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ORIGINAL ARTICLE
Cardiac Rehabilitation

Efficacy of Out-Patient Cardiac Rehabilitation in Low Prognostic Risk Patients After Acute Myocardial Infarction in Primary Intervention Era

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Background: The efficacy of out-patient cardiac rehabilitation (OPCR) in patients with a low prognostic risk after acute myocardial infarction (AMI) is unclear in the recent primary intervention era.

Methods and Results: A total of 637 AMI patients who participated in in-hospital cardiac rehabilitation were divided into 2 groups; low prognostic risk group (n=219; age <65 years, successful reperfusion, Killip class I, peak serum creatine kinase <6,000 U/L, and left ventricular ejection fraction ≥40%) and non-low prognostic risk group (n=418). The prevalence of coronary risk factors (CRF) was compared between the 2 groups. Then, in the low-risk group, the efficacy of OPCR was compared between active OPCR participants (n=52; ≥20 sessions/3 months) and non-active participants (n=60; <6 sessions/3 months). Compared with the non-low prognostic risk group, the low prognostic risk group had a significantly higher prevalence of current smokers (72% vs. 49%, P<0.05) and patients with multiple CRF (3 or more; 49% vs. 39%, P<0.05). Among the low- risk group, active OPCR participants showed a significantly greater improvement in exercise capacity (peak $\dot{V}O_2$, P<0.05) and maintained a better CRF profile (total cholesterol, triglyceride and blood pressure, all P<0.05) than inactive participants at 3 months.

Conclusions: Low prognostic risk AMI patients have a higher prevalence of multiple CRF than non-low risk patients. Even in this low risk group, active participation in OPCR is associated with improved exercise capacity and better CRF profile. (*Circ J* 2011; **75:** 315–321)

Key Words: Acute myocardial infarction; Cardiac rehabilitation; Coronary risk factors; Exercise capacity; Low prognostic risk

Cardiac rehabilitation (CR) is a comprehensive intervention including medically supervised exercise training, risk factor control, patient education, and psychosocial counseling. CR has been reported to be effective in improving numerous intermediate endpoints, including exertional ischemic symptoms, overall feelings of wellness, exercise tolerance, and coronary risk factors (CRF) in patients with coronary artery disease (CAD).[1–6] In addition, recent meta-analyses of randomized studies on the effects of exercise-based CR in patients with CAD have demonstrated a statistically significant reduction in total and cardiac mortality ranging from 20% to 32%[7–9] in patients undergoing CR compared with those receiving standard medical care. The guidelines from the American College of Cardiology/American Heart Association and Japanese Circulation Society recommend the use of CR after acute myocardial infarction (AMI) as Class I.[10–14]

Recently, the widespread use of primary percutaneous coronary interventions (PCI) has enabled early ambulation of patients with AMI by reducing acute phase complications, resulting in minimal physical deconditioning. As a result, many AMI patients leave a hospital early without participating in a recovery phase (phase II) out-patient CR (OPCR) program.[15] However, the necessity and efficacy of OPCR remain unclear in AMI patients who are anticipated to be at low risk in terms of long-term prognosis (ie, non-elderly, successful reperfusion, absence of heart failure, and preserved left ventricular (LV) systolic function).

Accordingly, the purpose of the present study was to clarify the prevalence of CRF and to determine the efficacy of a 3-month OPCR program in such presumably low prognostic risk patients after AMI.

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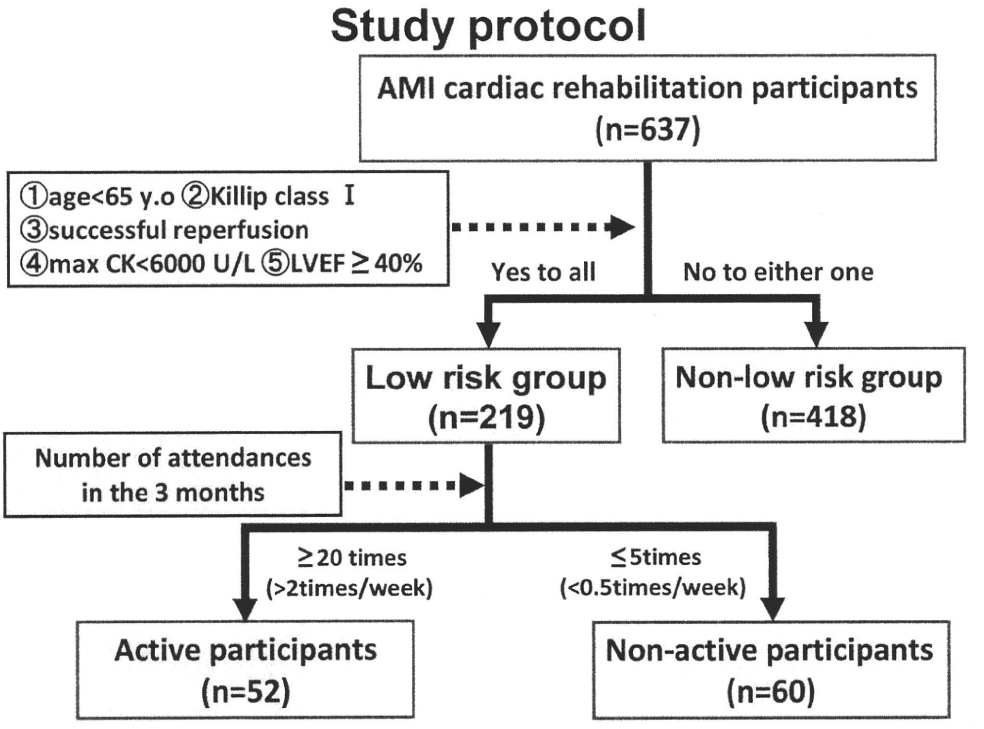

Figure 1. Schematic of study protocol. AMI, acute myocardial infarction; CK, serum concentration of creatine kinase; LVEF, left ventricular ejection fraction.

Methods

Patients

We studied a total of 637 consecutive patients with AMI who participated in a recovery phase CR program and underwent cardiopulmonary exercise testing (CPX) at the beginning and end of a 3-month program in our hospital. The patients were divided into 2 groups: a low prognostic risk group and a non-low prognostic risk group. The low prognostic risk group comprised of 219 patients who fulfilled all of the following criteria indicative of favorable prognosis; age under 65 years, successful reperfusion, Killip class I (an indicator of absence of acute phase heart failure), peak serum creatine kinase (CK) <6,000 U/L, LV ejection fraction (LVEF) ≥40%. The remaining 417 patients who did not fulfill 1 or more of the above 5 criteria were referred to as the non-low prognostic risk group.

As the first step of data analysis, the prevalence each of the CRF (hypertension, hyperlipidemia, diabetes mellitus, obesity and smoking habit) was compared between the low prognostic group and the non-low prognostic group.

As the second step, the efficacy of OPCR in AMI patients at low prognostic risk was examined by comparing the data for exercise capacity and CRF between active participants and non-active participants in the low prognostic risk group. Active participants were defined as patients who attended the OPCR sessions at least 20 times in 3 months (ie, approximately >2times/week), and non-active participants were those who attended OPCR less than 6 times in 3 months (ie, approximately <0.5times/week). There were 52 active participants and 60 non-active participants in the low prognostic group. We did not include the remaining 107 patients with intermediate attendance (patients with 6–19 attendances in 3 months) in the analysis, because the effect of OPCR in this patient group was considered to be modest, if any, and inclusion of this group in the analysis would dilute the measurable efficacy of OPCR. A schematic of the study protocol is provided in Figure 1.

CR Program

The CR program began approximately 1 week after AMI and continued after hospital discharge for 3 months. Patients who had angina or evidence of ischemic changes in their electrocardiogram (ECG) at a low level of exercise (walking test), uncontrolled heart failure, and serious arrhythmia were excluded. Program components included supervised exercise sessions (walking, bicycle ergometer and calisthenics) and education, as previously described.[16,17] The exercise intensity was determined individually at 50–60% of heart rate reserve (Karvonen's equation, k=0.5–0.6)[18,19] or a heart rate of anaerobic threshold (AT) level obtained in a maximal symptom-limited CPX testing or at level 12–13 ('a little hard') of the 6–20 scale perceived rating of exercise (original Borg's scale).[20] The exercise program was started with supervised sessions for 2 weeks, followed by home exercise combined with once or twice-a-week supervised sessions for the remaining 10 weeks. Home exercise consisted mainly of brisk walking at a prescribed heart rate for 30 to 60 min, 3–5 times a week.

Patients were encouraged to attend the education classes that were held 4 times a week with lectures on CAD, secondary prevention, diet, smoking cessation, medication, and

Table 1. Comparisons of Clinical Characteristics in the Low and Non-Low Prognostic Risk Groups

	Low-risk group (n=219)	Non-low-risk group (n=418)	P value
Age (years)	55±7	65±9	<0.01
Male (%)	88	83	NS
Killip class ≥II (%)	0	13	<0.01
Peak CK (U/L)	2,458±1,444	3,339±2,639	<0.01
CK ≥6,000 U/L (%)	0	17	<0.001
Unsuccessful reperfusion (%)	0	24	<0.001
LVEF (%)	49.1±6.8	44.4±10.4	<0.01
LVEF <40% (%)	0	34	<0.001
BNP (pg/ml)	75.7±70.9	209.8±202.0	<0.001
HT (%)	57	56	NS
DM/IGT (%)	47	42	NS
HLP (%)	59	49	<0.05
Obesity (%)	28	27	NS
Smoking habit (%)	72	49	<0.001
Coronary risk factors ≥3 (%)	49	39	<0.05

CK, serum concentration of creatine kinase; LVEF, left ventricular ejection fraction; BNP, brain natriuretic peptide; HT, hypertention; DM, diabetes mellitus; IGT, impaired glucose tolerance; HLP, hyperlipidemia.
Values are mean±SD.

