exhaustion. During exercise testing, breathed gas was continuously collected to measure oxygen uptake ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) with a gas analyzer AE280 (Minato Medical Electronics, Osaka, Japan). Blood pressure was measured every minute and a 12-lead ECG was continuously monitored during exercise. Patients who showed angina or ischemic ECG changes at the initial exercise test were excluded.

Peak oxygen uptake ($P\dot{V}O_2$) was defined as the highest $\dot{V}O_2$ value achieved at peak exercise after reaching the respiratory compensation point. The $\dot{V}O_2$ value at the anaerobic threshold (AT) or ventilatory threshold was determined as the point at which $\dot{V}CO_2$ increased in a nonlinear fashion relative to the rate of $\dot{V}O_2$, according to the time trend of the ratio of minute ventilation ($\dot{V}E$) and $\dot{V}O_2$ ($\dot{V}E/\dot{V}O_2$), an abrupt increase in the respiratory exchange ratio, or the V-slope method[15,16]

QOL Questionnaires

At the beginning and end of the 3-month CCR program, all patients answered the 5 types of questionnaires assessing QOL: Specific Activity Scale (SAS), Sickness Impact Profile (SIP), MHW-QOL, State-Trait Anxiety Inventory (STAI) and Self-rating Depression Scale (SDS). SAS is a scale of functional capacity related to daily activities expressed by metabolic equivalents[17,18] and SIP comprises 136 items including 12 domains to assess patient behaviors, such as physical disorders (ambulation, mobility, body care and movement), psychosocial disorders (social interaction, alertness behavior, emotional behavior, communication) and other disorders (sleep and rest, eating, work, home management, recreation and pastimes), expressed by the percentage of acquired scores[19,20] It has been successfully used in the field of CCR[20–22] MHW-QOL has both generic and disease-related scales and mainly assesses the psychosocial and mental aspects of QOL[5–7] It comprises 39 items, including 3 domains (2 generic domains and 1 disease-specific domain) for subjective evaluation of health (8 items), social attitude and subjective wellbeing (21 items), and disease-specific conditions (10 items). In the present study we used a total score for the 39 items (so-called "broad sense score") as the MHW-QOL score. STAI is a scale of anxiety and comprises 2 domains of state-anxiety and trait-anxiety, the former representing an anxiety state that a patient faces and the latter mainly representing an anxious personality. Each domain comprises 20 items with 4-point scales[23] SDS evaluates depression by 20 items with 4-point scales[24] A state of anxiety and/or depression was judged when the percent score of STAI and/or SDS was above 50%. Higher scores indicate a more favorable QOL trait in SAS and MHW-QOL, whereas lower scores indicate a more favorable QOL trait in SIP, STAI and SDS.

Data Analysis

Data were analyzed in 3 steps. First, data for exercise capacity and QOL were compared between the 2 time points (ie, before and after the 3-month CCR) in the whole group of patients. Second, to assess the influence of baseline exercise capacity on the improvement in QOL scores after CCR, QOL data were compared between the 2 time points in the subgroups of preserved and impaired exercise capacity. Because the average $P\dot{V}O_2$ measured by CPX at the beginning of the CCR was 21.7±1.7 ml·min^{-1}·kg^{-1}, patients were divided into 2 groups according to their initial $P\dot{V}O_2$ value: Low $P\dot{V}O_2$ group ($P\dot{V}O_2$ <21.7 ml·min^{-1}·kg^{-1}, n=22) and Preserved $P\dot{V}O_2$ group ($P\dot{V}O_2$ ≥21.7 ml·min^{-1}·kg^{-1}, n=22). Finally, QOL data were compared between the 2 time points in the subgroups with and without initial anxiety (STAI score ≥50% or <50%, respectively) and with and without initial depression (SDS score ≥50% or <50%, respectively).

Statistical Analysis

All values are expressed as mean±SD. The paired t-test was used to compare paired variables before and after CCR within a group. Comparisons between groups were made by unpaired t-test. Statistical analysis was performed using StatView software (Abacus, Cupertino, CA, USA). A p-value less than 0.05 was considered statistically significant.

