[3] Kugiyama K, Doi H, Takazoe K, Kawano H, Soejima H, Mizuno Y, et al. Remnant lipoprotein levels in fasting serum predict coronary events in patients with coronary artery disease. Circulation 1999;99:2858–60.
[4] Karpe F, Boquist S, Tang R, Bond GM, de Faire U, Hamsten A. Remnant lipoproteins are related to intima-media thickness of the carotid artery independently of LDL cholesterol and plasma triglycerides. J Lipid Res 2001;42:17–21.
[5] McNamara JR, Shah PK, Nakajima K, Cupples LA, Wilson PW, Ordovas JM, et al. Remnant-like particle (RLP) cholesterol is an independent cardiovascular disease risk factor in women: results from the Framingham Heart Study. Atherosclerosis 2001;154:229–36.
[6] Imke C, Rodriguez BL, Grove JS, McNamara JR, Waslien C, Katz AR, et al. Are remnant-like particles independent predictors of coronary heart disease incidence? The Honolulu Heart study. Arterioscler Thromb Vasc Biol 2005;25:1718–22.
[7] Steinberg D, Witztum JL. Is the oxidative modification hypothesis relevant to human atherosclerosis? Do the antioxidant trials conducted to date refute the hypothesis? Circulation 2002;105:2107–11.
[8] Mertens A, Holvoet P. Oxidized LDL and HDL: antagonists in atherothrombosis. FASEB J 2001;15:2073–84.
[9] Itabe H. Oxidized low-density lipoproteins: what is understood and what remains to be clarified. Biol Pharm Bull 2003;26:1–9.
[10] Toshima S, Hasegawa A, Kurabayashi M, Itabe H, Takano T, Sugano J, et al. Circulating oxidized low density lipoprotein levels. A biochemical risk marker for coronary heart disease. Arterioscler Thromb Vasc Biol 2000;20:2243–7.
[11] Holvoet P, Mertens A, Verhamme P, Bogaerts K, Beyens G, Verhaeghe R, et al. Circulating oxidized low density lipoprotein is a useful marker for identifying patients with coronary artery disease. Arterioscler Thromb Vasc Biol 2001;21:844–88.
[12] Kugiyama K, Sugiyama S, Soejima H, Kawano H, Sakamoto T, Takazoe K, et al. Increase in plasma levels of oxidized low-density lipoproteins in patients with coronary spastic angina. Atherosclerosis 2001;154:463–7.
[13] Holvoet P, Vanhaecke J, Janssens S, Van de Werf F, Collen D. Oxidized LDL and malondialdehyde-modified LDL in patients with acute coronary syndromes and stable coronary artery disease. Circulation 1998;98:1487–94.
[14] Ehara S, Ueda M, Naruko T, Haze K, Itoh A, Otsuka M, et al. Elevated levels of oxidized low density lipoprotein show a positive relationship with the severity of acute coronary syndromes. Circulation 2001;103:1955–60.
[15] Nordin Fredrikson G, Hedblad B, Berglund G, Nilsson J. Plasma oxidized LDL: a predictor for acute myocardial infarction? J Intern Med 2003;253:425–9.
[16] Shimada K, Mokuno H, Matsunaga E, Miyazaki T, Sumiyoshi K, Miyauchi K, et al. Circulating oxidized low-density lipoprotein is an independent predictor for cardiac event in patients with coronary artery disease. Atherosclerosis 2004;174:343–7.
[17] Shimada K, Mokuno H, Matsunaga E, Miyazaki T, Sumiyoshi K, Kume A, et al. Predictive value of circulating oxidized LDL for cardiac events in type 2 diabetic patients with coronary artery disease. Diabetes Care 2004;27:843–4.
[18] Meisinger C, Baumert J, Khuseyinova N, Loewel H, Koenig W. Plasma oxidized low-density lipoprotein, a strong predictor for acute coronary heart disease events in apparently healthy, middle-aged men from the general population. Circulation 2005;112:651–7.
[19] Palinski W, Horkko S, Miller E, Steinbrecher UP, Powell HC, Curtiss LK, et al. Cloning of monoclonal autoantibodies to epitopes of oxidized lipoproteins from apolipoprotein E-deficient mice. Demonstration of epitopes of oxidized low density lipoprotein in human plasma. J Clin Invest 1996;98:800–14.
[20] Nakajima K, Saito T, Tamura A, Suzuki M, Nakano T, Adachi M, et al. Cholesterol in remnant-like lipoproteins in human serum using monoclonal anti apo B-100 and anti apo A-I immunoaffinity mixed gels. Clin Chim Acta 1993;223:53–71.
[21] Nakajima K, Okazaki M, Tanaka A, Pullinger CR, Wang T, Nakano T, et al. Separation and determination of remnant-like particles in human serum using monoclonal antibodies to apo B-100 and apo A-I. J Clin Ligand Assay 1996;19:177–83.
[22] Nakada Y, Kurosawa H, Tohyama J, Inoue Y, Ikewaki K. Increased remnant lipoprotein in patients with coronary artery disease—evaluation utilizing a newly developed remnant assay, remnant lipoproteins cholesterol homogenous assay (RemL-C). J Atheroscler Thromb 2007;14:56–64.
[23] Kotani K, Maekawa M, Kanno T, Kondo A, Toda N, Manabe M. Distribution of immunoreactive malondialdehyde-modified low-density lipoprotein in human serum. Biochim Biophys Acta 1994;1215:121–5.
[24] Miyazaki T, Shimada K, Sato O, Kotani K, Kume A, Sumiyoshi K, et al. Circulating malondialdehyde-modified LDL and atherogenic lipoprotein profiles measured by nuclear magnetic resonance spectroscopy in patients with coronary artery disease. Atherosclerosis 2005;179:139–45.
[25] Definition and the diagnostic standard for metabolic syndrome—committee to evaluate diagnostic standards for metabolic syndrome. Nippon Naika Gakkai Zasshi 2005;94:794–809 [in Japanese].
[26] Eberly LE, Stamler J, Neaton JD. Multiple Risk Factor Intervention Trial Research Group. Relation of triglyceride levels, fasting and nonfasting, to fatal and nonfatal coronary heart disease. Arch Intern Med 2003;163:1077–83.
[27] Jeppesen J, Hein HO, Suadicani P, Gyntelberg F. Triglyceride concentration and ischemic heart disease: an eight-year follow-up in the Copenhagen Male Study. Circulation 1998;97:1029–36.
[28] Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. J Cardiovasc Risk 1996;3:213–9.
[29] Fruchart JC, Nierman MC, Stroes ES, Kastelein JJ, Duriez P. New risk factors for atherosclerosis and patient risk assessment. Circulation 2004;109:III15–9.
[30] Packard CJ, Saito Y. Non-HDL cholesterol as a measure of atherosclerotic risk. J Atheroscler Thromb 2004;11: 6–14.
[31] Hitsumoto T, Takahashi M, Iizuka T, Shirai K. Relationship between preheparin lipoprotein lipase mass concentration in serum and bare metal stent restenosis. J Cardiol 2006;48:65–73.
[32] Itabe H, Takeshima E, Iwasaki H, Kimura J, Yoshida Y, Imanaka T, et al. A monoclonal antibody against oxidized lipoprotein recognizes foam cells in atherosclerotic lesions. Complex formation of oxidized phosphatidylcholines and polypeptides. J Biol Chem 1994;269:15274–9.
[33] Ky B, Burke A, Tsimikas S, Wolfe ML, Tadesse MG, Szapary PO, et al. The influence of pravastatin and atorvastatin on markers of oxidative stress in hypercholesterolemic humans. J Am Coll Cardiol 2008;51:1653–62.
[34] Itabe H, Yamamoto H, Imanaka T, Shimamura K, Uchiyama H, Kimura J, et al. Sensitive detection of oxidatively modified low density lipoprotein using a monoclonal antibody. J Lipid Res 1996;37:3745–53.

[35] Holvoet P, Kritchevsky SB, Tracy RP, Mertens A, Rubin SM, Butler J, et al. The metabolic syndrome, circulating oxidized LDL, and risk of myocardial infarction in well-functioning elderly people in the health, aging, and body composition cohort. Diabetes 2004;53:1068–73.
[36] Ford ES, Mokdad AH, Giles WH, Brown DW. The metabolic syndrome and antioxidant concentrations: findings from the Third National Health and Nutrition Examination Survey. Diabetes 2003;52:2346–52.
[37] Zambon A, Hokanson JE, Brown BG, Brunzell JD. Evidence for a new pathophysiological mechanism for coronary artery disease regression: hepatic lipase-mediated changes in LDL density. Circulation 1999;99:1959–64.
[38] Weinbrenner T, Schröder H, Escurriol V, Fito M, Elosua R, Vila J, et al. Circulating oxidized LDL is associated with increased waist circumference independent of body mass index in men and women. Am J Clin Nutr 2006;83: 30–5.
[39] Yasue H, Nakagawa H, Itoh T, Harada E, Mizuno Y. Coronary artery spasm—clinical features, diagnosis, pathogenesis, and treatment. J Cardiol 2008;51:2–17.
[40] Nishi K, Itabe H, Uno M, Kitazato KT, Horiguchi H, Shinno K, et al. Oxidized LDL in carotid plaques and plasma associates with plaque instability. Arterioscler Thromb Vasc Biol 2002;22:1649–54.
[41] Ehara S, Ueda M, Naruko T, Haze K, Matsuo T, Ogami M, et al. Pathophysiological role of oxidized low-density lipoprotein in plaque instability in coronary artery diseases. J Diabetes Complications 2002;16:60–4.
[42] Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. Am J Cardiol 1983;51:606.
[43] Navab M, Berliner JA, Subbanagounder G, Hama S, Lusis AJ, Castellani LW, et al. HDL and the inflammatory response induced by LDL-derived oxidized phospholipids. Arterioscler Thromb Vasc Biol 2001;21:481–8.