Table 2. Baseline Characteristics of Active Participants and Non-Active Participants in the Low-Risk Group

	Active participants (n=52)	Non-active participants (n=60)	P value
Age (years)	57.0±7.3	52.8±7.0	<0.01
Male (%)	83	95	<0.001
Peak CK (U/L)	2,361.1±1,264.2	2,419.5±1,357.1	NS
LVEF (%)	51.4±7.5	47.4±5.7	<0.01
BNP (pg/ml)	83.7±106.0	82.8±74.8	NS
OPCR attendance (times/3 months)	25.5±5.1	1.3±1.7	<0.001
HT (%)	58	52	NS
DM/IGT (%)	44	52	NS
HLP (%)	58	58	NS
Obesity (%)	29	30	NS
Smoking habit (%)	56	75	<0.05
ACE-I/ARB (%)	42	52	NS
β-blocker (%)	19	43	<0.01
Ca channel blocker (%)	40	40	NS
DM medications (%)	8	15	NS
Statin (%)	44	43	NS
Rest HR (/min)	72.6±10.8	71.5±14.9	NS
Rest sBP (mmHg)	123.1±20.2	119.8±21.0	NS
Rest dBP (mmHg)	77.7±11.0	74.7±12.0	NS
Peak WR (W)	132.3±25.2	136.0±31.3	NS
AT ($ml \cdot min^{-1} \cdot kg^{-1}$)	11.1±2.5	11.6±2.6	NS
Peak $\dot{V}O_2$ ($ml \cdot min^{-1} \cdot kg^{-1}$)	23.4±4.2	23.6±5.0	NS
Peak $\dot{V}O_2$ (%predict)	78.5±14.5	73.7±14.3	NS

Values are mean±SD.
OPCR, outpatient cardiac rehabilitation; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HR, heart rate; sBP, systolic blood pressure; dBP, diastolic blood pressure; WR, work rate; AT, anaerobic threshold; Peak $\dot{V}O_2$, peak oxygen uptake. Other abbreviations see in Table 1.

physical activities 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 nurse at the time of hospital discharge and the end of the 3-month CR program. Patients were scheduled to undergo blood tests at the beginning and the end of the 3-month CR program.

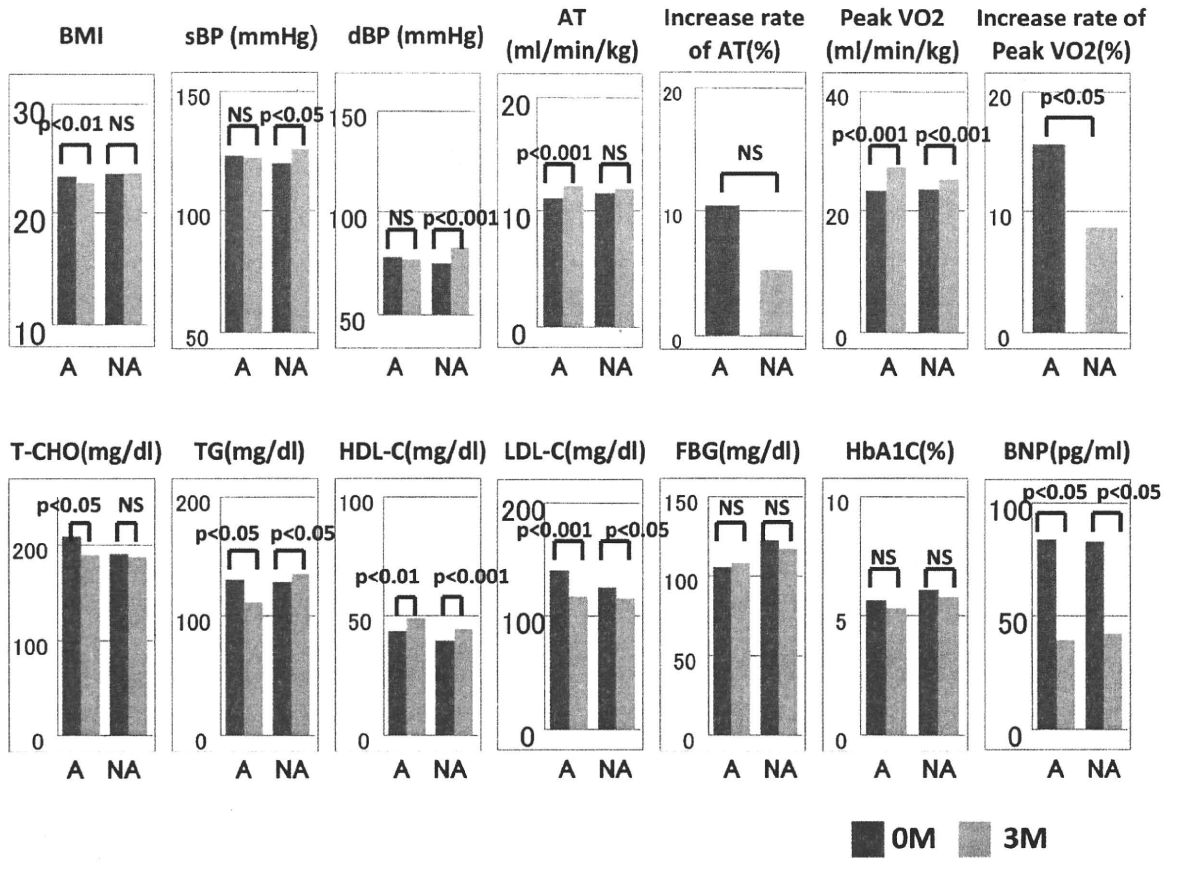

Figure 2. Comparison of the active participants and non-active participants before and after 3 months of outpatient cardiac rehabilitation program. A, active participants; NA, non-active participants; BMI, body mass index; sBP, systolic blood pressure; dBP, diastolic blood pressure; AT, anaerobic threshold; Peak $\dot{V}O_2$, peak oxygen uptake; T-CHO, serum concentration of total cholesterol; TG, serum concentration of triglyceride; HDL-C, serum concentration of high density lipoprotein cholesterol; LDL-C, serum concentration of low density lipoprotein cholesterol; FBG, fasting blood glucose; HbA_{1c}, hemoglobin A_{1c}; BNP, brain natriuretic peptide.

CPX

Patients were scheduled to undergo a symptom-limited CPX at the beginning and the end of the 3-month CR program.[21] After a 2-min rest on the bicycle ergometer in the upright position, the patients started pedaling at an intensity of 0 W for 1 min (warm-up), and then performed an incremental exercise test with a ramp protocol (10 or 15 W/min) until exhaustion. Twelve-lead ECG was continuously monitored and blood pressure (BP) was measured once-a-min with a sphygmomanometer. Expired gas was collected and analyzed continuously with an AE-300S gas analyzer (Minato Co, Osaka, Japan). Peak oxygen uptake (peak $\dot{V}O_2$) was defined as the highest $\dot{V}O_2$ value achieved at peak exercise. Ventilation ($\dot{V}E$) and carbon dioxide output ($\dot{V}CO_2$) were measured and the $\dot{V}O_2$ value at AT or ventilatory threshold was determined as the point at which $\dot{V}CO_2$ increased in a non-linear fashion relative to the rate of $\dot{V}O_2$ (according to the $\dot{V}E/\dot{V}O_2$ time trend, the respiratory exchange ratio flection point, or the V-slope method).[19,22]

Statistical Analysis

Baseline characteristics between the 2 groups were compared using unpaired t-test and chi-square test. Data at baseline and after the 3-month OPCR were compared by paired t-test. A P-value less than 0.05 was considered statistically significant. Data are presented as the mean±standard deviation.

Results

Prevalences of CRF in Low Prognostic Risk Group vs. Non-Low Prognostic Risk Group

Clinical characteristics in the low prognostic risk group and the non-low prognostic risk group are summarized in Table 1. Compared with the non-low prognostic risk group, the low prognostic risk group was on average significantly younger, and did not have heart failure on admission or unsuccessful reperfusion, but had lower peak CK and B-type natriuretic peptide (BNP) concentrations and preserved LVEF. Although these findings were anticipated by the definition of the group, they reconfirm that the patients in the low prognostic group were undoubtedly at low prognostic risk. However, when the prevalence of CRF was compared between the 2 groups, the percentage of patients with dyslipidemia, smoking habit and multiple CRF (equal to or more

than 3) was significantly higher in the low prognostic risk group than in the non-low prognostic risk group.