Results

Changes in Exercise Capacity and QOL Scores in the Whole Group

As shown in Table 1, which summarizes the baseline

Table 1 Characteristics of 44 Patients After Acute Myocardial Infarction

	Total (n=44)	Preserved $\dot{P}VO_2$ group (n=22)	Low $\dot{P}VO_2$ group (n=22)	p value
Age (years)	58±10	57±11	59±9	NS
Sex (M/F)	37/7	20/2	17/5	NS
Hypertension	21 (48%)	12 (55%)	9 (41%)	NS
Hyperlipidemia	18 (41%)	10 (45%)	8 (36%)	NS
Diabetes mellitus	12 (27%)	6 (27%)	6 (27%)	NS
Obesity (BMI ≥26 kg/m^2)	10 (23%)	4 (18%)	6 (27%)	NS
Smoking	23 (52%)	14 (64%)	9 (41%)	NS
Family history	9 (20%)	4 (18%)	5 (23%)	NS
Killip class ≥2 (numbers)	2	0	2	NS
PCI/CABG/none	38/2/5	18/1/3	20/1/2	NS
peak CK (IU/ml)	3,255±2,588	3,009±1,986	3,384±2,796	NS
LVEF (%)	44.5±8.2	45.9±6.6	42.9±9.6	<0.05
$\dot{P}VO_2$ (ml·kg^{-1}·min^{-1})	21.7±4.9	24.7±3.6	18.1±3.8	<0.001

Values are mean±SD. P values for comparisons between Preserved $\dot{P}VO_2$ and Low $\dot{P}VO_2$ groups.
$\dot{P}VO_2$, peak oxygen uptake; Preserved $\dot{P}VO_2$ group, patients whose baseline $\dot{P}VO_2$ values were equal to or above average ($\dot{P}VO_2$ ≥21.7 ml·kg^{-1}·min^{-1}); Low $\dot{P}VO_2$ group, patients whose baseline $\dot{P}VO_2$ value were below average ($\dot{P}VO_2$ <21.7 ml·kg^{-1}·min^{-1}); BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CK, serum concentration of creatine kinase; LVEF, left ventricular ejection fraction.

Table 2 Exercise Capacity and QOL Scores Before and After Comprehensive Cardiac Rehabilitation in All Patients

	Before CCR	After CCR	p value
Peak R	1.26±0.12	1.24±1.0	NS
$\dot{P}VO_2$ (ml·kg^{-1}·min^{-1})	21.7±1.7	24.7±2.6	<0.01
$\dot{V}O_2$ at AT (ml·kg^{-1}·min^{-1})	11.8±2.3	13.1±2.5	<0.01
SAS (METs)	4.5±1.7	5.3±0.7	<0.05
SIP (% scores)			
Total	7.9±5.6	5.5±4.9	<0.05
Physical disorders	7.2±3.1	1.5±1.6	<0.01
Psychosocial disorders	6.0±4.4	5.8±7.4	NS
Other disorders	11.5±7.5	10.6±8.4	NS
MHW-QOL (scores)	57.4±12.7	58.6±20.5	NS
STAI (% scores)			
Total	49.3±10.9	46.9±13.2	NS
State-anxiety	48.2±11.7	45.3±12.2	NS
Trait-anxiety	49.7±12.0	47.1±12.3	NS
SDS (% scores)	45.3±9.5	43.4±7.9	NS

Values are mean±SD.
QOL, quality of life; CCR, comprehensive cardiac rehabilitation; Peak R, respiratory exchange ratio at peak exercise; $\dot{P}VO_2$, peak oxygen uptake; AT, anaerobic threshold (or ventilatory threshold); SAS, specific activity scale; METs, metabolic equivalents; SIP, sickness impact profile; MHW-QOL, QOL score of the Ministry of Health and Welfare in Japan; STAI, state-trait anxiety inventory; SDS, self-rating depression scale.