Hypertension Research (2009) 32, 392–398

www.nature.com/hr

ORIGINAL ARTICLE

Influence of nifedipine coat-core and amlodipine on systemic arterial stiffness modulated by sympathetic and parasympathetic activity in hypertensive patients

Michinari Fukuda[1], Takashi Masuda[1], Misao N Ogura[1], Tatsumi Moriya[2], Keiji Tanaka[2], Kazuya Yamamoto[3], Akira Ishii[3], Ryusuke Yonezawa[4], Chiharu Noda[4] and Tohru Izumi[4]

The aim of this study was to compare the effects of nifedipine coat-core (once daily formulation) and amlodipine on systemic arterial stiffness in patients with hypertension. Study drugs were assigned by the randomized open-label crossover method. After the blood pressure was maintained below 130/85 mm Hg for 8 months by treatment with either drug in 48 hypertensive patients (aged 63.2 ± 6.9 years; 64.5% men), they were switched to the other drug for another 8 months. The blood pressure, heart rate, plasma catecholamine level and brachial-ankle pulse wave velocity were measured before and after a bicycle ergometer testing. Heart rate recovery was calculated from the change of the heart rate after treadmill exercise testing. The high-frequency and low-frequency components of the heart rate variability spectrum were analyzed from 24-h Holter electrocardiograms. The change of blood pressure after exercise testing showed no significant difference between the two medications. However, the increases of heart rate, noradrenalin and branchial-ankle pulse wave velocity after exercise were significantly smaller with nifedipine treatment than with amlodipine (P=0.0472, P=0.006 and P=0.0472, respectively). Heart rate recovery was significantly faster with nifedipine treatment (P=0.0280). The nighttime high-frequency component of heart rate variability was significantly larger after nifedipine treatment than after amlodipine (P=0.0259), while the nighttime low/high-frequency ratio was significantly smaller with nifedipine (P=0.0429). Nifedipine reduced functional arterial stiffness and improved heart rate recovery by altering the autonomic activity balance in hypertensive patients.
Hypertension Research (2009) **32**, 392–398; doi:10.1038/hr.2009.18; published online 17 April 2009

Keywords: amlodipine; arterial stiffness; autonomic activity; nifedipine coat-core

INTRODUCTION

It has been pointed out that autonomic activity are involved in the development of a cardiovascular event due to arteriosclerosis.[1,2] The imbalance of autonomic activity induced by sympathetic and parasympathetic nervous action, in particular, is closely related with arterial stiffness.[3] Increased arterial stiffness may lead to overload on the heart in terms of increases in heart rate (HR) and blood pressure (BP), and adversely influences the prognosis of a patient.[4–5] It is important in the treatment of hypertension to avoid an undesirable influence on the autonomic activity as well as to achieve strict BP reduction. The brachial-ankle pulse wave velocity (Ba-PWV) is currently used as an indicator of arterial stiffness,[6,7] whereas the spectral analysis of heart rate variability[8,9] and measurement of plasma catecholamines are methods of evaluating autonomic function. Long-acting calcium channel blockers (CCBs) have been demonstrated to prevent cardiovascular events in large-scale clinical trials,[10,11] but it remains unclear whether these drugs influence the arterial stiffness and autonomic activity balance. It has also been reported that dihydropyridine CCBs vary with respect to their antihypertensive and antiatherogenic effects.[12–14]

This study was designed to compare the effects of long-acting nifedipine (NIF) and amlodipine (AML), which are two CCBs commonly used to treat hypertension, on systemic arterial stiffness and autonomic activity balance in Japanese patients with hypertension.

METHODS

Subjects

This study enrolled outpatients of Kitasato University Hospital from March 2004 to March 2006. The study was approved by the Ethics Committee of Kitasato University Hospital, and written informed consent was obtained from all patients after they received a detailed explanation of the study protocol. Forty-eight patients with essential hypertension were enrolled by the continual registration method. Essential hypertension was defined as the mean systolic blood pressure (SBP) > 140 mm Hg and/or diastolic blood pressure

[1]Department of Rehabilitation, Kitasato University School of Allied Health Sciences, Kanagawa, Japan; [2]Department of Endocrinology, Diabetes and Metabolism, Kitasato University School of Medicine, Kanagawa, Japan; [3]Department of Angiology and Cardiology, Kitasato University Graduate School of Medical Sciences, Kanagawa, Japan and [4]Department of Cardio-angiology, Kitasato University School of Medicine, Kanagawa, Japan
Correspondence: Dr T Masuda, Department of Rehabilitation, School of Allied Health Sciences, Kitasato University, 1-15-1 Kitasato, Sagamihara, Kanagawa, 228-8555 Japan.
E-mail: tak9999@med.kitasato-u.ac.jp
Received 10 August 2008; revised 29 January 2009; accepted 10 February 2009; published online 17 April 2009

(DBP) > 90 mm Hg at the outpatient clinic on several visits, after a secondary hypertension was ruled out. Inclusion criteria were sinus rhythm on an electrocardiogram (ECG) and current treatment with antihypertensive agents. Exclusion criteria were frequent extrasystoles, significant coronary stenosis, unstable angina pectoris, prior myocardial infarction, heart failure, chronic renal failure, or diabetes mellitus.

Treatments and study design

Using 20 or 40 mg tablets of NIF and 2.5 or 5.0 mg tablets of AML, the dosages were set as follows: AML at 2.5 mg day^{-1}=NIF at 20 mg day^{-1} and AML at 5.0 mg day^{-1}=NIF at 40 mg day^{-1}. This was done on the basis of previous Japanese clinical studies indicating that these dosages have an equivalent antihypertensive effect.[15,16] The study was performed by the open-label cross-over method.

Patients were randomized to the NIF-first group or AML-first group and then took NIF or AML once daily after breakfast for 8 months. If other CCBs were already being administered, those agents were switched to the study drug, while administration of other non-CCB antihypertensive agents was continued without changing the dosage. The dose titration period of each study drug was for 2 months to achieve the target BP, which was less than 130/85 mm Hg. If the target BP was not attained during the dose titration period by study drugs, the patient was a dropout for the study. After the dosage was fixed, each treatment was continued at that dose for 6 months (totally 8 months treatment period). At the end of the first treatment period, exercise tests were done using a bicycle ergometer and a treadmill to assess systemic arterial stiffness and exercise tolerance, respectively, and measurement of biochemical variables was performed. Then the patients were switched to the other study drug for a further 8 months, with exercise testing and laboratory studies being done in the same manner at the end of the second treatment period.

Assessment of systemic arterial stiffness and heart rate recovery

Exercise testing was carried out with a bicycle ergometer (Well Bike BE-360, Fukuda Denshi, Tokyo, Japan) at the end of each 8-month treatment period to assess systemic arterial stiffness by measuring Ba-PWV (Omron Colin, Tokyo, Japan). The BP, HR and Ba-PWV were measured two times in the supine position, that is, after the patient had rested for 15 min and also at 10 min after the exercise test (Figure 1). Then the changes from the baseline BP, HR and Ba-PWV at rest to those determined after exercise were calculated (ΔBP, ΔHR and ΔBa-PWV, respectively) and a functional arterial stiffness was assessed by ΔBa-PWV,[7] with a negative value indicating greater vascular compliance. The bicycle ergometer exercise test was performed according to the following protocol. After resting for 15 min, patients started exercise on the ergometer at 15 watts for 3 min (warming-up period). Then the target HR was achieved within 3 min by increasing the workload and was maintained for another 10 min (exercise period). The target HR was set at 75% of the maximum HR measured during a treadmill exercise test performed according to the Bruce protocol.[17] After 10 min of rest following 3 min of cooling down, Ba-PWV was re-measured. The 10-min period was enough time to allow the elevated catecholamine levels due to exercise to return to normal.[18,19] All patients were instructed to pedal at 50 r.p.m. during the exercise test. HR and the ECG were monitored continuously using a Stress Test system (ML-1800, Fukuda Denshi), and BP was measured at 1-min intervals by the cuff method using an automatic sphygmomanometer (FB-300, Fukuda Denshi).

Heart rate recovery (HRR) was assessed during a treadmill exercise test (ML-6500, Fukuda Denshi) performed according to the Bruce protocol at the end of the 8-month treatment period. It was calculated as the decrease of HR from the maximum during the exercise test to that at 1 min after completion, and was used as an indicator of parasympathetic activity.[20]

Assessment of autonomic activity

A 24-h Holter ECG recording (FM-300, Fukuda Denshi) was obtained at the end of each treatment period to assess the autonomic activity on the basis of spectral analysis of heart rate variability. The variability of the R-R interval over 24 h was analyzed with MemCalc software (MemCalc, Suwa Trust, Tokyo, Japan) to obtain the low-frequency component (0.04–0.15 Hz) and the high-frequency component (0.15–0.4 Hz) of the power spectrum (LF and HF, respectively), as well as calculating entropy.[21] The HF component of the power spectrum is known to reflect parasympathetic activity, and the LF/HF ratio indicates the balance between sympathetic and parasympathetic activity. The average values of the HR, HF component, LF/HF ratio and entropy were calculated over 24 h, during the daytime (0800 to 1700 hours) and during the nighttime (0000 to 0600 hours). Then the daytime/nighttime ratios of these parameters were calculated (HR_{total}, HR_{day}, HR_{night}, $HR_{day/night}$, HF_{total}, HF_{day}, HF_{night}, $HF_{day/night}$, LF/HF_{total}, LF/HF_{day}, LF/HF_{night}, $LF/HF_{day/night}$, $Entropy_{total}$, $Entropy_{day}$, $Entropy_{night}$ and $Entropy_{day/night}$, respectively).

Plasma concentrations of noradrenalin (NORA) and adrenalin (ADRN), plasma renin activity (PRA) and the plasma aldosterone level (ALDST) were measured before and after the bicycle ergometer test that was performed to assess Ba-PWV. Then the changes from the baseline NORA, ADRN, PRA and ALDST to those after exercise were calculated (ΔNORA, ΔADRN, ΔPRA and ΔBa-PWV, respectively) to determine the response of sympathetic activity to exercise (Figure 1).

Investigation of cardiac and vascular endothelial function

The left atrial dimension (LAD), left ventricular end-diastolic dimension (LVDd), left ventricular end-systolic dimension (LVDs), left ventricular ejection fraction (LVEF) and left ventricular mass (LVM) were measured by echocardiography (Sonos 7500, Philips, Bothell, WA, USA) at the end of each 8-month treatment period. LVM was calculated according to the formula of Devereux and was adjusted for the body surface area.[22] All echocardiographic measurements were performed according to the recommendations of the American Society of Echocardiography by an observer who was blinded to the biochemical data.[23] Blood samples were obtained from an antecubital vein after an overnight fast for measurement of the serum concentrations of brain natriuretic peptide (BNP), von Willebrand factor (vWF), thrombomodulin and high sensitivity C-reactive protein (hs-CRP) at the end of each treatment period.