Efficacy of OPCR in Low Prognostic Risk Group: Comparison Between Active and Non-Active Participants

Baseline characteristics in active participants and non-active participants in the low prognostic risk group are summarized in Table 2. Although active participants were significantly older than the non-active participants, they were both non-elderly (less than 65 years old). Peak CK was low and LVEF was relatively preserved in both groups. These findings reconfirm that both active and non-active participants are apparently at low prognostic risk. Although there were minor differences in the prevalence of male patients, smokers and β-blocker use, there were no significant differences in exercise capacities at baseline between the 2 groups.

During the 3-month OPCR period, only a few patients experienced changes in medication; statins were introduced in 3 patients (5.8%) in the active participants and 2 patients (3.3%) in the non-active participants, and diabetic medications were started in 2 patients (3.3%) in the non-active participants. Thus, the baseline clinical characteristics of active and non-active participants were almost equivalent, except for the frequency of OPCR attendance.

Figure 2 depicts comparisons of parameters before and after the 3-month OPCR between active and non-active participants in the low prognostic risk group. After the 3-month OPCR, only active participants, and not the non-active participants, showed significant improvements in body mass index (BMI; 23.3±2.5 to 22.9±2.5, P<0.01), AT (11.1±2.5 to 12.7±2.5 $ml \cdot min^{-1} \cdot kg^{-1}$, P<0.001), total cholesterol (208.4±33.7 to 188.8±26.4 mg/dl, P<0.05), and triglyceride (130.0±77.4 to 111.0±63.7 mg/dl, P<0.05). In addition, while peak $\dot{V}O_2$ increased in both groups (active participants 23.4±4.2 to 27.3±5.0 $ml \cdot min^{-1} \cdot kg^{-1}$, P<0.001; non-active participants 23.7±5.0 to 25.3±5.3 $ml \cdot min^{-1} \cdot kg^{-1}$, P<0.001), the magnitude of the increase was significantly greater in the active participants (15.6% vs. 8.6%, P<0.05). In contrast, only non-active participants showed significant worsening in systolic and diastolic BP (systolic BP: from 119.8±21.0 to 126.1±20.4 mmHg, P<0.05, diastolic BP: from 74.7±12.0 to 82.4±11.8 mmHg, P<0.001) and triglyceride (128.0±57.1 to 135.3±63.9 mg/dl, P<0.05). The following parameters showed significant improvements both in the active and non-active participants; high density lipoprotein cholesterol (HDL-C: 43.6±14.1 to 49.0±12.2 mg/dl, P<0.01; 39.7±11.0 to 44.8±11.6 mg/dl, P<0.001), low density lipoprotein cholesterol (LDL-C: 140.1±31.9 to 117.6±25.9 mg/dl, P<0.001; 124.8±31.2 to 115.3±19.7 mg/dl, P<0.01), and BNP (83.7±106.0 to 39.7±44.8 pg/ml, P<0.05; 82.9±74.8 to 42.4±51.7 pg/ml, P<0.05).

Discussion

The major findings of the present study are that the low prognostic risk AMI patients had a higher prevalence of smoking habit, dyslipidemia and multiple CRF than the non-low prognostic risk patients, and that in the low prognostic risk group, active participation in OPCR was associated with better CRF profile (ie, BP, dyslipidemia, and obesity) and exercise capacity. These findings suggest that, by actively participating in OPCR after AMI, even the low prognostic risk patients might gain clinical benefits such as better CRF modification and physical functioning.

Previous Studies

Various guidelines for management of post-AMI (or established CAD) patients recommend aggressive modifications of CRF for secondary prevention,[10,12,13] and adherence to these recommendations and/or reduction of CRF have been shown to improve long-term prognosis.[23–26] In contrast, Thrombolysis In Myocardial Infarction (TIMI) risk score[27] and Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) risk score[28] have demonstrated that 1-year mortality is very low in AMI patients with age <65 years, successful reperfusion, absence of acute phase heart failure, and preserved LV function, which are compatible with the patient characteristics of the low prognostic risk group in the present study. However, little is known about the prevalence of CRF or clinical significance of accumulation of multiple CRF in such low prognostic risk patients. In relation to this, it is of note that, Lloyd-Jones and colleagues demonstrated that young subjects with accumulated CRF, despite low short-term risk, have a higher 'lifetime risks for CAD' and greater progression of subclinical coronary atherosclerosis compared with those at low lifetime risk.[29,30] These data suggest that apparently low prognostic risk patients stratified by TIMI or CADILLAC risk score are likely to have superb short-term (1 year) prognosis, but not necessarily favorable long-term or lifetime prognosis.

Present Study

The present study has explicitly demonstrated that the low prognostic risk patients actually have higher prevalence of multiple CRF than the non-low prognostic risk patients. Although the finding that younger AMI patients have higher prevalences of smoking and hyperlipidemia than elderly patients is in accordance with previous studies,[31] there has been no report demonstrating higher prevalence of multiple CRF in low prognostic risk AMI patients with successful reperfusion and preserved LVEF. According to TIMI risk score[27] or CADILLAC risk score,[28] this finding might appear confusing or counterintuitive. However, from the viewpoint of lifetime CAD risk,[29,30] this finding might have a significant impact on the long-term prognosis of apparently low prognostic risk AMI patients.

The second major finding in the current study is that active participation in OPCR improved CRF (BP, dyslipidemia, and obesity) and exercise capacity even in the low prognostic risk group. There have been no studies that reported the effect of OPCR in the low prognostic risk AMI patients. Taylor et al[9] reported in a meta-analysis of randomized controlled trials that the effect of OPCR on total mortality did not differ between studies before and after year 1995 (odds ratio 0.84 before 1995 vs. 0.62 after 1995, NS), but they did not assess the effect of OPCR on the low prognostic risk patients after successful reperfusion. Witt et al recently reported that participation in OPCR after AMI was associated with improved survival and reduced recurrent myocardial infarction (MI) at 3 years, but the rate of reperfusion was only 33% in their patients.[32] Squires et al reported that a 3-year coronary disease management program in OPCR for CAD patients was effective in achieving the secondary prevention goals, but their assessment did not target the low prognostic risk patients.[33] Thus, the present study has demonstrated for the first time the favorable effects of OPCR on CRF and exercise capacity in the low prognostic AMI patients.

Clinical Implications

It remains unknown whether the improvements in CRF profiles and exercise capacity achieved by active participation in OPCR can lead to an improved long term prognosis in the low prognostic risk AMI patients. However, Tani et al reported that successful life style modification with exercise, body weight reduction and smoking cessation for 6 months was associated with coronary plaque volume regression in low prognostic risk CAD patients.[34] Belardinelli et al reported in the ETICA (Exercise Training Intervention after Coronary Angioplasty) trial that a 6-month OPCR for the relatively low risk CAD patients after successful PCI (49% having AMI) reduced cardiac events and hospital re-admission during the follow-up period (33±7 months).[45] In addition, because the magnitude of the improvement in endothelial function afforded by OPCR does not correlate with the improvements in CRF,[30] the general consensus at present is that the favorable effect of OPCR on the long-term prognosis is mediated by a direct anti-atherosclerosis effect of exercise training rather than by improvements in CRF.[4] Therefore, further study is necessary to determine the long term effect of OPCR in AMI patients with low prognostic risk.

In the present study, significant differences were found between active and inactive OPCR participants in BMI, total cholesterol, triglyceride and BP, but not in LDL-C or glucose tolerance. One might argue that the prognostic impacts of BMI, total cholesterol, triglyceride and BP might be less powerful compared with those of LDL-C and diabetes. However, Nakatani et al reported that the metabolic syndrome, diagnosed from the combination of BMI, HDL-C, triglyceride, BP, and fasting blood glucose, was an independent predictor of subsequent combined cardiac events of cardiac death and non-fatal MI in Japanese patients after AMI.[37] Therefore, it is plausible that the improvements in BMI, triglyceride and BP observed in the present study might contribute to the improvement in the long-term prognosis in Japanese AMI patients.

Future Direction

In the present study, the rate of active OPCR participation was only 24% (52/219 patients) in the low prognostic risk group. To reduce lifetime CAD risk in these low prognostic risk AMI patients, a substantial increase in participation rate in OPCR is necessary. However, according to a recent nation-wide survey in 526 Japanese Circulation Society authorized cardiology training hospitals,[15] the implementation rate was 92% for emergency PCI, but only 9% for OPCR. In addition, Ades et al reported that, by multivariate analysis, the strength of the physician's recommendation for participation was the most powerful predictor of OPCR participation.[38] Thus, to increase the participation rate in OPCR, it is critically important to greatly increase the number of CR facilities and to enhance physicians' understanding of the benefits of OPCR after AMI.

Study Limitations

First, this study was a retrospective analysis and the number of patients was relatively small. The more active patients would be expected to participate in OPCR and this might have introduced a selection bias.

Second, the low prognostic risk group is anticipated to be at low risk in terms of short-term prognosis[27,28] and hence, whether improvements in CRF profile in such low prognostic risk patients are associated with actual improvements in outcome is uncertain. A longer follow-up in a larger number of patients is necessary to increase the statistical power to demonstrate the beneficial effect of OPCR on the long-term prognosis.

Conclusions

The low prognostic risk AMI patients have a higher prevalence of multiple CRF than the non-low risk patients. Active participation in OPCR program is associated with improved exercise capacity and CRF profile in such low prognostic risk patients. OPCR program can be effective in achieving secondary prevention goals even in the low prognostic risk AMI patients.