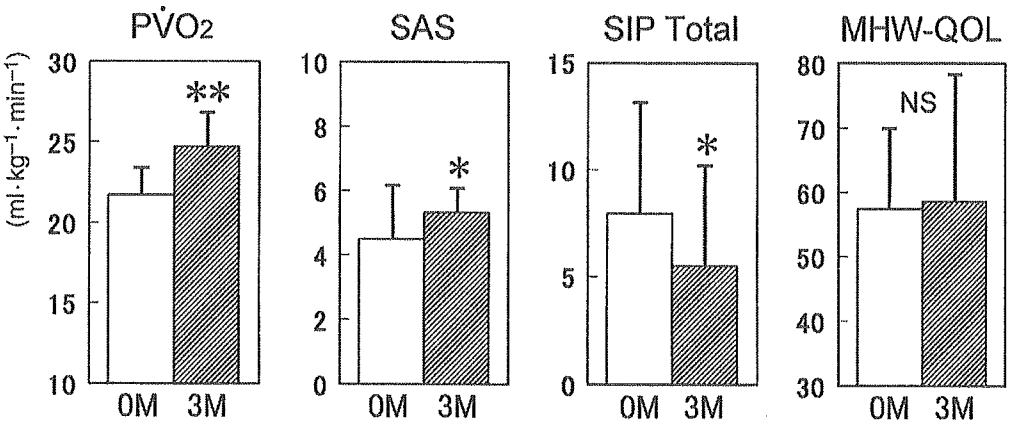

Fig 1. Comparisons of exercise capacity and quality of life (QOL) scores before and after 3-month comprehensive cardiac rehabilitation (CCR) in all 44 patients. $\dot{P}VO_2$, peak oxygen uptake; SAS, Specific Activity Scale; SIP total, Sickness Impact Profile total score; MHW-QOL, Ministry of Health and Welfare QOL broad sense score: 0M, baseline values (before CCR); 3M, values after 3-month CCR program. *p<0.05 and **p<0.01 compared with baseline values.

Table 3 Exercise Tolerance and QOL Related Scores Change in Subgroups

	Preserved $P\dot{V}O_2$ group (n=22)			*Low $P\dot{V}O_2$ group (n=22)*		
	Before CCR	*After CCR*	*p value#*	*Before CCR*	*After CCR*	*p value#*
$P\dot{V}O_2$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	*24.7±3.6*	*27.5±5.0*	*<0.01*	*18.1±3.8***	*21.3±5.4***	*<0.01*
$\dot{V}O_2$ at AT ($ml \cdot kg^{-1} \cdot min^{-1}$)	*13.2±1.8*	*14.5±2.3*	*0.05*	*10.2±1.7*	*11.6±1.8*	*<0.05*
SAS (METs)	*5.0±1.7*	*5.6±1.9*	*<0.05*	*3.9±1.5**	*4.9±1.3*	*<0.05*
SIP (% scores)						
Total	*7.7±5.8*	*6.0±4.8*	*<0.05*	*8.1±5.6*	*4.1±5.2*	*<0.05*
Physical disorders	*6.9±7.9*	*0.8±1.7*	*<0.01*	*6.8±5.8*	*2.1±3.4*	*<0.01*
Psychosocial disorders	*6.2±6.9*	*6.6±7.6*	*NS*	*4.8±5.5*	*2.7±5.6*	*<0.05*
Other disorders	*10.5±6.2*	*10.6±8.1*	*NS*	*12.7±8.8*	*8.6±7.9*	*<0.05*
MHW-QOL (scores)	*61.0±8.1*	*60.3±10.8*	*NS*	*53.1±10.0***	*56.6±9.3*	*<0.05*
STAI (% scores)						
Total	*47.7±10.1*	*47.9±15.3*	*NS*	*51.2±11.8*	*45.7±10.3*	*<0.05*
State-anxiety	*47.9±10.3*	*47.6±17.0*	*NS*	*49.6±13.2*	*44.4±10.3*	*<0.05*
Trait-anxiety	*47.6±11.1*	*48.3±14.7*	*NS*	*52.7±12.6*	*46.9±11.2*	*<0.05*
SDS (% scores)	*42.3±7.0*	*43.6±10.7*	*NS*	*49.2±10.5**	*44.4±6.7*	*<0.05*

Values are mean±SD.
*#Comparisons were made by paired t-test before and after CCR within the group; *p<0.05, **p<0.01 compared with corresponding values in the Preserved $P\dot{V}O_2$ group.*
Abbreviations as in Table 2.