Statistical analysis

This was a randomized open crossover study in which NIF coat-core was switched to AML or vice versa. The primary end points were Ba-PWV and the

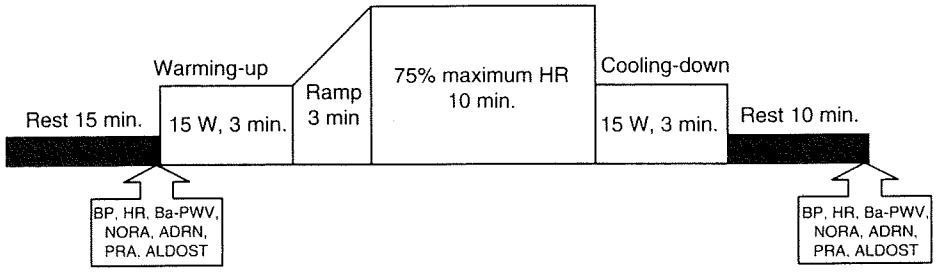

Figure 1 Exercise protocol for assessment of functional arterial stiffness. Exercise testing was performed with a bicycle ergometer (3-min warming-up period, 13-min exercise period and 3-min cooling-down period). The target heart rate (HR) was maintained for 10 min during the exercise period, and was set at 75% of the maximum HR reached during a treadmill exercise test using the Bruce protocol. BP: blood pressure, HR: heart rate, Ba-PWV: brachial-ankle pulse wave velocity, NORA: noradrenalin, ADRN: adrenalin, PRA: plasma renin activity, ALDOST: aldosterone.

levels of NORA and ADRN after the exercise test. Data were assessed by analysis of variance, including the terms sequence, treatment period, study drug and patient. Results are reported as the mean ± s.d. Comparisons of parameters between the two study drugs are also presented as differences between the drugs together with 95% confidence intervals. The paired *t*-test (two-tailed) was used to compare differences between other variables (LF, HF, Entropy, HRR, BNP, LVEF, LVMI, hs-CRP, vWF, etc.) measured during each treatment period. All statistical analyses were performed with SPSS 12.0J software (SPSS Japan, Tokyo), and $P<0.05$ was accepted as indicating significance.

RESULTS

The baseline characteristics of the patients are summarized in Table 1. The mean age of the patients was 63.2 ± 6.9 years and they consisted of 31 men and 17 women. Dyslipidemia was detected in 36.7% of the patients and 30.0% were smokers. The average daily doses of NIF and AML were 30.6 ± 13.1 mg and 4.5 ± 1.8 mg, respectively, at the time when the target BP (<130/85 mm Hg) was achieved. The other antihypertensive drugs used concomitantly were angiotensin II receptor blockers (53.3%), angiotensin-converting enzyme inhibitors (10.0%), β-blockers (40.0%), α-blockers (10.0%) and diuretics (23.3%). At the outpatient clinic, the average SBP/DBP and HR after treatments by AML or NIF were 125.3 ± 6.7/67.0 ± 6.6 mm Hg, 67.8 ± 7.9 beats min^{-1}, or 124.7 ± 6.9/66.5 ± 7.1 mm Hg, 66.6 ± 8.0 beats min^{-1}, respectively.

The values of BP, HR, Ba-PWV and neurohumoral factors measured before and after the bicycle ergometer exercise test are shown in Table 2. There were no significant differences of SBP and DBP before or after exercise between the two treatments. According to analysis of variance, there was no influence of the sequence and treatment period. Although no significant differences of baseline HR, Ba-PWV and neurohumoral factors were also shown between the two medications, there were significantly lower HR, Ba-PWV, NORA and PRA after the exercise test following NIF treatment compared with after AML treatment ($P=0.0472$, $P=0.0433$, $P=0.0006$ and $P=0.0082$, respectively).

Table 1 Baseline characteristics of the patients

Number of patients (male/female)	48 (31/17)
Age (years)	63.2 ± 6.9 (44–75)
Weight (kg)	64.2 ± 9.9
BMI ($kg\,m^{-2}$)	24.6 ± 2.9
Complications (%)	
Dyslipidemia	36.7
Smoking	30.0
Brood pressures (SBP/DBP)	
NIF	124.7 ± 6.9/66.5 ± 7.1
AML	125.3 ± 6.7/67.0 ± 6.6
Heart rate (b.p.m.)	
AML	67.8 ± 7.9
NIF	66.6 ± 8.0
Average dose ($mg\,day^{-1}$)	
NIF	30.6 ± 13.1
AML	4.5 ± 1.8
Treatment period (months)	
NIF	8.9 ± 1.5
AML	8.6 ± 1.6
Other medications (%)	
ARB	53.3
ACEi	10.0
β-blocker	40.0
α-blocker	10.0
Diuretics	23.3

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AML, amlodipine; ARB, angiotensin II receptor blocker; BMI, body mass index; b.p.m., beats per minute; DBP, Diastolic Blood Pressure; NIF, nifedipine coat-core; SBP, Systolic Blood Pressure.
Data are expressed as the mean ± s.d.

The changes of HR and Ba-PWV after the bicycle ergometer exercise test are shown in Figure 2. The increase of ΔHR was significantly smaller with NIF treatment than with AML treatment ($P=0.0472$). ΔBa-PWV were increased with AML treatment but decreased with NIF treatment ($P=0.0433$).

The changes of NORA, ADRN, PRA and ALDST after bicycle ergometer exercise are shown in Figure 3. The increase of ΔNORA and ΔPRA were significantly smaller in NIF treatment than in AML treatment ($P=0.0006$ and $P=0.0093$, respectively). There were no significant differences of ΔADRN or ΔALDST between the two medications.

The HR, HF component, LF/HF ratio and entropy over 24 hours, as well as during the daytime and nighttime, are listed in Table 3. Significantly lower HR_{night} and higher $HR_{day/night}$ were observed during NIF treatment compared with AML treatment ($P=0.0105$ and $P=0.0083$, respectively), although HR_{total} showed no significant difference between the two medications. Significantly higher HF_{night} and lower $HF_{day/night}$ values were observed during NIF treatment compared with AML treatment ($P=0.0259$ and $P=0.0374$, respectively). Significantly lower LF/HF_{night} and higher $LF/HF_{day/night}$ values were also found with NIF treatment than with AML treatment ($P=0.0429$ and $P=0.0166$, respectively). Both $entropy_{total}$ and $entropy_{night}$ showed significantly higher values during NIF treatment than during AML treatment ($P=0.0404$ and $P=0.0358$, respectively).

The HRR and cardiac function parameters are summarized in Table 4. Both HRR and LVEF were significantly greater during NIF treatment than during AML treatment ($P=0.0280$ and $P=0.0427$, respectively). In contrast, BNP and LVMI values were significantly smaller with NIF treatment than with AML treatment ($P=0.0418$).

Parameters of vascular endothelial function and inflammation are displayed in Figure 4. Both hs-CRP and vWF were significantly lower with NIF treatment than with AML treatment ($P=0.0382$ and $P=0.0263$, respectively).

DISCUSSION

Although there is abundant evidence that long-acting Ca antagonists can improve the prognosis of patients with cardiovascular disease,[10,11,24] it remains unclear how these drugs correct prognostic factors. This study showed that NIF significantly suppressed the increase of HR and decreased Ba-PWV[25] after exercise in hypertensive patients. It is well known that Ba-PWV reflects arterial stiffness more accurately in assessment of arterial pulse-wave velocity.[26,27] Although the antihypertensive effect of NIF was similar to that of AML, its influence on Ba-PWV was significantly stronger. Factors that increase arterial stiffness include hypertension, glucose intolerance, hypercholesterolemia and oxidative stress.[28] Arterial stiffness also increases when sympathetic activity is enhanced,[3] and such an increase is especially noted during exercise. To clarify the reason why the exercise-related increase of arterial stiffness was suppressed by NIF treatment, we investigated differences in the influence of NIF and AML on heart rate variability and neurohumoral factors. As a result, we found that the HF component (an indicator of parasympathetic

Table 2 Variables before and after exercise testing

Variable	Pre-exercise		Post-exercise		Difference	95% CI	P-value*
	AML	NIF	AML	NIF			
SBP (mm Hg)	130.7±10.9	129.8±10.0	131.5±13.0	130.3±12.1	−1.2	∼−4.911 to 2.522	0.5219
DBP (mm Hg)	77.2±7.4	77.4±6.5	79.1±8.1	77.1±7.5	−2.0	∼−3.899 to −0.101	0.0419
HR (beats min^{-1})	62.4±10.4	64.2±10.1	71.3±8.8	69.1±9.1	−2.2	∼−4.278 to −0.055	0.0472
Ba-PWV	1603±342	1604±331	1623±379	1564±310	−59.2	∼−116.000 to −2.354	0.0433
NORA (pg ml^{-1})	604.5±246.4	605.3±237.6	751.6±205.1	625.5±185.3	−126.1	∼−194.300 to −57.900	0.0006
ADRN (pg ml^{-1})	52.6±31.4	51.1±31.7	60.0±36.4	58.5±44.3	−1.5	∼−12.620 to 9.675	0.7847
PRA (ng ml^{-1} h^{-1})	2.4±3.5	2.4±3.1	3.4±4.0	2.0±2.5	−1.4	∼−2.346 to −0.393	0.0082
ALDOST (pg ml^{-1})	92.1±35.0	93.6±33.5	97.2±39.9	90.2±37.5	−7.0	∼−21.100 to 7.097	0.3093

Abbreviations: ADRN, adrenalin; ALDOST, aldosterone; AML, amlodipine; Ba-PWV, brachial-ankle pulse wave velocity; DBP, diastolic blood pressure; HR, heart rate; NIF, nifedipine coat-core; NORA, noradrenalin; PRA, plasma renin activity; SBP, systolic blood pressure.
Data are expressed as the mean±SD. **P*-values: AML *vs.* NIF after exercise by ANOVA.