Disclosure

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CASE REPORT

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Coronary vasospasm secondary to allergic reaction following food ingestion: a case of type I variant Kounis syndrome

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Abstract Coronary vasospasm can be induced by allergic reactions with some chemical mediators, and the angina and myocardial infarction secondary to allergy-induced coronary vasospasm are referred to as "Kounis syndrome." Only two cases of Kounis syndrome following food ingestion have been reported. However, they had pre-existing atheromatous coronary artery disease, and no provocation test to induce coronary vasospasm was done. We describe here another probable case of allergic vasospasm after food intake. To the best of our knowledge, this is the first documented report of a patient with food-induced allergic vasospasm subsequent to the provocation test with ergometrine maleate.

Key words Allergic vasospasm · Kounis syndrome · Ergometrine maleate · Histamine

Introduction

Coronary vasospasm is defined as abnormal contraction of an epicardial coronary artery resulting in myocardial ischemia, and is more common in Japanese patients with coronary disease than their Caucasian counterparts.[1] Coronary vasospasm is mainly induced by environmental stimuli (such as temperature), emotional stress, or physical exertion, but some cases with coronary vasospasm following acute allergic reaction have been reported.[2] In allergic episodes, chemical mediators such as histamine, leukotrienes, and neutral proteases are increased in the peripheral circulation, and the increase of such mediators could induce coronary artery spasm and atheromatous plaque rupture.[3,4] Allergic angina and allergic myocardial infarction caused by chemical mediators released through mast cell activation were recently described as "Kounis syndrome."[3,5]

In this report, we describe a probable case of coronary vasospasm secondary to allergic reaction following food ingestion. Although coronary angiogram revealed no severe stenosis in the present case, the provocation test with ergometrine maleate induced coronary vasospasm in the right coronary artery. To the best of our knowledge, this is the first documented report of a case of food-induced allergic vasospasm subsequent to the provocation test with ergometrine maleate.

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Case report

A 65-year-old woman, who had previous history of anaphylactic shock after ingestion of shellfish, began to feel itching all over the body approximately 30 min after eating Chinese noodles including shellfish, and then suffered from severe discomfort. She called emergency services and thereafter developed dizziness, cold sweating, vomiting, and skin rash in the ambulance. Her systolic blood pressure dropped to 60 mmHg, suggesting she had entered a state of shock. She had no history of chest pain, smoking, and no other risk factors for coronary artery disease; however, her electrocardiogram (ECG) monitor (II lead) in the ambulance showed elevation of ST segment and gradual prolongation of atrioventricular interval (Fig. 1A). Coronary artery disease was suspected, and she was transferred to our hospital. Before arriving, her blood pressure had recovered and the ECG change had normalized promptly by receiving no other treatment for the allergic reaction besides the saline infusion.

On admission, her vital signs were stable and symptoms had disappeared except red macules persisting over the entire body. The ECG was normal without ST elevation in any leads (Fig. 1B), and transthoracic echocardiography demonstrated normal left ventricular wall motion. In blood samples, cardiac enzymes and eosinocytes were not elevated, but IgE titer was elevated (510 IU/ml; normal range

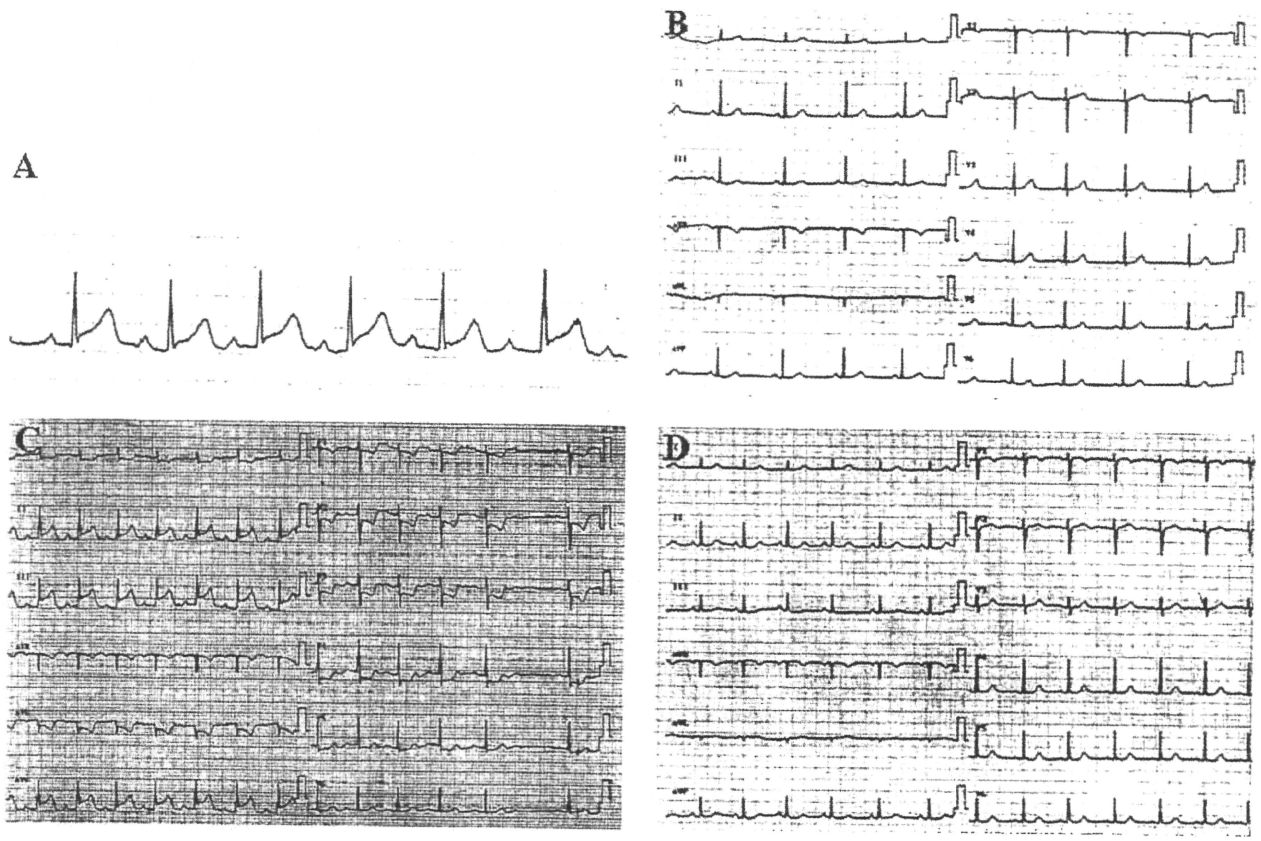

Fig. 1. A The electrocardiogram monitor (II lead) in the ambulance showed ST segment elevation and gradual prolongation of atrioventricular interval. **B–D** Serial electrocardiograms on admission without ST elevation in any leads (**B**), on the injection with ergometrine maleate into the right coronary artery showing ST segment elevation in II, III, aVF leads, and Wenckebach type second-degree atrioventricular block (**C**), and after intracoronary administration of nitroglycerin showing the disappearance of ST segment elevation and atrioventricular block (**D**)

<170 IU/ml). On the following day, coronary angiography was performed and revealed no severe stenosis in the left or right coronary artery (Fig. 2A,B). Because vasospasm in the right coronary artery was suspected, we subsequently performed a provocation test with ergometrine maleate.[6,7] After intracoronary administration of ergometrine maleate (40 μg) into the right coronary artery, she suffered from discomfort, dizziness, cold sweating, and nausea again as in the initial episode, but she had no chest pain. The ECG showed elevation of ST segments in II, III, and aVF leads, and Wenckebach type second-degree atrioventricular block (Fig. 1C), and the angiography revealed total occlusion in the middle part of the right coronary artery (Fig. 2C). Intracoronary administration of nitroglycerin (0.5 mg) resolved the obstruction immediately (Fig. 2D). Her symptoms were relieved, and the elevation of ST segments and atrioventricular block in her ECG disappeared (Fig. 1D). A probable diagnosis of coronary vasospasm was made. Because she developed coronary vasospasm only during anaphylaxis, we prescribed no medication to her. After discharge, she had no episode of coronary vasospasm.

Discussion

More than ten cases with ST segment elevation during anaphylaxis have been reported,[8] and the concept of allergic angina was first proposed by Kounis and Zavras in 1991.[3] They described that coronary vasospasm could be provoked by histamine-release during acute allergic reaction.

The acute coronary syndromes caused by mast cell activation, including allergic or anaphylactic insults, are referred to as "Kounis syndrome."[5] There are two variants of this syndrome; type I variant includes patients with normal coronary arteries and may represent a manifestation of microvascular angina or coronary vasospasm, and type II variant includes patients with culprit but quiescent preexisting atheromatous disease in whom acute allergic episode can induce plaque erosion or rupture, resulting in an acute coronary syndrome.