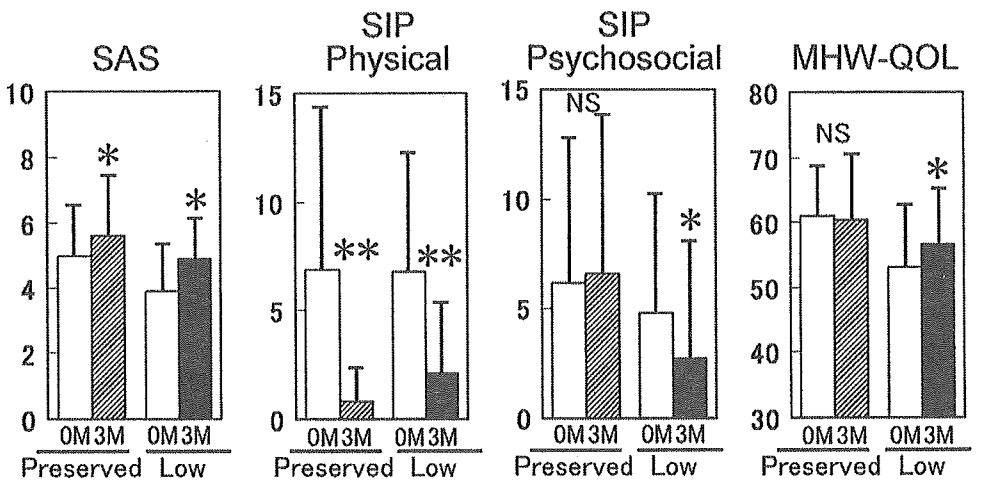

Fig 2. Changes in representative quality of life (QOL) scores before and after 3-month comprehensive cardiac rehabilitation program in patients with preserved and impaired exercise capacity. Patients with preserved exercise capacity showed improvements in Specific Activity Scale (SAS) and Sickness Impact Profile (SIP) physical score, but not in SIP psychosocial and Ministry of Health and Welfare (MHW)-QOL scores, whereas patients with impaired exercise capacity showed improvements in all 4 scores. SIP physical, SIP physical disorder score; SIP psychosocial, SIP psychosocial disorder score; Preserved, preserved exercise capacity group (peak $\dot{V}O_2$ ≥21.7 $ml \cdot min^{-1} \cdot kg^{-1}$); Low, impaired exercise capacity group (peak $\dot{V}O_2$ <21.7 $ml \cdot min^{-1} \cdot kg^{-1}$). *p<0.05 and **p<0.01 compared with baseline values.

clinical characteristics of the 2 groups with preserved and impaired exercise capacity, there were no significant differences except for LVEF and $P\dot{V}O_2$. Table 2 and Fig 1 summarize the data for exercise capacity and QOL scores before and after the 3-month CCR. The respiratory exchange ratio at peak exercise was sufficiently high both before and after CCR, suggesting that the measured $P\dot{V}O_2$ values are reliable. After 3 months of CCR, $P\dot{V}O_2$ (+13.8%, p<0.01), $\dot{V}O_2$ at AT (+11.0%, p<0.01) and SIP total score (–30.4%, p<0.05) improved significantly, as did the SAS (+17.8%, p<0.05) and SIP physical disorder score (–79.2%, p<0.01), both representing QOL related to physical function. However, other QOL scores such as the SIP score for psychosocial disorders and other disorders, MHW-QOL, STAI and SDS, all representing QOL related to psychosocial or mental function, did not change after 3 months of CCR.

Changes in QOL Scores in the Subgroups With Preserved and Impaired Exercise Capacity (Table 3, Fig 2)

In the Preserved $P\dot{V}O_2$ group, $P\dot{V}O_2$ (+11.3%, p<0.01), $\dot{V}O_2$ at AT (+9.8%, p=0.05), SIP total score (–22.1%, p< 0.05), and physical function-related QOL scores (ie, SAS (+12.0%, p<0.05) and SIP physical disorder score (–88.4%, p<0.01), significantly improved after CCR, but there was no significant change in the psychosocial and mental aspect-related QOL scores (ie, SIP psychosocial disorder score, SIP other disorder score, MHW-QOL, STAI, and SDS). In contrast, the Low $P\dot{V}O_2$ group showed significant improvements in $P\dot{V}O_2$ (+17.7%, p<0.01), $\dot{V}O_2$ at AT (+13.7%, p< 0.05), SIP total score (–49.4%, p<0.05), and both physical function-related QOL (SAS +25.6%, p<0.05; SIP physical disorder score –69.1%, p<0.01) and psychosocial/mental aspect-related QOL scores after CCR (SIP psychosocial disorder score –43.8%, p<0.05; MHW-QOL +6.7%, p<0.05;