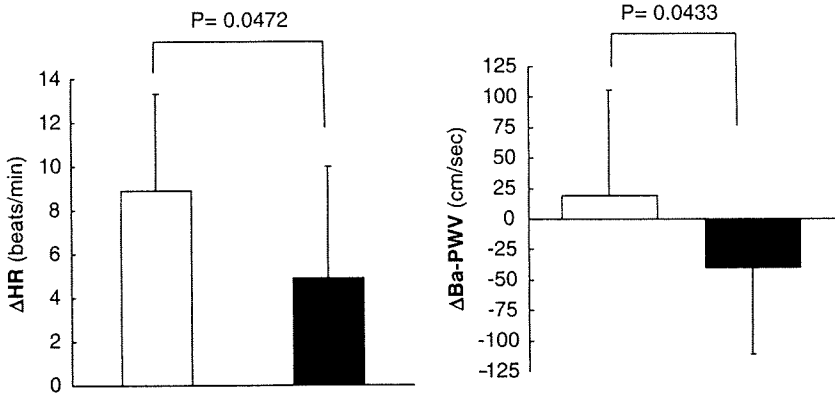

Figure 2 Changes of the heart rate (left) and Ba-PWV (right) during the bicycle ergometer exercise test. Open squares: amlodipine, closed squares: nifedipine coat-core. *P*-values: amlodipine *vs.* nifedipine coat-core by the paired *t*-test. HR: heart rate, Ba-PWV: brachial-ankle pulse wave velocity. ΔHR and ΔBa-PWV: the difference between baseline HR or Ba-PWV and the values measured after bicycle ergometer exercise.

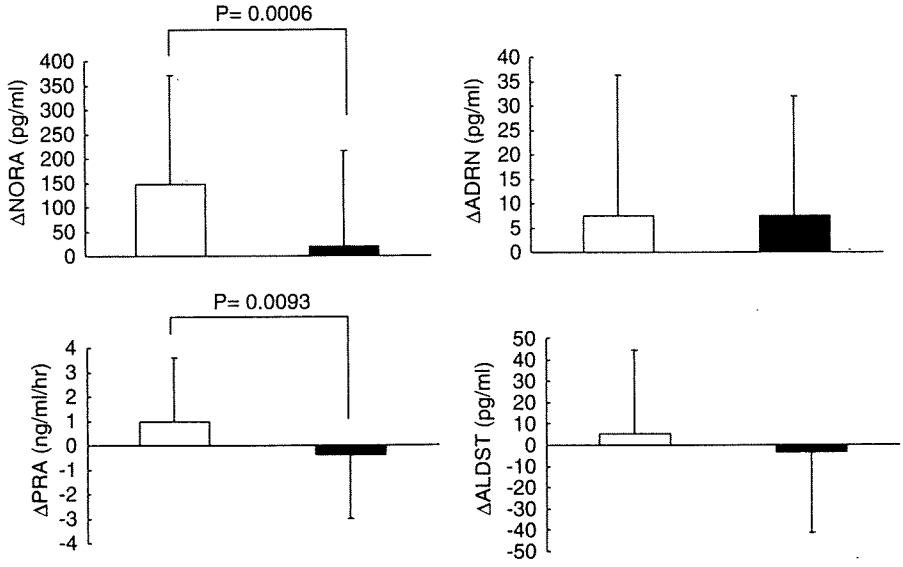

Figure 3 Changes of neurohumoral factors during the bicycle ergometer exercise test. Open squares, amlodipine; closed squares, nifedipine coat-core. *P*-values, amlodipine *vs.* nifedipine coat-core by the paired *t*-test. NORA, noradrenalin; ADRN, adrenalin; PRA, plasma renin activity; ALDOST, aldosterone. ΔNORA, ΔADRN, ΔPRA and ΔBa-PWV; the difference between baseline NORA, ADRN, PRA or ALDST and the values measured after bicycle ergometer exercise.

Table 3 Heart rate variability parameters

	AML	*NIF*	*P-value*
24-Hour			
HR (beats min^{-1})	67.66 ± 8.50	65.77 ± 9.66	0.2250
LF (ms^2)	503.58 ± 615.51	364.40 ± 421.38	0.0915
HF (ms^2)	193.95 ± 164.04	210.26 ± 192.14	0.5090
LF/HF	2.81 ± 1.76	2.43 ± 1.89	0.2479
Entropy	34.51 ± 8.34	39.26 ± 11.22	0.0404
Daytime			
HR (beats min^{-1})	69.31 ± 7.48	69.64 ± 7.75	0.8892
LF (ms^2)	431.35 ± 485.76	396.45 ± 526.98	0.9071
HF (ms^2)	178.68 ± 154.75	178.92 ± 132.29	0.7539
LF/HF	2.95 ± 2.31	2.91 ± 2.69	0.8910
Entropy	34.85 ± 11.08	38.50 ± 14.67	0.1206
Nighttime			
HR (beats min^{-1})	66.98 ± 8.76	61.83 ± 10.17	0.0105
LF (ms^2)	542.35 ± 725.28	319.89 ± 344.99	0.0133
HF (ms^2)	170.37 ± 143.72	253.40 ± 224.29	0.0259
LF/HF	3.36 ± 2.79	2.21 ± 2.18	0.0429
Entropy	33.60 ± 9.21	37.87 ± 10.24	0.0358
Daytime/Nighttime			
HR	1.05 ± 0.13	1.15 ± 0.20	0.0083
LF	1.14 ± 0.78	1.29 ± 0.72	0.3366
HF	1.08 ± 0.43	0.88 ± 0.39	0.0374
LF/HF	1.05 ± 0.57	1.86 ± 1.74	0.0166
Entropy	1.08 ± 0.34	1.04 ± 0.36	0.6472

Abbreviations: AML, amlodipine; LF and HF, low (0.04–0.15 Hz) and high (0.15–0.4 Hz) frequency components, respectively; NIF, nifedipine coat-core. Daytime and nighttime were from 0800 to 1700 hours and from 0000 to 0600 hours, respectively.
Data are expressed as the mean ± s.d. *P*-values: AML *vs.* NIF by the paired *t*-test.

Table 4 Heart rate recovery and cardiac function parameters

Variable	*AML*	*NIF*	*P-value*
HRR (beats min^{-1})	25.3 ± 8.3	29.6 ± 8.6	0.0280
BNP (pg ml^{-1})	27.9 ± 17.3	9.7 ± 15.9	0.0418
LVEF (%)	64.9 ± 4.1	66.7 ± 4.1	0.0427
LVMI (g m^{-2})	129.3 ± 28.8	120.7 ± 25.5	0.0504
LAD (mm)	40.7 ± 4.6	39.1 ± 5.1	0.0439
LVDd (mm)	49.8 ± 4.7	48.7 ± 4.9	0.0580
LVDs (mm)	30.1 ± 4.8	28.8 ± 4.9	0.0337
PWTH (mm)	9.8 ± 1.2	9.5 ± 1.2	0.1648
IVST (mm)	10.1 ± 1.4	9.9 ± 1.5	0.5603

Abbreviations: AML, amlodipine; BNP, brain natriuretic peptide; HRR, heart rate recovery; IVST, interventricular septal thickness; LAD, left atrial dimension; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NIF, nifedipine coat-core; PWTH, posterior left ventricular wall thickness.
Data are expressed as the mean ± s.d. *P*-values: AML *vs.* NIF by the paired *t*-test.

activity) was larger and the LF/HF ratio (an indicator of sympathetic activity) was smaller during NIF treatment than during AML treatment. In addition, the increase of entropy was significantly more marked during both daytime and nighttime when patients were receiving NIF than with AML treatment. Entropy is an indicator of the balance of autonomic activity, and an increase of entropy suggests appropriate regulation of autonomic function.[29] Nocturnal hypertension is one form of masked hypertension, and it is recognized as an important risk factor for stroke and other cardiovascular events. At night, parasympathetic activity should be dominant and reduce the blood pressure, but sympathetic activity still tends to be dominant in hypertensive patients even in the nighttime. Our findings suggested that NIF may improve the autonomic activity balance compared with the action of AML. This study also showed that ΔNORA and ΔPRA were significantly smaller after exercise during NIF treatment than during AML treatment. Champlain *et al.*[30] compared the effects of AML and NIF in patients with essential hypertension, and reported that the HR and NORA were significantly increased during the latter part of a 6-month treatment period with AML relative to the early part, whereas NORA was significantly reduced during NIF treatment. Our results support those findings and suggest that the significant reduction of ΔBa-PWV observed during NIF treatment is attributable to the improvement of systemic arterial stiffness secondary to correction of the imbalance of autonomic activity. The influence of NIF and AML on HRR, another prognostic factor, was also assessed in this study. Delayed recovery of the heart rate indicates suppression of parasympathetic activity after exercise,[31,32] whereas rapid recovery is considered to be an indicator of a good prognosis in patients with coronary artery disease.[33] Our results showed that HRR was significantly faster during NIF treatment than during AML treatment, suggesting that NIF had a more favorable influence on parasympathetic activity than AML.

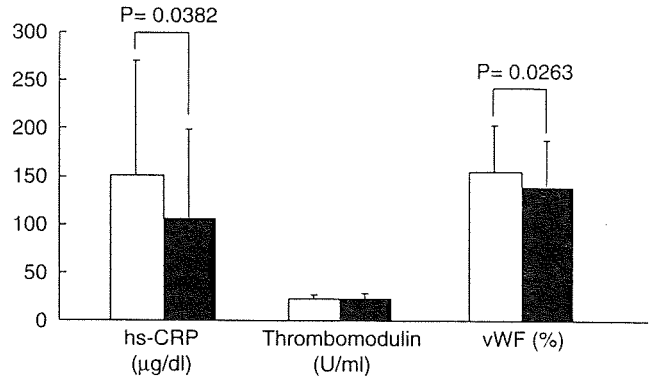

Figure 4 Parameters of vascular endothelial function and inflammation. Open bars, amlodipine; closed bars, nifedipine coat-core. *P*-values: amlodipine *vs.* nifedipine coat-core by the paired *t*-test. hs-CRP, high sensitivity C-reactive protein; vWF, von Willebrand factor.