Allergic and anaphylactic reactions are associated with mast cell degranulation and release of chemical mediators. Mast cells are found in most parts of the body including

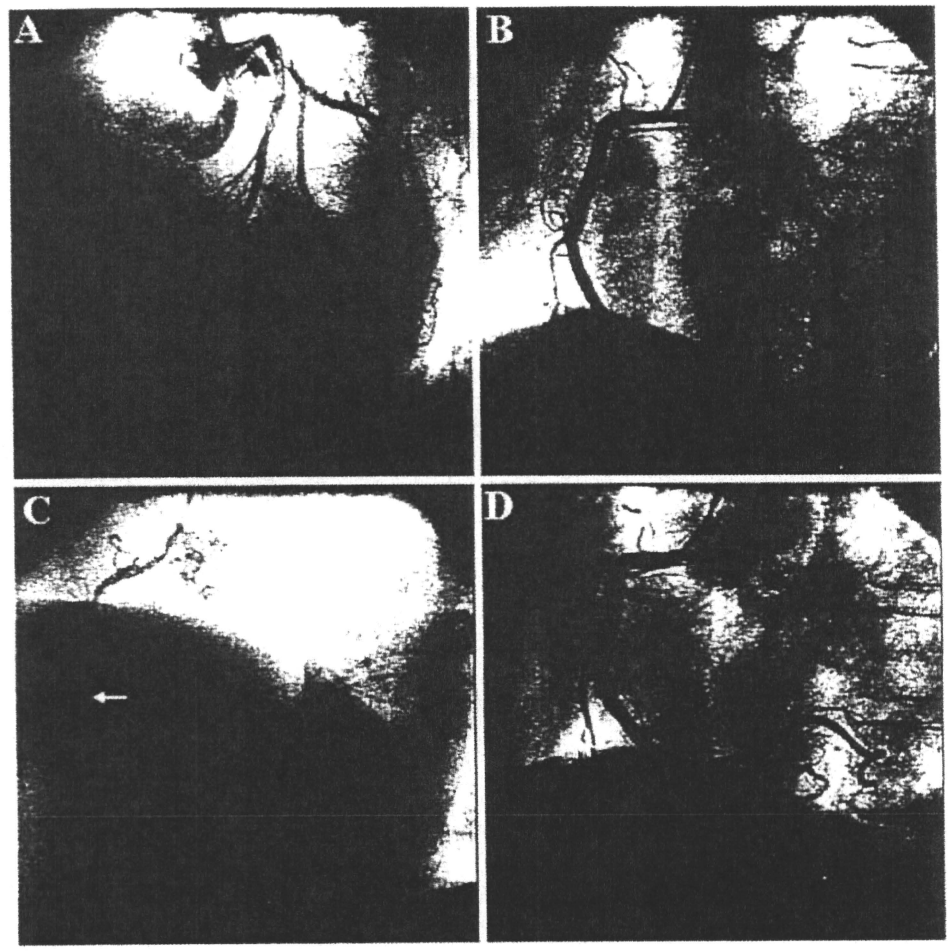

Fig. 2. Angiogram of the left coronary artery (left anterior oblique view) (**A**) and sequential angiograms of the right coronary artery (left anterior oblique view) performed before (**B**), immediately after the provocation test with ergometrine maleate (**C**), and after intracoronary administration of nitroglycerin (**D**). Angiography of **A** the left coronary artery and **B** the right coronary artery showed no stenosis. **C** Angiography showed total occlusion in the middle right coronary artery (*arrow*). **D** Angiography showed a complete resolution of the obstruction

coronary arteries,[5] and could release histamine, leukotrienes, tryptate, and chymase. Histamine and leukotrienes are powerful coronary vasoconstrictors, and tryptate and chymase are metalloproteinase activators that can trigger degradation of collagen and could induce plaque rupture.[9,10] Furthermore, conversion of angiotensin I to angiotensin II can be mediated by chymase, and this together with histamine action could aggravate the local coronary artery spasm.

Histamine is the most important chemical mediator, is widely distributed throughout the human body, and acts on many organs via its receptors.[11] During anaphylaxis, histamine bound to peripheral H1-histamine receptors can contribute to the vasodilatation and an increase in vascular permeability in the peripheral circulation.[5] On the other hand, it is known that histamine in coronary artery has a vasoconstrictive action mediated by H1-histamine receptors in smooth muscle cells.[9] Therefore, during an anaphylactic episode, histamine in the coronary artery could induce coronary vasospasm. More than ten cases of coronary vasospasm during anaphylactic reaction have been reported, and most of these were caused by drugs or hymenoptera stings.[2,12,13] Only two cases of type II variant of Kounis syndrome with pre-existing atheromatous coronary artery disease following food ingestion were reported,[11] but no provocation test was done in these two cases.

Concerning patients who had died within 2 days after the acute coronary events, infiltrates of activated mast cells at the site of coronary atheromatous erosion or rupture were found in a ratio of 200 to 1 compared with normal endothelial segments.[4] Since Kounis syndrome might play a role in a final trigger pathway implicated in cases of coronary artery spasm and plaque rupture,[5] mast cell surface membrane protection and stabilization might prove a novel way to attempt to prevent acute coronary syndrome.

On the other hand, Vivas et al. have previously reported a patient who suffered three documented episodes of angina with transient ST-segment elevation, two of which had a time-relationship to amoxycillin administration and allergic reaction, but not the third episode.[14] All the three episodes were finally related to metabolic acidosis, and other uncommon underlying mechanisms should be considered before the diagnosis of Kounis syndrome is established.

In the present case, we did not perform radioallergosorbent tests (RAST), of which the sensitivity and specificity were reported as from 60% to 95% and from 30% to 95%, respectively.[15] This case, however, met the diagnostic criteria for anaphylaxis, such as involvement of the skin-mucosal

tissue, reduced blood pressure, and persistent gastrointestinal symptoms.[16] Total IgE level was also elevated, although the diagnostic utility of this test was limited. The patient had no chest pain but had nausea, and ECG showed ST segment elevation in lead II and gradual prolongation of atrioventricular interval during anaphylaxis. On the provocation test with ergometrine maleate, nausea, coronary vasospasm in the right coronary artery, ST segment elevation in inferior leads, and Wenckebach type second-degree atrioventricular block were induced just as in the initial anaphylactic episode. It could be interpreted that coronary vasospasm was induced during anaphylaxis. In fact, it was reported that histamine and ergometrine maleate were both endothelium-dependent vasodilators by the release of nitric oxide in young healthy subjects, but caused vasoconstriction in patients with atherosclerosis.[1,7,17,18] Therefore, coronary vasospasm induced by histamine could be provoked with ergometrine maleate.

In summary, anaphylaxis by food ingestion is probably responsible for coronary vasospasm in the present case. To the best of our knowledge, this is the first report on type I variant of Kounis syndrome without pre-existing severe coronary stenosis following food ingestion.

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NOTE

Association of plasma B-type natriuretic peptide levels with obesity in a general urban Japanese population: the Suita study

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Abstract. The inverse association between plasma B-type natriuretic peptide (BNP) levels and body mass index (BMI) has been reported in Western populations. Here we analyzed the relationship between plasma BNP and obesity in a general urban Japanese population. We recruited 1,759 subjects without atrial fibrillation or history of ischemic heart disease aged 38-95 years (mean age ± standard deviation 64.5 ± 10.9 years, 56.1% women, mean BMI 22.8 ± 3.1 kg/m^2) from the participants in the Suita Study between August 2002 and December 2003. In multivariable regression analyses adjusted for age, systolic blood pressure, pulse rate, serum creatinine, left ventricular hypertrophy in ECG, the inverse relationships between BNP levels and BMI (kg/m^2) was found in both sexes (both $p<0.001$). Multivariable-adjusted mean plasma BNP levels in the group of BMI<18.5, 18.5≦BMI<22, 22≦BMI<25, and 25≦BMI were 23.4, 17.9, 14.0 and 13.0 pg/mL, respectively (trend $p<0.001$). The negative association of body fat (percentage and mass), skin fold thickness, or waist circumference with BNP levels was observed in both sexes ($p<0.01$). Among the obesity indices, body fat mass is most tightly associated with BNP. In conclusion, plasma BNP was inversely associated with obesity-related markers such as body fat mass, skinfold thickness and waist circumferences after adjusted for relevant covariates in a Japanese population.

Key words: BNP, BMI, Body fat mass, Japanese

B-TYPE natriuretic peptide (BNP) is a cardiac hormone, synthesized in, processed in and secreted from heart [1]. The secretion of BNP is stimulated in heart failure along with its severity. Plasma BNP is clinically utilized to diagnose the existence or the severity of the cardiac failure [2]. BNP levels are affected by demographic variables such as age, gender, and clinical characteristics such as hypertension [3, 4], atrial fibrillation [5], and renal function [6].

Several recent studies have suggested that obesity, as indexed elevated body mass index (BMI), also affects BNP levels, with lower circulating levels in those with higher BMI in subjects with and without heart failure [7-12]. In addition, the Dallas Heart Study revealed that BNP is closely associated with lean mass than with fat mass [8]. However, these studies were mostly conducted in Western countries, where BMI is much higher than in other parts of the world. It is not unclear whether this relationship could apply in a general Japanese population whose BMI levels are lower than in Western countries [13].

Therefore, the aim of the present study is to evaluate the association between BMI and BNP levels in a general urban Japanese population. To further elucidate the mechanisms of the relationship between obesity and BNP levels, we examine the relationship between BNP levels and various obesity related factors such as lean body mass, body fat mass, skin fold thickness, and waist circumferences.