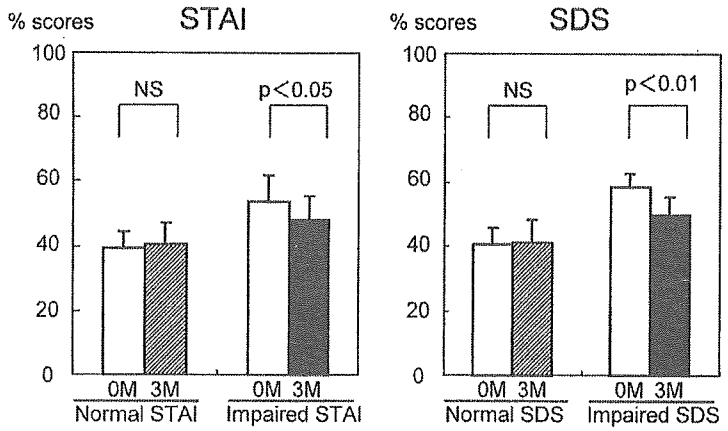

Fig 3. Changes in anxiety (STAI) and depression (SDS) scores before and after 3-month comprehensive cardiac rehabilitation (CCR) program in patients with normal and impaired mental function. Anxiety scores (STAI: State-Trait Anxiety Inventory) and depression scores (SDS: Self-rating Depression Scale) improved after CCR only in patients with impaired STAI score and impaired SDS score at baseline. 0M, baseline values (before CCR); 3M, values after 3-month CCR. *p<0.05 and **p<0.01 compared with baseline values.

Table 4 Correlation Matrix of Different Types of QOL Scores

	$P\dot{V}O_2$	$\dot{V}O_2$ at AT	SAS	SIP total	SIP physical	SIP psychosocial	STAI	SDS
MHW-QOL	0.14	0.21	0.49***	0.36***	0.27*	0.38***	0.77***	0.69***
$P\dot{V}O_2$		0.74***	0.29**	0.01	0.08	0.09	0.07	0.09
$\dot{V}O_2$ at AT			0.32**	0.14	0.20	0.01	0.04	0.18
SAS				0.35**	0.32**	0.30**	0.37***	0.43***
SIP total					0.74***	0.81***	0.31**	0.25*
SIP physical						0.40***	0.12	0.18
SIP psychosocial							0.37***	0.28**
STAI								0.73***

Correlation coefficients and their statistical significance are presented.
Data both before and after 3-month comprehensive cardiac rehabilitation for all 44 patients were included for regression analysis.
*Abbreviations as in Table 2. *p<0.05, **p<0.01, ***p<0.001.*

STAI −10.7%, p<0.05; SDS −9.8%, p<0.05).

Changes in Anxiety and Depression (Fig 3)

When the patients were divided into 2 groups according to the initial STAI score ≥ or <50%, 22 patients (50.0%) with STAI score ≥50% (ie, anxiety state) showed a significant improvement after CCR (58.2±6.1 to 53.0±9.3, p< 0.05), but the remaining 22 patients with initial STAI score <50% (ie, normal) showed no significant change. When the patients were divided into 2 groups according to the initial SDS score ≥ or <50%, 12 patients (27.3%) with SDS score ≥50% (ie, depressive state) showed a significant improvement in SDS score after CCR (58.2±4.4 to 49.7±6.4, p< 0.01), butthe remaining 32 patients with initial SDS score <50% (ie, normal) showed no significant change.

Correlations Between MHW-QOL and Other QOL Scores (Table 4)

The MHW-QOL score significantly correlated with SAS (r=0.49, p<0.001) and SIP total score (r=0.36, p<0.001), indicating that MHW-QOL represents the overall QOL of cardiac patients. Intriguingly, the MHW-QOL score correlated very tightly with the SIP psychosocial disorder score (r=0.38, p<0.001), STAI (r=0.77, p<0.001) and SDS (r=0.69, p<0.001), but less tightly with the SIP physical disorder score (r=0.27, p<0.05) and not significantly with $P\dot{V}O_2$ (r=0.14, NS) or $\dot{V}O_2$ at AT (r=0.21, NS). These findings suggest that in cardiac patients MHW-QOL mainly reflects the psychosocial and mental aspects of QOL rather than physical aspects.