This study also demonstrated significant improvement of left ventricular hypertrophy along with a decrease of BNP during NIF treatment compared with AML treatment. Cardiac hypertrophy has been reported to progress as a result of reduced nighttime parasympathetic activity,[34,35] so our finding that the nighttime HF component was larger during NIF treatment than during AML treatment may be associated with the inhibitory effect of NIF on ventricular hypertrophy.

The results of 24-h Holter monitoring showed an increase of nighttime parasympathetic activity during NIF treatment compared with AML treatment. Taken together with the difference of HRR after daytime exercise, it seems that NIF rather prevents suppression of parasympathetic activity at night when it should be dominant and improves arterial stiffness by normalizing the autonomic activity balance.

AML and NIF have different effects on sympathetic and parasympathetic activity for the following reasons. First, AML is a highly lipophilic drug with a much higher affinity for cardiac and vascular cell membranes than other dihydropyridines.[36] Because AML sub-

stantially inhibits Ca channel activity for a long period, it is possible that long-term AML treatment could lead to excessive suppression of vascular compliance so that the vessels no longer respond properly to autonomic regulation. Testa and colleagues[37] found that AML treatment had a negative influence on perceived general health, vitality and sleep compared with nifedipine GITS when they surveyed health-related quality of life in hypertensive patients. The controlled-release preparation used in this study maintains an adequate plasma concentration of nifedipine,[38] which presumably results in appropriate autonomic regulation of the cardiovascular system. Secondly, our study demonstrated that NIF treatment significantly reduced the levels of hs-CRP and vWF compared with AML, and it suggested that NIF treatment may improve the vascular endothelial function. These findings are supported by reports that NIF has stronger anti-inflammatory activity[39] and stronger anti-atherosclerotic effects including an antioxidant action[40,41] than other CCBs. Recently, the ENCORE study from Europe[42] demonstrated that long-acting nifedipine GITS improves acetylcholine sensitivity in patients with coronary artery disease, suggesting that NIF treatment could also improve vascular endothelial function.

Study limitations

There are some limitations also on this study as follows: (1) The sample size was not calculated statistically, because the study was exploratory. (2) We have observed the effects of either NIF or AML on arterial stiffness and autonomic balance by measuring of 24-h circadian dynamic change of autonomic activities on 24-h Holter ECG, because the office blood pressures of both drugs were equivalent. We also need to examine nocturnal blood pressure in both drugs by using ambulatory blood pressure monitoring. (3) All of the recruited patients were already treated with any of the CCBs. We could not perform ergometer exercise for baseline measurement after washout of treating CCBs because of the ethical reason. (4) This study did not show the relationship between the improvement of autonomic imbalance and the change of arterial stiffness directly, because both were not measured simultaneously.

Even there are limitations in this study as written above, our results may propose the following hypothesis, which is expected to be proven by further studies.

In conclusion, both NIF and AML controlled the BP well in hypertensive patients without inducing excessive activation of sympathetic nervous system, and in addition, NIF improved systemic arterial stiffness by correcting the imbalance of autonomic activity. Furthermore, our results suggested that NIF had a superior anti-inflammatory effect and improved vascular endothelial function compared with AML.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

1 La Rovere MT, Specchia G, Mortara A, Schwartz PJ. Baroreflex sensitivity, clinical correlates, and cardiovascular mortality among patients with a first myocardial infarction. *A prospective study. Circulation* 1988; **78**: 816–824.
2 Farrell TG, Paul V, Cripps TR, Malik M, Bennett ED, Ward D, Camm AJ. Baroreflex sensitivity and electrophysiological correlates in patients after acute myocardial infarction. *Circulation* 1991; **83**: 945–952.
3 Nakao M, Nomura K, Karita K, Nishikitani M, Yano E. Relationship between brachial-ankle pulse wave velocity and heart rate variability in young Japanese men. *Hypertens Res* 2004; **27**: 925–931.
4 Safar ME, Levy BI, Strujiker-Boudier: current perspective on arterial stiffness and pulse pressure in hypertension and cardiovascular diseases. *Circulation* 2003; **107**: 2864–2869.
5 Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, Ducimetiere P, Benetos A. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001; **37**: 1236–1241.
6 Yamashita A, Tomiyama H, Takeda K, Tsuda H, Arai T, Hirose K, Koji Y, Hori S, Yamamoto Y. Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens Res* 2002; **25**: 359–364.
7 Munakata M, Nunokawa T, Tayama J, Yoshinaga K, Toyota T. Brachial-ankle pulse wave velocity as a novel measure of arterial stiffness: present evidence and perspectives. *Curr Hypertens Rev* 2005; **12**: 223–234.
8 Widgren BR, Wikstrand J, Berglund G, Andersson OK. Increased response to physical and mental stress in men with hypertensive patients. *Hypertension* 1992; **20**: 606–611.
9 Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. *Circulation* 1996; **93**: 1043–1065.
10 Lubsen J, Wagner G, Kirwan BA, Brouwer S, Poole-Wilson PA. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with symptomatic stable angina and hypertension: the ACTION trial. *J Hyperten* 2005; **23**: 641–648.
11 Nissen SE, Tuzcu EM, Libby P, Thompson PD, Ghali M, Garza D, Berman L, Shi H, Buebendorf E, Topol EJ, for the CAMELOT Investigators. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure. The CAMELOT Study: a randomized controlled trial. *JAMA* 2004; **292**: 2217–2226.
12 Kono I, Kugiyama K. Evaluation on antihypertensive effect of nifedipine coat-core and change in pulse pressure in elderly hypertensive patients refractory to amlodipine therapy. *Ther Res* 2005; **26**: 491–497.
13 Saito I, Saruta T, ADVANCE-Combi Study Group. Controlled release nifedipine and valsartan combination therapy in patients with essential hypertension: the Adalat CR and Valsartan Cost-Effectiveness Combination (ADVANCE-Combi) Study. *Hypertens Res* 2006; **29**: 789–796.
14 Shinoda E, Yui Y, Kodama K, Hirayama A, Nonogi H, Haze K, Sumiyoshi T, Hosoda S, Kawai C, Japan Multicenter Investigation for Cardiovascular Diseases-B Study Group. Quantitative coronary angiogram analysis: nifedipine retard versus angiotensin-converting enzyme inhibitors (JMIC-B Side arm study). *Hypertension* 2005; **45**: 1153–1158.
15 Ishii M, Matsuoka H, Iimura O, Yoshinaga K, Yagi S, Saruta T, Kurokawa K, Takeda T, Ogihara T, Fujishima M, Arakawa K, Fukiyama K, Ohashi Y. Clinical efficacy of BAY a 1040-OD (sustained-release nifedipine) in patients with essential hypertension: multicenter open trials of monotherapy and combined therapy (in Japanese). *Jpn Pharmacol Ther* 1997; **25**: 1839–1868.
16 Masuyama Y, Arita M, Iimura O, Yoshinaga K, Abe K, Inagaki Y, Ishii T, Kuramoto K, Saruta T, Kajiwara N, Mizuno Y, Kumahara Y, Ito K, Arakawa K. A multicenter trial of amlodipine besilate in patients with essential hypertension (in Japanese). *Jpn Pharmacol Ther* 1991; **19**: 2853–2871.
17 Bruce RA, Rowell LB, Blackmon JR, Doan A. Cardiovascular function tests. *Heart Bull* 1965; **14**: 9–14.
18 Hagberg JM, Hickson RC, McLane JA, Ehsani AA, Winder WW. Disappearance of norepinephrine from the circulation following strenuous exercise. *J Appl Physiol* 1979; **47**: 1311–1314.
19 Todd EP, Vick RL. Kalemotropic effect of epinephrine: analysis with adrenergic agonists and antagonists. *Am J Physiol* 1971; **220**: 1964–1969.
20 Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS. Heart rate recovery immediately after exercise as a predictor of mortality. *N Engl J Med* 1999; **341**: 1351–1357.
21 Ohtomo N, Kamo T, Watanabe M, Yoneyama K, Tanaka Y, Hayashi R. Power spectral densities of temporal variations of blood pressures. *Jpn J Appl Physiol* 1996; **35**: 5571–5582.
22 Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 1990; **322**: 1561–1566.
23 Pearlman A, Gardin J, Martin R, Parisi AF, Popp RL, Quinones MA, Stevenson JG. Guidelines for optimal physician training in echocardiography. Recommendations of the American Society of Echocardiography committee for physician training in echocardiography. *Am J Cardiol* 1987; **60**: 158–163.
24 ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial.: major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288**: 2981–2997.
25 Yamashina A, Tomiyama H, Takeda K, Tsuda H, Arai T, Hirose K, Koji Y, Hori S, Yamamoto Y. Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens Res* 2002; **25**: 359–364.
26 Schimmler W, Hooffacker M. Spontaneous changes in blood pressure and aortic pulse wave velocity in normotensive subjects (results of a long-term study in 183 men) [author's transl.]. *Basic Res Cardiol* 1975; **70**: 521–530.
27 Bercu BB, Haupt R, Johnsonbaugh R, Rodbard D. The pulse wave arrival time (QKd interval) in normal children. *J Pediatr* 1979; **95**: 716–721.
28 Tomiyama H, Kushiro T, Okazaki R, Yoshida H, Doba N, Yamashina A. Influence of increased oxidative stress on endothelial function, platelet function, and fibrinolysis in hypertension associated with glucose intolerance. *Hypertens Res* 2003; **26**: 295–300.
29 Khalfen ESh, Temkin BM. Clinical value of the study of cardiac rhythm entropy in patients with myocardial infarction. *Kardiologiia* 1983; **23**: 37–41.