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Methods

Study Sample

The Suita Study [14-16], an epidemiological study of cerebrovascular and cardiovascular disease, was based on a random sampling of 15,200 (30–79 years of age at enrollment) Japanese residents of Suita. They were all invited, by letter, to attend regular cycles of follow-up examination (every 2 years). Subjects were recruited into the Suita Study between August 2003 and December 2004 in this study (n=2,007). Subjects with chronic atrial fibrillation at time of referral (n=40) and history of ischemic heart disease (n= 97) were excluded. After applying this exclusion, 1,759 individuals were included in this analysis. The study design was approved by the institutional review board of the National Cardiovascular Center. Informed consent was obtained from all subjects.

Routine physical examination, 12-lead surface ECG, several blood chemical variables and plasma BNP measurements were performed. A physician or nurse interviewed each patient personal history of cardiovascular disease, including angina pectoris and/or myocardial infarction. Blood pressure was measured after at least 5 minutes of rest in a sitting position. Systolic and diastolic blood pressures (SBP and DBP) were the means of two measurements by well-trained doctors (recorded at least 1 min apart) [16]. BMI was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured in a standing position at the umbilical level by well-trained technicians [15]. Lean body mass and body fat mass were calculated by the bioelectrical impedance analyzer [17]. Brachial triceps and subscapular skin fold thickness was measured using keys calipers by trained physician epidemiologists with standard methods.

Measurement of BNP

Blood sample was collected into tubes containing EDTA. Plasma BNP was measured by validated and commercially available immunoassay kit (Shionogi, Osaka, Japan). The measurable range of the BNP assay is 4.0 to 2000 pg/mL. Average intra- and inter-assay coefficients of variation were 3.7% and 4.5%, respectively.

Statistical Analyses

Continuous data are presented as means ± standard deviations (SDs) for normally distributed variables and as medians (interquartile range) in case of skewed distribution. Categorical data are presented as numbers and percentage. Comparison of clinical characteristics between patients each BMI category were performed using Kruskal-Wallis test for continuous data and χ^2 test for categorical data. Variables with skewed distributions underwent logarithmic transformation to create normal distributions. The value less than the lower detection limit of the BNP assay (BNP < 4.0 pg/mL) were found 9.0% of all subjects. For analyses examining continuous BNP levels, we treated lower detection limit of the BNP assay for 4.0 pg/mL and performed multivariable linear regression with log-transformed BNP as the dependent variables. Covariates examined for inclusion in the multivariable models were age, sex, systolic blood pressure, pulse rate, serum creatinine, and left ventricular hypertrophy (LVH) in ECG. Sex-specific regression analyses were also performed. In additional models, we replaced the continuous BMI variable with BMI categories (BMI<18.5, 18.5 ≦ BMI< 22, 22 ≦ BMI < 25, and 25 kg/m^2 ≦ BMI). The results of the multivariable analyses were also used to examine the relations of BMI category to adjusted plasma BNP levels. Since models used log-transformed dependent variables, we exponentiated the β coefficient for BMI to characterize its multiplicative effect on absolute plasma BNP levels. Because of the skewed nature of the BNP distributions and potential violations of assumptions inherent in the least-squares model, we used multivariable logistic regression analyses to analyze correlations of normal plasma BNP levels (BNP<18.4 pg/mL). We estimated odds ratios for having normal BNP levels according to BMI category, with lowest BMI individuals as the referent group. Odds ratios were adjusted for the same covariates used in the linear models.

All data were analyzed with the JMP version 6.0 (SAS Corporation, Cary, NC, USA) statistical software package.

Results

Baseline Characteristics

The clinical characteristics of study population (mean ± SDs age 64.5 ± 10.9 years, mean BMI 22.8 ± 3.1 kg/m^2, 56.1% women) stratified by BMI category are listed in Table 1. Increasing BMI was associated with an increased likelihood of being men; higher systolic blood pressure, and lower BNP levels.

Table 1 Baseline characteristics stratified by BMI: the Suita Study.

	BMI<18.5 (n=139)	18.5 ≦ BMI<22 (n=590)	22 ≦ BMI<25 (n=642)	25 ≦ BMI (n=388)	*p* value
Age, y	65.6 ± 11.5	64.2 ± 11.5	64.7 ± 10.6	64.0 ± 10.3	0.471
Men, %	28.1	35.3	50.5	51.8	<0.001
Smoking (ever), %	88.5	82.5	72.0	74.7	<0.001
Alcohol (ever), %	97.1	97.5	96.3	97.2	0.658
Hypertension, %	23.7	23.4	37.1	48.7	<0.001
Diabetes Mellitus, %	4.3	4.1	8.9	13.7	<0.001
Dyslipidemia, %	11.5	21.7	26.3	30.7	<0.001
Left ventricular hypertrophy, %	7.2	10.0	11.4	7.2	0.119
Height, cm	157.2 ± 8.0	157.3 ± 8.0	159.0 ± 9.3	158.7 ± 8.9	0.003
Weight, kg	43.2 ± 5.1	50.9 ± 5.8	59.4 ± 7.3	68.5 ± 9.4	<0.001
Skinfold thickness, mm	21.1 ± 6.8	26.5 ± 7.5	31.3 ± 8.9	37.9 ± 11.4	<0.001
Body fat mass, kg	7.9 ± 1.8	12.3 ± 2.3	16.1 ± 2.6	22.1 ± 4.5	<0.001
Lean body mass, kg	35.4 ± 4.9	38.6 ± 5.9	43.3 ± 8.0	46.4 ± 8.9	<0.001
Waist circumference, cm	71.6 ± 5.0	78.9 ± 5.3	86.5 ± 5.1	94.6 ± 6.6	<0.001
Systolic blood pressure, mmHg	117 ± 21	120 ± 18	125 ± 19	131 ± 19	<0.001
Diastolic blood pressure, mmHg	71 ± 11	74 ± 10	76 ± 10	80 ± 10	<0.001
Pulse rate, bpm	68 ± 10	67 ± 10	67 ± 9	67 ± 10	0.252
Serum creatinine, mg/dL	0.69 ± 0.21	0.68 ± 0.17	0.71 ± 0.16	0.72 ± 0.23	<0.001
Fasting plasma glucose, mg/dL	93 ± 18	94 ± 15	100 ± 21	105 ± 22	<0.001
HbA1c, %	5.4 ± 0.8	5.3 ± 0.5	5.5 ± 0.7	5.6 ± 0.8	<0.001
Triglyceride, mg/dL	80 ± 55	92 ± 55	109 ± 72	133 ± 86	0.722
Total cholesterol, mg/dL	208 ± 31	210 ± 32	211 ± 33	211 ± 32	<0.001
HDL cholesterol, mg/dL	73 ± 17	64 ± 15	59 ± 14	54 ± 13	<0.001
BNP, pg/mL	23.2 (14.7, 41.8)	18.6 (9.0, 32.6)	14.5 (7.5, 26.0)	13.2 (6.4, 24.2)	<0.001

Results presented are mean ± SD for continuous variables or percentage for categorical variables.
BNP levels are presented as median (25th, 75th percentile).
Comparison of clinical characteristics between patients each BMI category were performed using Kruskal-Wallis test for continuous data and χ^2 test for categorical data.

When BNP level was categorized by quartile (data not shown), increasing BNP levels was associated with an increased likelihood of being women and older; lower BMI, and pulse rate; an increased likelihood of having LVH; and higher systolic blood pressure.

Association between BMI and BNP Levels

Results of multivariable regression models are shown in Table 2. After adjustment for age, systolic blood pressure, pulse rate, serum creatinine, and LVH, BMI was inversely associated with plasma BNP levels, with 5% decrease associated with each 1 unit increase in BMI in both sexes (p<0.001 for both). There was also a progressive decrease in plasma BNP levels with increasing BMI category. In men, highest BMI group (BMI ≧ 25) had 29% lower plasma BNP levels compared with lowest BMI group (BMI < 18.5) (p<0.001). In women, highest BMI group (BMI ≧ 25) had 23% lower plasma BNP levels compared with lowest BMI group (BMI < 18.5) (p<0.001). Multivariable-adjusted mean levels of plasma BNP were shown in Fig. 1 for each BMI category. For both sexes, adjusted BNP levels decreased in a stepwise fashion across categories of increasing BMI (p<0.001 for trend for all comparisons).