Discussion

The major findings of the present study are that (1) exercise capacity and physical function-related QOL scores (ie, SAS and SIP physical disorder score) significantly improved, whereas psychosocial and mental aspect-related QOL scores (SIP psychosocial disorder score, MHW-QOL, STAI, and SDS) did not change in the whole patient group participating in the 3-month CCR program after AMI, (2) patients with impaired exercise capacity at baseline showed significant improvements in all QOL scores including both physical function-related scores and psychosocial and mental aspect-related scores, whereas patients with preserved exercise capacity showed improvements only in physical function-related QOL scores, (3) patients with anxiety or depression at baseline showed an improvement in each score after CCR, whereas those without anxiety or depression showed no change, and finally, (4) the MHW-QOL score correlated more tightly with psychosocial/mental function-related QOL scores rather than with physical function-related aspects.

Previous Studies

Many previous studies have demonstrated the benefits of CCR for QOL in patients after AMI[1–4,6,7,20–22] but most have used only 1 or 2 QOL instruments and assessed changes in QOL scores after CCR in the whole group. In other words, few studies have investigated which aspect of QOL (physical, psychosocial or mental aspects) is most improved by CCR, which QOL instruments are most sensitive to changes occurring during CCR, and what type of patients obtain the

greatest benefit from CCR after AMI. In fact, Jolliffe et al noted in their meta-analysis that it was not possible to combine the data from studies reporting health-related QOL as an outcome, because 18 different instruments were used in the 11 randomized studies reporting it as an outcome[25] Shephard et al also noted that there were few direct comparisons between different types of QOL instruments!

One direct comparisons was made by Taylor et al, who utilized 3 generic QOL instruments, including SIP, to assess changes in QOL over time in 88 patients after AMI, and found that all 3 QOL instruments had modest sensitivity[26] Smith et al[27] compared 4 QOL instruments, including the Medical Outcome Study 36-item Short Form Survey (SF-36),[28] in 22 cardiac patients before and after CCR, and found that only 1 of the SF-36 subscales, vitality, significantly improved over time, from which they concluded that all 4 QOL measures lacked sensitivity to change. In Japan, where most QOL questionnaires invented in Western countries and written in English cannot be directly applied to Japanese patients, comparative assessments of the different QOL instruments during CCR has not been done so far. Yoshida et al studied the MHW-QOL, STAI and SDS in patients with AMI participating in 2-week hospitalized CCR, but did not analyze correlations among the measures[6] Seki et al also investigated SF-36, STAI and SDS in elderly patients with coronary artery disease participating in phase III CCR, but did not analyze correlations among the measures[29] Thus, the optimal QOL test instrument or the best method of interpreting the resultant scores there has not been established!

Present Study

In the present study, we compared 5 different QOL instruments in Japanese patients participating in a 3-month CCR program with supervised exercise training and education after AMI. This enabled us to analyze which aspect of QOL improves after CCR and what type of patients gain the greatest improvement in QOL from CCR after AMI. In addition, we were able to determine the nature of the Japan-invented MHW-QOL by assessing the correlations between MHW-QOL and other established QOL scales.

Improvement in QOL After CCR

The present study has shown that $P\dot{V}O_2$, SAS, SIP total score and SIP physical disorder score significantly improved, whereas the SIP psychosocial disorder score, MHW-QOL, STAI, and SDS did not change in the whole patient group after CCR, which indicates that overall the physical function-related QOL scores improved, but the psychosocial and mental aspect-related QOL scores did not. Therefore, not all aspects of QOL (or all types of QOL scores) necessarily improve after CCR in patients with AMI.