30 Champlain J, Karas M, Nguyen P, Cartier P, Wistaff R, Toal CB, Nadeau R, Larochelle P. Different effects of nifedipine and amlodipine on circulating catecholamine levels in essential hypertensive patients. *J Hypertens* 1998; **16**: 1357–1369.
31 Imai K, Sato H, Hori M, Kusuoka H, Ozaki H, Yokoyama H, Takeda H, Inoue M, Kamada T. Vagally mediated heart rate recovery after exercise is accelerated in athletes but blunted in patients with chronic heart failure. *J Am Coll Cardiol* 1994; **24**: 1529–1535.
32 Pierpont G, Stolpman D, Gornick C. Heart rate recovery post-exercise as an index of parasympathetic activity. *J Auton Nerv Syst* 2000; **80**: 169–174.
33 Vivekananthen DP, Blackstone EH, Pothier CE, Lauer MS. Heart rate recovery after exercise in a predictor of mortality, independent of the angiographic severity of coronary disease. *Am J Cardiol* 2003; **42**: 831–838.
34 Petretta M, Marciano F, Bianchi V, Migaux ML, Valva G, De Luca N, Salemme L, Berardino S, Bonaduce D. Power spectrum analysis of heart period variability in hypertensive patients with left ventricular hypertrophy. *AJH* 1995; **8**: 1206–1213.
35 Kuwajima I, Suzuki Y, Shimosawa T, Kanemaru A, Hoshino S, Kuramoto K. Diminished nocturnal decline in blood pressure in elderly hypertensive patients with left ventricular hypertrophy. *Am Heart J* 1992; **123**: 1307–1311.
36 Manson RP, Campbell SF, Wang SD, Herbette LG. Comparison of location and binding for the positively charged 1,4-dihydropyridine calcium channel antagonist amlodipine with uncharged drugs of this class in cardiac membranes. *Mol Pharmacol* 1989; **36**: 634–640.
37 Testa MA, Turner RR, Simonson DC, Krafcik MB, Calvo C, Luque-Otero M. Quality of life and calcium channel blockade with nifedipine GITS versus amlodipine in hypertensive patients in Spain. *J Hypertens* 1998; **16**: 1839–1847.
38 Nakamichi N, Yanagida T, Hikima Y, Kobayashi N, Shiga K, Tsuji S, Tanaka T, Tamagawa K, Sekino H. Phase-1 study of nifedipine sustained-released formation (BAY a 1040-OD tablets): single administration study. *Jpn Pharmacol Ther* 1995; **23**: S241–S255 (in Japanese).
39 Matsumori A, Nunokawa Y, Sasayama S. Nifedipine inhibits activation of transcription factor NF-Kb. *Life Sci* 2000; **67**: 2655–2661.
40 Fukuo K, Yang J, Yasuda O, Mogi M, Suhara T, Sato N, Suzuki T, Morimoto S, Ogihara T. Nifedipine indirectly upregulates superoxide dismutase expression in endothelial cells via vascular smooth muscle cell-dependent pathways. *Circulation* 2002; **106**: 356–361.
41 Berkels R, Egink G, Marsen TA, Bartels H, Roesen R, Klaus W. Nifedipine increases endothelial nitric oxide bioavailability by antioxidative mechanisms. *Hypertension* 2001; **37**: 240–245.
42 The ENCORE Investigators. Effect of nifedipine and cerivastatin on coronary endothelial function in patients with coronary artery disease, The ENCORE I Study (Evaluation of nifedipine and cerivastatin on recovery of coronary endothelial function). *Circulation* 2003; **107**: 422–428.

Effects of Phase II Cardiac Rehabilitation on Job Stress and Health-Related Quality of Life After Return to Work in Middle-Aged Patients With Acute Myocardial Infarction

Ryusuke YONEZAWA,[1] MSc, Takashi MASUDA,[2] MD, Atsuhiko MATSUNAGA,[2] PhD, Yumi TAKAHASHI,[3] Masakazu SAITOH,[1] MSc, Akira ISHII,[1] MSc, Toshiki KUTSUNA,[1] MSc, Takuya MATSUMOTO,[1] MSc, Kazuya YAMAMOTO,[1] MSc, Naoko AIBA,[1] MSc, Miyako HARA,[1] MSc, *and* Tohru IZUMI,[4] MD

SUMMARY

The aim of the present study was to clarify the effects of phase II cardiac rehabilitation (CR) on job stress and health-related quality of life (HRQOL) after return to work in middle-aged patients with acute myocardial infarction (AMI). A total of 109 middle-aged outpatients (57 ± 7 years) who completed a phase I CR program after AMI were enrolled, 72 of whom participated in a phase II CR program for 5 months after hospital discharge (CR group) and 37 who discontinued the phase II CR program after the discharge (non-CR group). Job stress was assessed at 6 months after the AMI using a brief job stress questionnaire containing questions related to job stressors, worksite support, level of satisfaction with work or daily life, and psychological distress. HRQOL was assessed using the short-form 36-item health survey (SF-36) at hospital discharge and at 3 and 6 months after the AMI. There were no significant differences in clinical and occupational characteristics between the CR and non-CR groups. The CR group patients exhibited significantly better results for job stressors and psychological distress and higher SF-36 scores at 6 months after the AMI, as compared with those in the non-CR group. These findings suggest that discontinuing a phase II CR program induced chronic psychosocial stress after return to work in these middle-aged post-AMI patients. (Int Heart J 2009; 50: 279-290)

Key words: Myocardial infarction, Rehabilitation, Middle-aged, Stress, Quality of life

PATIENT-PERCEIVED health-related quality of life (HRQOL) is one of the most important and fundamental parameters in the evaluation of the health

From the [1] Graduate School of Medical Sciences, and [2] Department of Rehabilitation, School of Allied Health Sciences, Kitasato University, [3] Cardiovascular Center, Kitasato University Hospital, [4] Department of Internal Medicine and Cardiology, School of Medicine, Kitasato University, Sagamihara, Kanagawa, Japan.

Address for correspondence: Takashi Masuda, MD, Kitasato 1-15-1, Sagamihara, Kanagawa 228-8555, Japan.

Received for publication November 25, 2008.

Revised and accepted December 26, 2008.

condition in patients recovering from coronary artery disease (CAD).[1] Although physical activity, psychological status, socioeconomic status, and social role are known to influence the HRQOL in patients with acute myocardial infarction (AMI),[1-3] this influence appears to differ widely between middle-aged and more aged patients. Retired and aged patients with CAD have been reported to readily develop depression because of physical inactivity, living alone, and low socioeconomic status.[4] On the other hand, middle-aged patients with CAD may often experience anxiety and depressed mood due to loss of social position and economic instability.[4] Most patients who were working before AMI desire to return to work soon after hospital discharge, because they hope to regain their social position, or need to support their family.[4,5] It has been reported that post-AMI patients who could successfully return to work exhibited greater emotional well-being after hospital discharge than those who could not.[3-5] Return to work is thus one of the most important goals of the phase II CR program after an AMI for middle-aged patients.

On the other hand, job stress by itself has recently been shown to be a risk factor for AMI and for other cardiovascular events such as life-threatening arrhythmias, recurrence of AMI, and sudden death.[6] Although an appropriate level of job stress is required for fruitful work, excessive stress induced by a highly demanding occupation, low job latitude, or low work-related social support can exaggerate psychosomatic symptoms, including anxiety, depression, and fatigue.[7] Healthcare managers thus need to recognize that in addition to being a risk factor for coronary events, job stress can also produce deterioration of the HRQOL in AMI patients after return to work.

Some studies have suggested that education of patients about their disease, behavioral counseling, and the use of a psychosocial approach as part of a comprehensive CR program may decrease stress related to work and daily life in post-AMI patients.[7-9] In addition, some studies have examined the effects of comprehensive CR on the success rate of return to work in middle-aged patients.[9] However, few reports have documented the beneficial effects of CR programs on the job stress perceived by AMI patients who returned to their work. The purpose of the present study was to clarify the beneficial effects of a phase II CR program on the job stress level, psychosocial aspects of life, including the status of depression and anxiety, and HRQOL in middle-aged AMI patients returning to work after hospital discharge.

METHODS

Patients: The study protocol was approved by the Ethics Committee of Kitasato University on Human Research. Patients who were admitted to the Cardiovas-

cular Center of Kitasato University Hospital from September 2003 to July 2006 with AMI and who underwent phase I CR during hospitalization were enrolled as eligible candidates for the present study. Patients were excluded if they had limitation of activities of daily living caused by central neurologic disease or orthopedic disorder or were 65 years of age or older. A total of 266 patients who met the eligibility criteria were given information about the purpose and method of the study and provided consent for participation in the questionnaire surveys to evaluate the job stress level, HRQOL, and the severity of anxiety and depression. Of the 266 middle-aged post-AMI patients, 109 (90 men and 19 women; mean age, 56 ± 7 years; range, 35 to 64 years) who had undergone percutaneous coronary intervention (n = 78) or coronary artery bypass grafting (n = 31) during the hospitalization and returned to their previous jobs after hospital discharge participated. The patients decided of their own will whether they participated in a phase II CR or not after completion of a phase I CR program. The patients were divided into the following two groups: a CR group, consisting of 72 patients who underwent phase II CR as outpatients for 5 months after hospital discharge, and a non-CR group comprised of 37 patients who discontinued CR and did not attend the phase II CR program for outpatients after hospital discharge. The patients were also interviewed to determine the job stress level at 6 months after the AMI, and given questionnaires for determining the HRQOL and status of anxiety and depression at the time of hospital discharge, and at 3 and 6 months after AMI.

Measurements of the clinical and occupational characteristics: Age, sex, number of stenotic coronary arteries, and left ventricular ejection fraction (LVEF) were assessed on admission, and the body mass index, exercise capacity, muscle strength of the lower limbs, duration of hospital stay, and score for type A behavior pattern were evaluated at hospital discharge. LVEF, exercise capacity, and muscle strength of the lower limbs were reevaluated at 6 months after the AMI in the CR and non-CR groups. The duration from hospital discharge to return to work, job description, and working conditions after return to work were assessed 6 months after the AMI as occupational characteristics. Exercise capacity was calculated from the exercise time on treadmill exercise testing using the Bruce protocol. Muscle strength of the lower limbs was measured using a hand-held dynamometer (μTas MT-1, Anima, Tokyo) while patients performed isometric knee extension in a sitting position. The mean peak muscle strength (kg) in the right and left legs was normalized to the body weight and expressed as a percentage of the body weight (%BW) for statistical analysis. The type A behavior pattern score was measured by the discrimination test for the type A behavior pattern, which was developed for Japanese subjects.[10]

Assessment of job stress: Job stress was assessed using a brief job stress ques-

tionnaire[11] containing questions related to four main categories: job stressors (quantitative job overload, qualitative job overload, physical demand, interpersonal conflict, poor physical environment, job control, skill underutilization, suitable job and rewarding job), worksite support (supervisor support, coworker support and family support), level of satisfaction with work or daily life and psychological distress (lack of vigor, irritability, fatigue, anxiety, depressed mood, and somatic symptoms), while the quantitative job overload and qualitative job overload represented the psychological job demand. Each of the topic subscales was graded from 1 to 5 and adjusted for age and sex. A score of 3 represented the mean score for age-matched healthy workers, and lower scores indicated greater stress in AMI patients after return to work.