For logistic regression analysis, the BNP levels were considered as a categorical variable, pooling the subjects into two distinct groups: <18.4 pg/mL (nor-

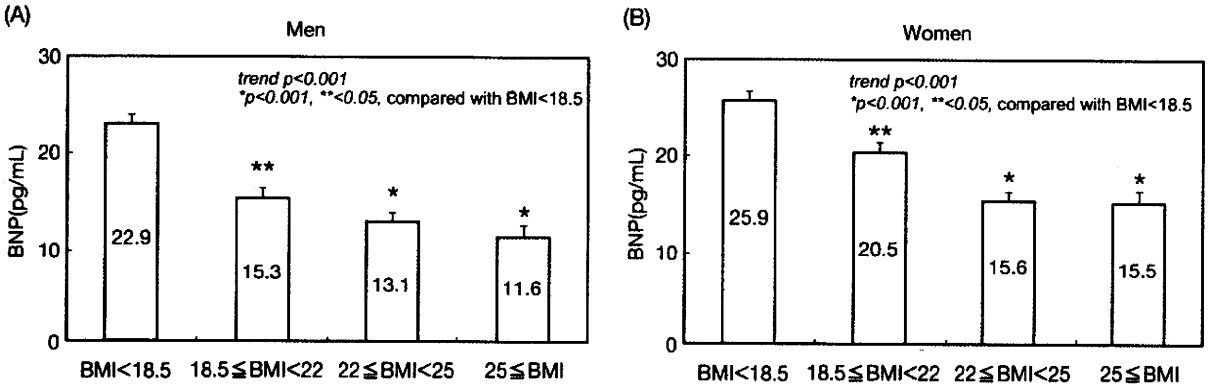

Fig. 1 Adjusted BNP levels stratified by BNP categories. Mean levels and SE of BNP for men (A) and women (B) are shown. Covariates used for adjustment are listed in Table 2.

mal) and ≧ 18.4 pg/mL (abnormal); the same covariates were evaluated in these models as in the linear regression models described above. The adjusted odds ratios of having normal BNP levels are shown in Table 3. After multivariable adjustment, highest BMI (25 kg/m^2 <BMI) was associated with having a 2.1- to 2.3-fold increase in the odds of having normal BNP levels (p<0.001). Overall, for each 1 unit increase in BMI, there was a 11% to 16% greater chance of having normal BNP (p<0.01).

Association between Body Composition and BNP Levels

Results of multivariable regression models relating plasma BNP levels with various obesity related factors are shown in Table 4. Model 1 used BMI as a measure of obesity, and model 2 replaced BMI with percent of body fat. In model 3, percent body fat was replaced by body fat mass and lean body mass. Model 4 replaced BMI with skin fold thickness, and Model 5 replaced BMI with waist circumferences. After adjustment for the same covariates as in Table 2, inverse associations were confirmed between percent of body fat, body fat mass, skin fold thickness and waist circumferences and BNP levels in both sexes (all p<0.01). However, the inverse association with lean body mass was not significant for BNP (p=0.188 in men and p=0.079 in women).

Discussion

In the present study, we showed that higher BMI was significantly associated with lower plasma BNP levels in a general Japanese population. The finding is not attributable to underlying differences in cardiovascular risk factors between obese and non-obese subjects. We also showed that the inverse association between body fat mass, skin fold thickness and waist circumferences and BNP. This is the first report that analyzes the relations between BNP levels and various obesity related factors.

Several studies, including large, population-based cohorts [7, 8], have demonstrated that BMI was inversely correlated with BNP levels in patients with heart failure [9-12]. In the Dallas Heart Study [8], they focused on the body composition instead of BMI and showed an inverse association between plasma BNP and lean mass. However, these studies were conducted mostly in Western countries, where BMI is much higher than in other parts of the world.

In this study, where the average BMI levels (around 23 kg/m^2) was much lower in comparison with the general Western population (around 28 kg/m^2) [8], the association between higher BMI and lower BNP levels was observed after multivariable adjustment. Furthermore, we divided adiposity into its fat and lean mass components and found that fat mass was responsible for the association between higher BMI and lower BNP levels.

As it was already suggested, the natriuretic peptide system and adiposity are closely linked [18, 19]. Natriuretic peptide clearance receptors (NPR-C) are abundant in adipose tissue [18], and thus, it is suggested that adipocytes participate in a removal of BNP from circulation, which leads to the lower plasma BNP levels in obese patients. Furthermore, the Framingham Heart Study [7] showed that obese in-

Table 2 Multivariable linear models of plasma log BNP.

Models	Men		Women	
	β-coefficient (SE)	*p* value	β-coefficient (SE)	*p* value
Continuous BMI, per 1kg/m^2	-0.022 (0.005)	<0.001	-0.021 (0.004)	<0.001
BMI categories				
BMI < 18.5	Referent	-	Referent	-
18.5≦BMI<22	-0.087 (0.033)	0.009	-0.050 (0.019)	0.008
22≦BMI<25	-0.122 (0.032)	<0.001	-0.109 (0.019)	<0.001
25≦BMI	-0.148 (0.034)	<0.001	-0.112 (0.021)	<0.001

The multiplicative effect on plasma BNP levels can be estimated by exponentiating the β-coefficient. For instance, highest BMI (BMI ≦ 25) is associated with a 29% reduction in BNP levels in men, because $10^{(-0.148)} = 0.71$. All models are adjusted age, systolic blood pressure, pulse rate, serum creatinine, and left ventricular hypertrophy.

Table 3 Influence of BMI on odds of having normal plasma BNP levels (< 18.4 pg/mL).

BMI categories	Men		Women	
	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
BMI < 18.5	1.00 (referent)	-	1.00 (referent)	-
18.5≦BMI<22	1.66 (1.10-2.56)	0.019	1.33 (1.03-1.74)	0.033
22≦BMI<25	2.08 (1.38-3.19)	0.001	1.99 (1.52-2.63)	<0.001
25≦BMI	2.25 (1.47-3.51)	<0.001	2.13 (1.59-2.88)	<0.001
BMI (continuous), per 1kg/m^2	1.11 (1.04-1.18)	0.001	1.16 (1.11-1.23)	<0.001

Multivariable logistic regression models for low BNP levels are adjusted for age, systolic blood pressure, pulse rate, serum creatinine, and left ventricular hypertrophy.

Table 4 Multivariable associations between obesity related factors and BNP.

Models	Men		Women	
	β-coefficient (SE)	*p* value	β-coefficient (SE)	*p* value
Model 1				
BMI	-0.002 (0.005)	<0.001	-0.021 (0.004)	<0.001
Model 2				
Percent of body fat	-0.012 (0.003)	<0.001	-0.011 (0.002)	<0.001
Model 3				
Body fat mass	-0.014 (0.003)	<0.001	-0.013 (0.003)	<0.001
Lean body mass	0.004 (0.003)	0.188	0.007 (0.004)	0.079
Model 4				
Skinfold thickness	-0.007 (0.002)	<0.001	-0.004 (0.001)	0.001
Model 5				
Waist circumference	-0.006 (0.002)	<0.001	-0.006 (0.001)	<0.001

The multiplicative effect on plasma BNP levels can be estimated by exponentiating the β-coefficient. All models are adjusted for age, systolic blood pressure, pulse rate, serum creatinine, and left ventricular hypertrophy.

dividuals had higher odds of having low plasma N-terminal proANP. In the Dallas Heart Study [8], the association between higher BMI and lower NT-proBNP was observed. Since both N-terminal proANP and N-terminal proBNP are not cleared by clearance receptors, the findings of reduced N-terminal proANP levels and N-terminal proBNP levels in obese individuals indicate the mechanism other than the adipocyte clearance of the peptides exists. Recent investigations have raised the possibility that the relation between fat and BNP is bidirectional. Adipocytes also express natriuretic peptide receptor-A (NPR-A), which mediate the biologic effects of ANP and BNP [18]. Investigators have demonstrated activation of NPR-A on adipocytes induces lipolysis [19]. Thus, low BNP levels may lead to reduced lipolysis, additionally perpetuating the obese state.

Several limitations of our study deserve comment. First, since our study was cross-sectional study, we cannot demonstrate the cause-effect relation between low plasma BNP and obesity related factors. Second, plasma BNP levels are under the calculable levels of the assay detection limits in 9.0% of all subjects. Misclassification of BNP levels above and below the detection limit would be expected to cause a conservative bias. To overcome the potential bias, we also used logistic regression analyses to account for the left censoring of the BNP distribution. Finally, we cannot exclude the possibility that obese individuals might have had better cardiac function. However, since many previous studies suggest that obesity has been consistently associated with left ventricular hypertrophy [20, 21], dilatation [22] and the increase in the risk of overt heart failure [23], the possibility is highly unlikely.

In conclusion, higher BMI was associated with lower BNP levels in a general Japanese population, even after adjusted for relevant factors. Body fat mass was responsible for this relationship. Further studies will be needed to explore the underlying mechanism.

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ORIGINAL ARTICLE

The combined impact of blood pressure category and glucose abnormality on the incidence of cardiovascular diseases in a Japanese urban cohort: the Suita Study

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Few prospective studies have examined the combined impact of blood pressure (BP) categories and glucose abnormalities on the incidence of cardiovascular disease (CVD) in the general Asian population. This study aimed to examine the effect of the combined risks of these factors on the incidence of CVD in a general Japanese population. We studied 5321 Japanese individuals (aged 30–79 years), without CVD at baseline, who received follow-up for an average of 11.7 years. Serum fasting glucose categories were defined according to the 2003 American Diabetes Association recommendations. BP categories were defined by the 2009 Japanese Society of Hypertension Guidelines for the Management of Hypertension. The Cox proportional hazard ratios (HRs) for CVD according to the serum glucose and BP categories were calculated. In 62 036 person-years of follow-up, we documented 364 CVD events (198 stroke and 166 coronary heart disease (CHD)). Compared with normoglycemic subjects, the multivariable HRs (95% confidence intervals (CIs)) for CVD, CHD and stroke were 1.25 (1.00–1.58), 1.46 (1.04–2.04) and 1.11 (0.81–1.52), respectively, in individuals with impaired fasting glucose (IFG), whereas these values were 2.13 (1.50–3.03), 2.28 (1.34–3.88) and 2.08 (1.29–3.35), respectively, in individuals with diabetes mellitus (DM). Compared with normoglycemic and optimal blood pressure (BP) subjects, increased risks of CVD were observed in the normoglycemic subjects with high-normal BP or hypertension, the IFG subjects with normal or higher BP, and the DM subjects regardless of BP category (*P*-value for interaction=0.046). In conclusion, the high-normal BP subjects in all glucose categories and the normal BP subjects with IFG showed increased risk of CVD in this Japanese population. Further investigation of larger cohorts of DM subjects should be conducted to better understand this phenomenon.
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Keywords: blood pressure category; cardiovascular disease; cohort study; diabetes mellitus; impaired fasting glucose