Many previous studies have demonstrated an improvement in physical function-related QOL after CCR,[4,20,30–32] but the improvement in mental/psychosocial aspect-related QOL has been inconsistent; some studies have reported a significant improvement,[20,30–33] and others have not.[34–36] For example, Sledge et al[30] and Tyni-Lenne et al[31] reported significant improvements in all areas of QOL (overall, physical, and psychosocial scores) in an 8-week CR program in cardiac patients, whereas Worcester et al[35] and Daumer et al[36] reported no significant difference in the psychosocial and mental aspects of QOL between an exercise training group and a control group. Recently, Izawa et al,[37] using SF-36,[28] reported significant improvements in the physical function-related SF-36 subscales (ie, physical functioning, role-physical, general health) but not in the mental function-related subscales (ie, social functioning, role-emotional, mental health) after CCR in patients with AMI. Thus, whether or not QOL improves after CCR in cardiac patients appears to depend on the aspect of QOL and the type of QOL instrument.

Patient Characteristics Predicting Improved QOL After CCR

In the present study, patients with impaired exercise capacity at baseline showed significant improvements in all QOL scores, including both physical function-related QOL scores and psychosocial and mental aspect-related QOL scores, whereas patients with preserved exercise capacity showed improvements only in physical function-related QOL scores. A potential explanation for this new finding is that there might be a "ceiling effect" (ie, patients with lower initial values have a greater improvement),! because the low exercise capacity group in the present study tended to have worse QOL scores at the beginning of CCR (Table 3). In support of this, Lavie et al reported that elderly patients with coronary artery disease had a lower baseline $P\dot{V}O_2$ value, but a greater improvement in QOL score (SF-36), after CCR than younger patients,[38] although Oldridge et al reported that higher exercise tolerance at baseline predicts a greater improvement in the quality of well-being in patients with AMI participating in CCR.[39] The reason for this discrepancy is unclear, and further studies are necessary to address this issue.

The present study also demonstrated that patients with anxiety or depression at baseline showed a significant improvement in each score after CCR, whereas those without showed no change. This finding is in accordance with Oldridge et al[39] who stated that a poor baseline health-related QOL was the predominant predictor of improved generic and specific health-related QOL after CCR. Likewise, Milani et al showed that depressed patients exhibited a greater improvement in psychosocial/mental aspect-related QOL than did normal patients.[40] Again, this finding may well be explained by the ceiling effect! Taken together, the findings suggest that an improvement in QOL after CCR depends not only on the type of QOL instrument but also on the patient characteristics at baseline, and that patients with impaired QOL, anxiety, or depression at baseline should be strongly recommended to participate in CCR with an expectation of greater improvements than patients without these problems.

QOL Instruments for Japanese Cardiac Patients

Although MHW-QOL was originally invented in Japan, no study to date has systematically compared it with other established QOL instruments in patients with AMI participating in CCR. The present study has demonstrated that MHW-QOL reflects overall QOL, as indicated by a significant correlation with SIP total score, but that it mainly represents psychosocial/mental aspect-related QOL rather than physical aspect-related QOL, as indicated by the tight correlations with SIP psychosocial score, STAI and SDS (Table 4).

Recently, SF-36 (Japanese version) has become used more frequently in the field of CCR.[29,37] In fact, a recent review of generic health-related QOL instruments[41] suggests that the SF-36 health survey is the most commonly

used of the generic QOL instruments reviewed.[42] However, some studies have raised a concern that SF-36 may not be sufficiently sensitive to measure the changes in QOL following CCR in cardiac patients.[27,43] Because a perfect QOL instrument for cardiac patients has not been established in Japan, further studies are needed to comparatively assess multiple QOL instruments and to invent a more appropriate QOL instrument for Japanese cardiac patients.

Study Limitations

First, because the present study did not have a control group not participating in CCR, it is unclear whether the improvement in QOL observed is attributable to the favorable effect of CCR or the natural course after AMI. However, the purpose of the present study was to compare different types of QOL instruments rather than to examine the efficacy of CCR on QOL in patients with AMI. To determine whether CCR improves QOL in Japanese patients after AMI, a prospective randomized study will be needed.

Second, the present study did not employ SF-36;[25] however, as mentioned before, it remains unclear whether SF-36 is the most appropriate instrument to assess QOL in Japanese patients participating in CCR after AMI. Further studies are needed to directly compare the usefulness and validity of various QOL instruments, such as MHW-QOL, SIP, and SF-36, in Japanese patients participating in CCR.