Assessment of psychosocial aspects: HRQOL was assessed using the medical outcome study short-form 36-item health survey (SF-36) Japanese version 1.20.[12] The SF-36 includes eight subscales: physical functioning (PF), role-physical (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH). Norm-based scale scores were adjusted for age and sex to enable comparison between the CR and non-CR groups, with higher scores in each subscale indicating a better HRQOL. Anxiety and depression were assessed using the hospital anxiety and depression scale (HADS).[13] Scores on the HADS were graded from 0 to 16, with scores of 8 or higher indicating anxiety or depression. In addition, patients were instructed to fill out a self-reported questionnaire freely and concretely if they had any anxiety or problem related to working or daily life after hospital discharge.

CR program: At the Cardiovascular Center of Kitasato University Hospital, all patients are individually offered a comprehensive CR program, including exercise prescription, exercise training, dietary advice, instruction on medications and smoking cessation, referred to as phase I CR, during hospitalization. Before hospital discharge, the patients were briefed about the need to continue with CR and encouraged to participate in the comprehensive CR program, the phase II CR program for outpatients. The patients who participated in the phase II CR program received supervised exercise training and counseling as comprehensive CR for an hour once a week. The exercise session in the CR program included stretching, resistance training, aerobic exercise, and cool-down periods. After sufficient stretching of the quadriceps and triceps surae, the patients performed knee extensions with weights and calf raises for resistance training at a perceived exertion grade of 11-13. The exercise intensity in aerobic training was maintained at 65% of the peak heart rate determined during the treadmill exercise test. In the counseling session, a physical therapist confirmed the patients' physical condition, including the blood pressure, heart rate, arrhythmias, and leg

fatigue during the exercise training, and offered consultation for fitness conditioning for working and daily life.

Statistical analysis: The unpaired *t*-test and χ^2 test were used to examine the differences between the CR and non-CR groups in terms of the clinical and occupational characteristics, scores on the brief job stress questionnaire, and self-reported anxiety or problems in working or daily life. The paired *t*-test was used to compare the LVEF, exercise capacity, and muscle strength of the lower limbs measured at hospital discharge and 6 months after the AMI in the CR and non-CR groups. Two-way analysis of variance for repeated measures was used to examine the differences in the scores on the SF-36 and HADS between the two groups. All values are expressed as the mean ± standard deviation (SD), with *P* values of less than 0.05 considered to represent significant differences. All analyses were performed using SPSS 11.0J for Windows (SPSS Japan Inc., Tokyo).

Table I. Clinical and Occupational Characteristics of Patients

Groups	CR		Non-CR	
	Hospital discharge	6 months	Hospital discharge	6 months
Number	72		37	
Age (years)	57 ± 6		57 ± 7	
Sex (Man/Woman)	59/13		31/6	
Body mass index (kg/m^2)	23.4 ± 2.6		22.6 ± 4.0	
Multiple vessel disease (%)	46		55	
Treatment (%)				
Percutaneous coronary intervention	68		78	
Coronary artery bypass grafting	32		22	
Type A behavior pattern score (points)	15.7 ± 5.2		15.4 ± 3.8	
Duration of hospital stay (days)	23 ± 7		22 ± 9	
Left ventricular ejection fraction (%)	48.9 ± 10.7	53.1 ± 9.1*	47.2 ± 13.7	53.9 ± 6.8
Exercise capacity (METs)	9.2 ± 1.9	11.4 ± 2.0**	9.1 ± 2.4	10.4 ± 3.0
Muscle strength of the lower limbs (%BW)	56.3 ± 13.8	68.9 ± 16.3**	52.8 ± 11.6	60.1 ± 8.0
Duration to return to work (days)		29 ± 33		24 ± 23
Job description (%)				
Managerial posts		31		20
Independent business		32		13
Part-time job		4		38
White-collar work		25		13
Blue-collar work		21		13
Working condition after return to work (%)				
Decreased workload and work hours		13		18
Change of job		3		0
No change		83		82

Mean ± SD. CR indicates cardiac rehabilitation; 6 months, 6 months after acute myocardial infarction; MET, metabolic equivalent; BW, body weight; *, $P < 0.05$ and **, $P < 0.01$ versus hospital discharge in the CR group.

RESULTS

Clinical and occupational characteristics: The clinical and occupational characteristics of the patients in the CR and non-CR groups are shown in Table I. There were no significant differences in the clinical or occupational characteristics between the two groups at hospital discharge and 6 months after AMI. LVEF, exercise capacity, and muscle strength of the lower limbs were significantly improved at 6 months after the AMI as compared with the respective values measured at hospital discharge in the CR group ($P < 0.05$, $P < 0.01$ and $P < 0.01$, respectively), while no significant changes were observed during the study period in the non-CR group. No significant difference was found between the two groups in regard to the duration from hospital discharge to return to work. Sixty patients (83%) in the CR group and 30 patients (82%) in the non-CR group could return to their previous workplace under the same working conditions, and 31% in the CR group and 20% in the non-CR group were engaged in managerial work. There were no significant differences between the two groups in the job description or working conditions after return to work.

Brief job stress questionnaire: The scores on the brief job stress questionnaire are shown in Table II. Although no significant differences were found between

Table II. Scores on the Brief Job Stress Questionnaire

Groups	CR	Non-CR
Job stressors		
Quantitative job overload	3.5 ± 1.1	2.8 ± 1.5
Qualitative job overload	2.8 ± 1.1	2.4 ± 1.3
Physical demand	2.9 ± 0.9	2.5 ± 1.0
Interpersonal conflict	3.6 ± 1.1	3.4 ± 1.0
Poor physical environment	4.2 ± 0.9	3.7 ± 1.1
Job control	4.0 ± 0.9	4.3 ± 1.0
Skill underutilization	4.1 ± 1.0	3.7 ± 0.6
Suitable job	3.6 ± 1.2	3.1 ± 1.0
Rewarding job	3.9 ± 1.1*	2.8 ± 1.3
Worksite support		
Supervisor support	3.9 ± 0.7	3.9 ± 0.6
Coworker support	3.5 ± 0.9	3.3 ± 0.9
Family support	4.2 ± 1.1	4.3 ± 0.9
Level of satisfaction with work or daily life	3.6 ± 1.0	3.5 ± 1.1
Psychological distress		
Lack of vigor	4.2 ± 0.7**	3.1 ± 0.8
Irritability	4.0 ± 1.0*	3.3 ± 1.1
Fatigue	3.9 ± 0.7**	3.0 ± 0.4
Anxiety	3.5 ± 0.8	3.1 ± 0.7
Depressed mood	4.0 ± 1.0**	2.7 ± 0.5
Somatic symptoms	3.6 ± 1.0*	2.5 ± 1.0

Mean ± SD. CR indicates cardiac rehabilitation; *, $P < 0.05$ and **, $P < 0.01$ versus non-CR group.

the two groups in regard to worksite support or level of satisfaction with work or daily life, the score for 'rewarding job' in job stressors was significantly higher in the CR group than in the non-CR group ($P < 0.01$). The scores for lack of vigor, irritability, fatigue, depressed mood, and somatic symptoms in psychological distress were significantly higher in the CR group than in the non-CR group ($P < 0.01$, $P < 0.05$, $P < 0.01$, $P < 0.01$ and $P < 0.05$, respectively).

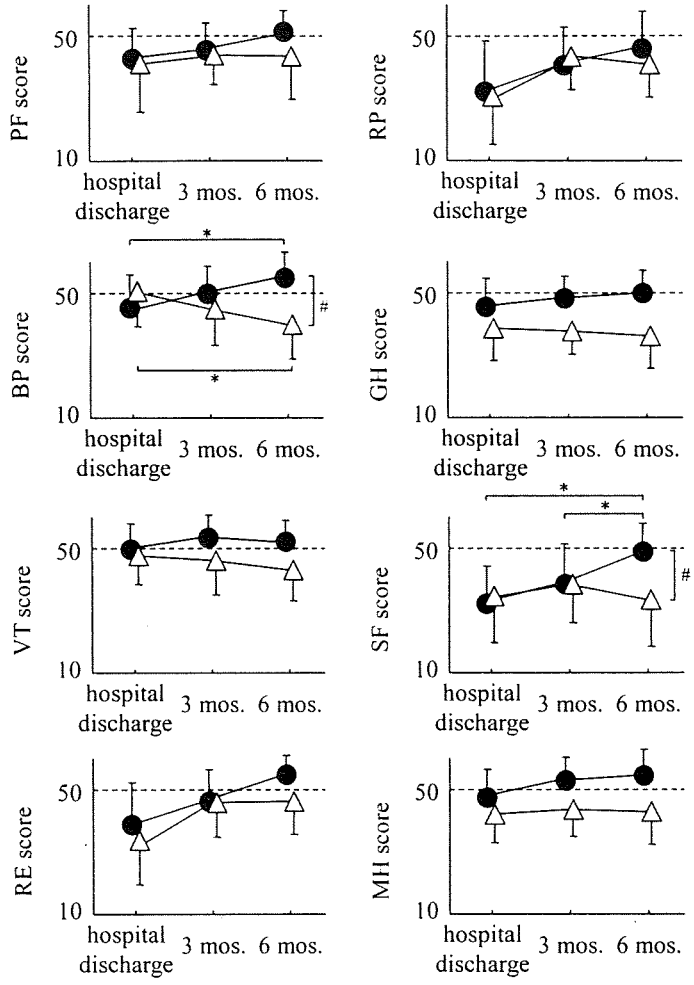

Figure 1. Changes in the norm-based scale scores for the subscales of SF-36.
● indicates CR group; ○, non-CR group; CR, cardiac rehabilitation; 3 mos., 3 months after acute myocardial infarction; 6 mos., 6 months after acute myocardial infarction; PF, physical functioning; RP, role-physical; BP, bodily pain; GH, general health perceptions; VT, vitality; SF, social functioning; RE, role-emotional; MH, mental health; *, $P < 0.05$ versus 6 months after acute myocardial infarction and #, $P < 0.05$ between the CR and non-CR groups.