INTRODUCTION

Hypertension is one of the strongest risk factors for increased incidence of cardiovascular disease (CVD) worldwide.[1–3] Recently, high-normal blood pressure (BP)[1,2] and prehypertension[3] have also been recognized as risk factors for CVD.[4–6] Increased BP is the most likely precipitator of CVD and stroke.[5,7,8] Furthermore, the prevalence of glucose intolerance and obesity has increased greatly in recent years.[9,10] Diabetes mellitus (DM) has become a major public health problem[11,12] as well as a risk factor for all-cause mortality[11] and CVD.[10,13–15] Recently, prediabetic hyperglycemia has been recognized to confer an increased risk for CVD.[16] However, a few population studies[17] have reported a positive association between CVD and impaired fasting glucose (defined as blood glucose of 5.6–6.9 mmol l^{-1} according to the 2003 American Diabetes Association definition).[18]

Evaluation of the combined impact of these two major borderline risk factors is essential in preventing CVD because elevated BP is the highest population attributable fraction (PAF) of CVD incidence, and the incidence of hyperglycemia is increasing in Asian and Western countries. There have been a few population studies on the association between the occurrence of hypertension together with DM and the risk of stroke[19–21] and coronary heart disease (CHD).[22] However, few population cohort studies have evaluated the impact of the combination of BP categories (optimal BP, normal BP, high-normal BP (or prehypertension) and hypertension) and fasting glucose categories (normoglycemia, impaired fasting glucose (IFG) and DM) on the risk

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of CVD. Thus, the aim of this study was to examine the combined impact of BP categories and blood glucose abnormalities on the incidence of CVD in a general urban Japanese population.

METHODS

Study subjects

The Suita Study, a cohort study for CVD in urban residents, was established in 1989. The details of this study have been described elsewhere.[5,23–29] Briefly, 6485 individuals (aged 30 to 79 years) underwent regular health checkups between September 1989 and March 1994. Some cohort members were excluded for the following reasons: past or present history of CVD at baseline (n=208); missing data (n=170); nonfasting blood collections (n=173); or lost from follow-up (n=613). After applying these exclusions, a total of 5321 subjects (aged 30 to 79 years) participated in the baseline examination. Informed consent was obtained from all participants. This study was approved by the institutional review board of the National Cardiovascular Center.

Measurement of BP and fasting glucose

Measurement of BP has been described elsewhere.[5] In brief, well-trained physicians measured the BP of each individual three times in a seated position using a mercury column sphygmomanometer, an appropriately sized cuff and a standard protocol. Before the initial BP reading was obtained, participants were seated at rest for at least 5 min. Systolic (SBP) and diastolic (DBP) blood pressures were recorded as the average of the second and third measurements, which were taken more than 1 min apart.

At the time of the baseline examination, subjects were classified into one of the following BP categories based on the 2009 Japanese Society of Hypertension Guidelines for the Management of Hypertension:[2] optimal BP (SBP, $<$120 mm Hg and DBP, $<$80 mm Hg); normal BP (SBP, 120 to 129 mm Hg and DBP, 80 to 84 mm Hg); high-normal BP (SBP, 130 to 139 mm Hg and DBP, 85 to 89 mm Hg); and hypertension (SBP, $\geqslant$140 mm Hg or DBP, $\geqslant$90 mm Hg or antihypertensive drug use). If the SBP and DBP readings for a subject were in different categories, then the subject was categorized into the higher of the two categories.

We performed routine fasting blood collection and immediately measured serum glucose and total cholesterol levels using the same autoanalyzer (Toshiba TBA-80, Toshiba, Tokyo, Japan). Fasting serum glucose categories were defined as follows:[18] DM (fasting serum glucose $\geqslant$7.0 mmol l^{-1} (126 mg per 100 ml) or medications for DM); IFG (fasting serum glucose levels 5.6 to 6.9 mmol l^{-1} (100 to 125 mg per 100 ml)); and normoglycemia (fasting serum glucose levels $<$5.6 mmol l^{-1} ($<$100 mg per 100 ml)). Hypercholesterolemia was defined as total serum cholesterol levels $\geqslant$5.7 mmol l^{-1} (220 mg per 100 ml) or current use of antihyperlipidemic medications. Physicians or nurses administered questionnaires addressing personal habits and present illness at the baseline examination. Body mass index was calculated as weight (kg) divided by height (m) squared.

Confirmation of stroke and coronary heart disease and end point determination

Medical records were reviewed by registered hospital physicians or research physicians who were blinded to the baseline data. Strokes were defined according to the US National Survey of Stroke criteria.[30] For each stroke subtype (that is, cerebral infarction (thrombotic or embolic infarction), intracerebral hemorrhage and subarachnoid hemorrhage), a definite diagnosis was established based on examination of computed tomographic scans, magnetic resonance images or autopsies. Definite and probable myocardial infarctions were defined according to the criteria set out by the MONICA project.[31] The criteria for a diagnosis of CHD included first ever acute myocardial infarction, sudden cardiac death within 24 h after the onset of acute illness or coronary artery disease followed by coronary artery bypass surgery or angioplasty. In this study, CVD was defined as stroke or CHD.

To detect CHD and stroke occurrences, each participant's health status was checked during clinical visits to the National Cardiovascular Center every 2 years. Yearly questionnaires by mail or telephone were also completed by all participants. In addition, to complete our surveillance for fatal strokes and CHD, we conducted a systematic search for death certificates. All data were checked against medical records to confirm the incidence of CVD. When informed consent could not be obtained for a medical records survey (19.5%), we identified possible strokes or CHD using information from (1) questionnaires for present illness of stroke and CHD at the health examination and/or (2) death certificates bearing a diagnosis of probable stroke or CHD. The end point of the follow-up period for each participant was, whichever of the following options occurred first: (1) date of the first diagnosis of CHD or stroke event; (2) date of death; (3) date of leaving Suita; or (4) 31 December, 2005.

Statistical analysis

Analyses of variance and χ^2-tests were used to compare mean values and frequencies. The Cox proportional hazard ratios (HRs) and 95% confidence intervals (95% CIs) were fitted to each glucose category (normoglycemia, IFG and DM) after adjusting for sex and age in 5-year increments as stratified variables and other potential confounding factors at baseline, including BP category (optimal, normal, and high-normal BP and hypertension), hypercholesterolemia (positive or negative), body mass index (continuous variable), smoking status (never, ex-smoker and current smoker) and drinking status (never, ex-drinker and current drinker). Test for effect modification by glucose category was conducted with an interaction term generated by multiplying BP category by glucose category. We conducted tests for trend across the BP categories and tested the significance of this variable.

To express the combined impact of glucose and BP categories on the incidence of CVD in these participants, we estimated the PAF as follows:

$$PAF = Pe \times (HR - 1)/HR,$$

where Pe is the proportion of incident cases in the combination of glucose and BP categories, and HR is the multivariable-adjusted hazard ratio.[32] All statistical analyses were conducted using the SAS statistical software package (release version 8.2; SAS Institute, Cary, NC, USA).

RESULTS

The frequencies of IFG and DM increased with age in both men and women (Figure 1). Table 1 shows the distribution of CVD risk factors at baseline according to fasting glucose categories at baseline. Both men and women with DM were older and had a higher body mass index as well as a higher prevalence of hypertension, hypercholesterolemia and medication for hypertension than those without DM. Men with DM had a lower frequency of never drinking than men without DM.

In 62 036 person-years of follow-up (an average of 11.7 years of follow-up), we documented 364 CVD (198 strokes and 166 CHD) events. Table 2 shows the age- and sex-adjusted HRs and multivariable-adjusted HRs for incidence of CVD according to glucose categories in men and women. Compared with normoglycemic subjects, the multivariable HRs (95% CIs) for CVD, CHD and stroke were 1.25 (1.00–1.58), 1.46 (1.04–2.04) and 1.11 (0.81–1.52), respectively in IFG subjects, whereas these values were 2.13 (1.50–3.03), 2.28 (1.34–3.88) and 2.08 (1.29–3.35), respectively in DM subjects. Compared with normoglycemic subjects, IFG and DM were risk factors for CVD and CHD in women, and DM was a risk factor for CVD and stroke in men.

Figure 2 shows the multivariable HRs of CVD for the combined impact of the fasting glucose and BP categories. Compared with normoglycemic subjects with optimal BP, the following groups showed increased risk of CVD: the normoglycemic subjects with high-normal BP or hypertension (P-value for trend of BP category$<$0.001); the IFG subjects with normal or higher BP (P-value for trend of BP category=0.001); and the DM subjects in any BP category (P-value for trend of BP category=0.41). After excluding subjects taking diabetic medication, the P-value for the BP category trend was not statistically significant in the DM subjects.