Third, the present study assessed changes in QOL in a relatively short-term (ie, 3 months) CCR program. Assessment of the effects of a longer term CCR on QOL in patients with AMI may also be necessary. Finally, because the present study included only a small number of elderly (6 patients (14%) >70 years of age) and female patients (7 (16%) female patients), the present results cannot be directly applied to such specific populations.

Conclusion

In patients with AMI, physical function-related QOL scores improve after 3-month CCR, whereas psychosocial and mental aspect-related QOL scores improve only in those with impaired exercise tolerance or impaired mental function at baseline. Thus, changes in QOL after CCR depend on the type of QOL scales and the patient's baseline status of physical and mental function. In addition, the present study demonstrated for the first time that MHW-QOL mainly reflects psychosocial/mental aspect-related QOL, as well as overall QOL, in Japanese cardiac patients.

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B-Type Natriuretic Peptide Strongly Reflects Diastolic Wall Stress in Patients With Chronic Heart Failure

Comparison Between Systolic and Diastolic Heart Failure

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OBJECTIVES We explored the stimulus for B-type natriuretic peptide (BNP) secretion in the clinical setting of heart failure (HF).

BACKGROUND Increasingly, plasma BNP levels are being incorporated into the clinical assessment and management of systolic heart failure (SHF) as well as diastolic heart failure (DHF). However, heterogeneity in BNP levels among individuals with HF can cause some confusion in interpreting results.

METHODS In 160 consecutive patients presenting with HF, we measured plasma BNP levels and performed echocardiography and cardiac catheterization. Systolic and diastolic meridional wall stress was calculated from echocardiographic and hemodynamic data.

RESULTS Although plasma BNP had a significant correlation ($r^2 = 0.296$ [$p < 0.001$]) with left ventricular end-diastolic pressure (EDP) as previously reported, the correlation between plasma BNP and end-diastolic wall stress (EDWS) ($r^2 = 0.887$ [$p < 0.001$]) was more robust. In a subanalysis of 62 patients with DHF, a similar result was obtained ($r^2 = 0.143$ for EDP and $r^2 = 0.704$ for EDWS). In a comparison between SHF and DHF, the BNP level was significantly higher in SHF ($p < 0.001$). Although EDP did not show any difference, EDWS was significantly higher in SHF than in DHF ($p < 0.001$).

CONCLUSIONS The present study shows that plasma BNP levels reflect left ventricular EDWS more than any other parameter previously reported, not only in patients with SHF, but also in patients with DHF. The relationship of left ventricular EDWS to plasma BNP may provide a better fundamental understanding of the interindividual heterogeneity in BNP levels and their clinical utility in the diagnosis and management of HF. (J Am Coll Cardiol 2006;47:742–8)
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Plasma B-type natriuretic peptide (BNP) levels are reported not only to be a strong marker of left ventricular (LV) dysfunction, but also a marker to predict morbidity and mortality accurately in patients with chronic heart failure (HF) (1,2). Recently, BNP-guided therapy for chronic HF has been suggested. Troughton et al. (3) demonstrated that pharmacotherapy guided by BNP levels reduces cardiovascular events and delays time to first cardiovascular event compared with intensive clinically guided therapy. Recent reports also demonstrated the contribution of LV diastolic function to plasma BNP levels and the usefulness of BNP in the diagnosis of diastolic HF (4).

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However, heterogeneity in BNP levels among individuals with HF has been recognized, and it has caused some confusion in interpreting results (5). Previous human studies have suggested correlations between BNP levels and cardiac functional or dimensional indexes such as end-diastolic pressure (EDP), ejection fraction (EF), pulmonary capillary wedge pressure, and LV volume, none of which sufficiently explain the heterogeneity (6–9). Therefore, it is essential to determine the stimulus for BNP secretion in the clinical setting of HF. In vitro studies have clarified the mechanism of secretion and regulation of BNP precisely (10). Stretch of cardiomyocytes is reported to be the most important stimulus of BNP regulation (11). It is also believed that BNP in humans may be released from the heart in response to increased wall stress. However, there have been few human studies exploring a direct relationship between wall stress and BNP regulation (12). Vanderheyden et al. (13) have very recently demonstrated, for the first time, in 40 patients with aortic stenosis (AS), a significant correlation of BNP with LV end-diastolic wall stress (EDWS). In their study, however, subjects were limited to patients with AS. Hence, there now is a need for the same assessment in patients

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