SF-36 and HADS: The changes in the norm-based scale scores of the SF-36 in the CR and non-CR groups are shown in Figure 1. There were significant interactions in the changes of the BP and SF scores between the CR and non-CR groups ($F = 5.17$, $P < 0.05$ and $F = 3.32$, $P < 0.05$, respectively). The BP score was significantly improved at 6 months after the AMI as compared with that at hospital discharge in the CR group ($P < 0.05$), whereas it was significantly decreased in the non-CR group ($P < 0.05$). The SF score was significantly improved at 6 months after the AMI as compared with those at hospital discharge and at 3 months after the AMI in the CR group ($P < 0.05$ and $P < 0.05$, respectively), while no significant changes were observed during the study period in the non-CR group. The BP and SF scores at 6 months after the AMI were significantly higher in the CR group than in the non-CR group ($P < 0.05$ and $P < 0.05$, respectively).

The changes in the anxiety and depression scores in the CR and non-CR groups are shown in Figure 2. There were no significant differences in the anxiety or depression scores between the CR and non-CR groups throughout the study period.

Self-reported anxieties or problems on the job or in daily living: The self-reported anxieties or problems on the job or in daily living are shown in Table III. The percentage of patients who had anxieties or problems related to work or daily living was significantly higher in the non-CR group than in the CR group ($P < 0.01$). Nine patients had anxieties or problems related to work or daily living in the CR group (13%), including those related to recurrence of AMI (89%), self-management of medication or diet (22%), smoking cessation (22%), and physical activity (22%). On the other hand, 17 patients had anxieties or problems in

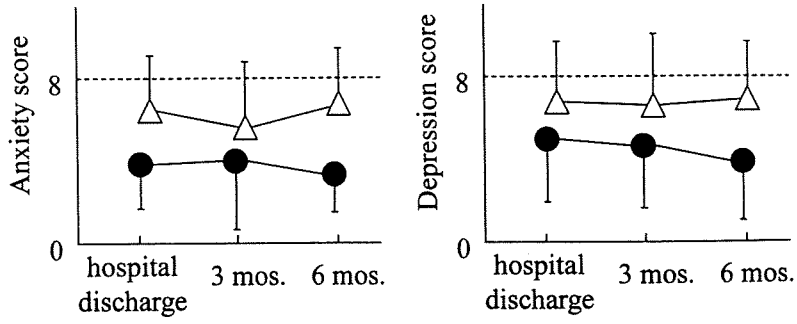

Figure 2. Changes in the anxiety and depression scores in HADS.
● indicates CR group; △, non-CR group; CR, cardiac rehabilitation; 3 mos., 3 months after acute myocardial infarction and 6 mos., 6 months after acute myocardial infarction.

Table III. Self-Reported Anxieties or Problems on the Job or in Daily Living

	CR	Non-CR
Do you have any anxieties or problems related to work or daily living?		
No (%)	87	54
Yes (%)	13	46*
Breakdown of anxieties or problems		
Recurrence of AMI (%)	89	18
Self-management of medication usage or diet (%)	22	35
Smoking secession (%)	22	6
Physical activities (%)	22	53

CR indicates cardiac rehabilitation; AMI, acute myocardial infarction and *, $P < 0.01$ analyzed by the chi-square test.

the non-CR group (46%), including those related to recurrence of AMI (18%), self-management of medication or diet (35%), smoking cessation (6%), and physical activity (53%).

In the non-CR group, the reasons for discontinuation of CR into the phase II CR were patient refusal in 29 patients and the long time needed to come to the hospital in 8 patients.

Discussion

It was recently reported that 50% of AMI patients returned to work as early as within a month after the occurrence of AMI,[14] and that 75% begin to work again under the same conditions as those before the admission.[15] In the present study, the mean duration from hospital discharge to return to work was 29 days in the CR group and 24 days in the non-CR group, and more than 80% of the patients in both groups returned to their previous work and working conditions within 6 months after the AMI. These findings suggest that in Japan many middle-aged post-AMI patients return to work early after hospital discharge and continue to work with few disadvantages arising out of the absence from work, findings which are similar to those for other countries.[14,15]

In the brief job stress questionnaire survey conducted at 6 months after the AMI in the present study, no significant differences were found between the CR and non-CR groups in most of the subscales of job stressors, worksite supports, and level of satisfaction with work or daily life, although many subscales of psychological distress showed that the patients in the CR group felt less stressed than those in the non-CR group. It is believed that the main reason for the absence of any influence of the phase II CR on the scores of job stressors and worksite support is that the CR program provided did not include active intervention in the patients' work environment. The European Commission, Directorate-General for Employment and Social Affairs, recommended redesigning

of the job surroundings, ie, avoiding overload, improving worksite support, and adjusting occupational settings to suit a worker's abilities, in order to prevent recurrence of health hazards such as depression, psychosomatic disorders, and CAD.[16] It thus appears important for healthcare managers to collaborate with industrial specialists to improve the working conditions to accommodate the changes in the patients' cardiac and physical functions.

In regard to job stress, it has been reported that higher job demand, lower job control or lower worksite support represent greater risk in terms of psychological distress and cardiovascular disease.[17] However, the present study revealed scores of above 3 for many subscales of job stressors and worksite support in both the CR and non-CR groups, suggesting that middle-aged post-AMI patients had less job stress than expected after return to work. Such patients appear to be able to build up close personal relationships in their social lives soon after hospital discharge or return to work, with sufficient support from the supervisors, coworkers, and family. Additional stressors such as limitation of physical activity or social isolation should also be considered in the assessment of the psychological distress in AMI patients.

It was reported that workers who exercised regularly during the previous 6 months showed greater job satisfaction than those who did not.[18] The phase II CR program provides an opportunity for patients to engage in exercise and to consult with healthcare managers about their fears and problems related to physical activities or daily living. We speculated that such a supportive environment would enhance exercise capacity and physical activity levels in patients after return to work, to produce high motivation and job satisfaction levels at work. Furthermore, it has been reported that workers who felt that their job was rewarding, even if the job was excessively demanding, showed lower psychological distress than those who did not feel that way.[19] The present study results also suggested that a low score for 'rewarding job', observed in the non-CR group, resulted in high psychological distress or decreased HRQOL.

The present study showed no significant changes in the subscales of SF-36 in the non-CR group, and in particular, the BP score decreased significantly during the study period. It has been reported that the BP score in patients who feel fatigue is lower than that in healthy persons.[20] The decreased BP score in the non-CR group suggested that the patients continued to work while experiencing fatigue and somatic symptoms for 6 months after AMI, because they showed no improvement in their physical functions. Furthermore, the anxiety and depression manifested by patients with AMI have been reported to be strong indicators of poor HRQOL on long-term follow-up after hospital discharge.[21] Anxieties and depressive mood may be induced by the prospect of the disadvantages in life, health, social roles, and employment in patients with AMI, because of the

sudden and unexpected turn of events.[22] As the patients in the non-CR group had fewer opportunities to receive advice from healthcare managers after return to work, it was considered that chronic anxieties derived from working or daily life induced higher psychological distress and lower HRQOL in middle-aged post-AMI patients after return to work.

We recommend that middle-aged post-AMI patients undergo frequent evaluation of their physical and psychosocial conditions by experienced healthcare managers, not only during the period of hospitalization, but also after discharge, and that when possible, they should participate in a phase II CR program to maintain a better physical and psychological status after returning to work.

Study limitations: It was ethically unacceptable to randomize the patients in the present study, because it is well known that a comprehensive CR program reduces mortality and prevents recurrence of AMI.[23-25] Although the patients decided of their own will whether or not they would participate in a phase II CR, there were no significant differences in the clinical and occupational characteristics of the patients, subscale scores of SF-36, or anxiety and depression scores of HADS at hospital discharge between the CR and non-CR groups. In addition, it was reported that the psychological problems including depression or anxiety disorder observed during hospitalization did not prevent cardiac patients from participating in a phase II CR program.[26] Therefore, we believe that the psychological problems and HRQOL could be compared between the CR and non-CR groups in spite of the nonrandomized design of the study.

REFERENCES

1. Brown N, Melville M, Gray D, *et al*. Quality of life four years after acute myocardial infarction: short form 36 scores compared with normal population. Heart 1999; 81: 352-8.
2. Spertus JA, Salisbury AC, Jones PG, Conaway DG, Thompson RC. Predictors of quality-of-life benefit after percutaneous coronary intervention. Circulation 2004; 110: 3789-94.
3. Simpson E, Pilote L. Quality of life after acute myocardial infarction: a systematic review. Can J Cardiol 2003; 19: 507-11. (Review)
4. Special considerations. In: Williams MA, ed. *Guidelines for cardiac rehabilitation and secondary prevention programs*. 4th ed. Champaign, IL: Human Kinetics, 2003: 135-75.
5. Smith GR Jr, O'Rourke DF. Return to work after a first myocardial infarction. A test of multiple hypotheses. JAMA 1988; 259: 1673-7.
6. Tofler GH, Stone PH, Maclure M, *et al*. Analysis of possible triggers of acute myocardial infarction (the MILIS study). Am J Cardiol 1990; 66: 22-7.
7. Oldridge N, Guyatt G, Jones N, *et al*. Effects on quality of life with comprehensive rehabilitation after acute myocardial infarction. Am J Cardiol 1991; 67: 1084-9.
8. Frasure-Smith N, Prince R. The ischemic heart disease life stress monitoring program: impact on mortality. Psychosom Med 1985; 47: 431-45.
9. Engblom E, Korpilahti K, Hämäläinen H, Rönnemaa T, Puukka P: Quality of life and return to work 5 years after coronary artery bypass surgery. Long-term results of cardiac rehabilitation. J Cardiopulm Rehabil 1997; 17: 29-36.
10. Maeda S. Type A behavior pattern as a risk factor for coronary heart disease. Nippon Rinsho 1994; 52: