Table 2 Cardiovascular clinical trials conducted in PROBE fashion and their primary end points

				Hard end points							*Soft endpoints*				
Trial name	*Publication year*	*Comparison*	*Primary end point description*	*Non-fatal MI*	*Non-fatal stroke*	*Fatal MI*	*Fatal stroke*	*Sudden death/ resuscitated cardiac arrest*	*Other cardio-vascular deaths*	*All-cause deaths*	*Worsening angina/ unstable angina*	*Exacer-bation of heart failure*	*Any-cause hospital-ization*	*PCI*	*Significant difference in the primary endpoint*
Western trials															
HOT[a]	1998	Three levels of therapeutic BP targets	Major cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death)	○	○	○	○		○						No
STOP-hypertension2[b]	1999	BP lowering new *vs.* old drugs	Fatal stroke, fatal myocardial infarction, sudden death and other cardiovascular deaths			○	○	○	○						No
CAPPP[c]	1999	Captopril *vs.* conventional drugs	Combination of fatal and nonfatal myocardial infarction and stroke, and other cardiovascular deaths	○	○	○	○		○						No
NORDIL[d]	2000	Diltiazem *vs.* β-blockers and/or diuretics	Fatal and nonfatal stroke, fatal and non-fatal myocardial infarction and other cardiovascular death	○	○	○	○		○						No
ANBP2[e]	2003	ACE-I *vs.* diuretics	All fatal events+non-fatal cardiovascular events	○	○	○	○	○	○	○	○	○			Yes
SPORTIF III[f]	2003	Ximelagatran *vs.* warfarin	All strokes (ischemic and hemorrhagic) and systemic embolic events		○		○								No
INVEST[g]	2003	Ca blocker *vs.* non-Ca blocker	All cause mortality, nonfatal MI or nonfatal stroke	○	○					○					No
LoWASA[h]	2004	Fixed low dose warfarin+aspirin *vs* aspirin	Cardiovascular event (cardiovascular death or reinfarction or stroke) and cardiovascular death	○	○				○						No
IDEAL[i]	2005	Statin therapy usual *vs.* intensive	MACE (nonfatal AMI, coronary death or resuscitated cardiac arrest)	○		○		○							No
CIBIS III[j]	2005	Enalapril→bisoprolol *vs* bisoprolol→enalapril	Combined end point of mortality (death from any cause) and first all-cause hospitalization							○			○		No
ASCOT-BPLA[k]	2005	CCB/ACE-I *vs.* β-blocker/ diuretics	Non-fatal MI fatal CHD	○		○									No
MOSES[l]	2005	Eprosartan *vs.* nitrendipine	Composite of all-cause mortality and the number of cardiovascular and cerebrovascular events including all recurrent events	○	○	○	○			○					No
ACTIVE W[m]	2006	Aspirin+clopidogrel *vs.* warfarin	First occurrence of stroke, non-CNS systemic embolism, myocardial infarction or vascular death	○	○	○	○		○						Yes*
ESPRIT[n]	2006	Aspirin+dypiridamole *vs.* aspirin	Combined event of 'death from all vascular causes', non-fatal stroke, non-fatal myocardial infarction or major bleeding complication	○	○	○	○		○						Yes
BAFTA[o]	2007	Adjusted dose warfarin *vs.* aspirin	Incidence of fatal or non-fatal disabling stroke (ischemic or hemorrhagic), intra-cranial hemorrhage or significant arterial embolism		○		○								Yes
Japanese trials															
MEGA[p]	2006	diet *vs.* diet+pravastatin		○		○		○			○			○	Yes

Table 2 Continued

Trial name	Publication year	Comparison	Primary end point description	Hard end points: Non-fatal MI	Non-fatal stroke	Fatal MI	Fatal stroke	Sudden death/ resuscitated cardiac arrest	Other cardio-vascular deaths	All-cause deaths	Soft endpoints: Worsening angina/ unstable angina	Exacer-bation of heart failure	Any-cause hospital-ization	PCI	Significant difference in the primary endpoint
JIKEI-HEART[q]	2007	Valsartan *vs.* non-ARB	Fatal or nonfatal myocardial infarction, sudden cardiac death, development of unstable angina and coronary revascularization procedures, either coronary artery bypass grafting or percutaneous coronary intervention Stroke, new or recurrent transient ischemic attack, new or recurrent acute myocardial infarction, new occurrence or exacerbation of heart failure, new occurrence or exacerbation of angina pectoris, dissecting aneurysm of the aorta, lower limb arterial obstruction, transition to dialysis, doubling of plasma Cr levels	○	○	○	○				○	○			Yes
JELIS[r]	2007	EPA+statin *vs.* statin	Sudden cardiac death, fatal and nonfatal MI, unstable angina pectoris including hospitalization for documented ischemic episodes, and events of angioplasty/stenting or CABG	○		○		○			○			○	Yes
CASE-J[s]	2008	Candesartan *vs.* amlodipine	Sudden death, new occurrence or recurrence of stroke or TIA, new occurrence, aggravation or recurrence of heart failure, angina pectoris or acute myocardial infarction, renal dysfunction, new occurrence or aggravation of dissecting aneurysm of aorta, arteriosclerotic occlusion of peripheral artery	○	○	○	○	○			○	○			No

Abbreviations: ACE-I, angiotensin converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; BP, blood pressure; CABG, coronary artery bypass graft; CCB, calcium blocker; CNS, central nervous system; EPA, eicosapentaenoic acid; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous intervention; PROBE, prospective randomized open-label blinded end-point.
[a]Hypertension Optimal Treatment Study.[21]
[b]Swedish Trial in Old Patients with Hypertension-2 Study.[22]
[c]Captopril Prevention Project.[23]
[d]Nordic Diltiazem Study.[24]
[e]Australian National Blood Pressure Study 2.[25]
[f]Stroke Prevention using an ORal Thrombin Inhibitor in patients with atrial Fibrillation III Study.[18]
[g]International Verapamil-Trandolapril Study.[26]
[h]Low-dose Warfarin and Aspirin Study.[27]
[i]Incremental Decrease in End Points Through Aggressive Lipid Lowering Study.[28]
[j]Cardiac Insufficiency Bisoprolol Study III.[29]
[k]Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm.[30]
[l]Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention Study.[31]
[m]Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events.
[n]European/Australian Stroke Prevention in Reversible Ischaemia Trial.[32]
[o]Birmingham Atrial Fibrillation Treatment of the Aged Study.[19]
[p]Management of Elevated Cholesterol in the Primary Prevention Group of the Adult Japanese Study.[33]
[q][35]
[r]Japan EPA Lipid Intervention Study.[36]
[s]Candesartan Antihypertensive Survival Evaluation in Japan.[37]
* The result was siginificantly in favor of warfarin.

Table 3 The number of end points in JIKEI HEART Study

	Number of events valsartan group (%)	*Number of events non-ARB treatment group (%)*	*P-value*
Primary end point			
Composite end point of stroke, new or recurrent transient ischemic attack, new or recurrent acute myocardial infarction, new occurrence or exacerbation of heart failure, new occurrence or exacerbation of angina pectoris, dissecting aneurysm of the aorta, lower limb arterial obstruction, transition to dialysis, doubling of plasma Cr levels	92 (6.0)	149 (9.7)	0.0002
Secondary end points			
Stroke or transient ischemic attack	29 (1.9)	48 (3.1)	0.0280
New or recurrent acute myocardial infarction	17 (1.1)	19 (1.2)	0.7545
New occurrence or exacerbation of angina pectoris needing hospitalization[a]	19 (1.2)	53 (3.4)	0.0001
New occurrence or exacerbation of heart failure needing hospitalization[a]	19 (1.2)	36 (2.3)	0.0293
Dissecting aneurysm of the aorta	2 (0.1)	10 (0.6)	0.0340
Transition to dialysis, doubling of serum creatinine levels	7 (0.5)	8 (0.5)	0.8966
All-cause mortality	28 (1.8)	27 (1.8)	0.7537
Cardiovascular mortality	9 (0.6)	9 (0.6)	0.9545

[a]End points that are considered to be 'soft end points'.
Modified from *Lancet*. 2007 April 28; **369** (9571):1431–1439.

blocker (valsartan) to conventional treatment was effective in reducing cardiovascular events in Japanese patients with cardiovascular disease. Although the successful lowering of blood pressure was similar in both the valsartan and non-valsartan groups, it was shown that the addition of valsartan to conventional treatment prevented more cardiovascular events than conventional treatment. This superiority of valsartan to other blood pressure-lowering agents, which goes beyond its blood pressure-lowering effect, has not been shown in other clinical trials conducted in a double-blind fashion;[38,39] this is one of the other reasons that the results of this trial interested many individuals. When examined in greater detail, it is obvious that the differences in the number of soft end points are the factors that mainly contributed to the favorable results for valsartan in this study (Table 3). The primary end point of this study is a composite of several pre-specified events, and its components are not clearly shown. However, the number of each component is shown as secondary end points, which is a good indication of the composition of the primary end point. In fact, hard end points such as myocardial infarction or cardiovascular mortality did not differ significantly between the two groups. As is questioned in the editorial that accompanied the article,[40] it cannot be totally ruled out that there might have been underreporting of events in the valsartan group. It is also of great interest that although most studies conducted in the West produced no significant difference as regards the primary end point, results of three of the four studies conducted in Japan were significantly in favor of the study drug, the manufacturer of which was the sponsor (Table 2). These could be considered as examples showing that the results of PROBE-designed trials should be evaluated carefully, especially in cases wherein the results with soft end points are widely discrepant from those with hard end points.

CONCLUSION

Epidemiological studies conducted in prospective cohort design have established cardiovascular risk factors such as hypertension, hyperlipidemia, smoking and age. By applying the ideas and methodologies developed in epidemiological studies, many clinical trials have been conducted to prove the benefits of various medicines.

Randomized, controlled, double-blind clinical trials report the most scientifically accurate results. However, they usually entail high costs, render the recruitment of patients more difficult and are rather discrepant from usual clinical care. The PROBE study design is a feasible alternative to double-blind studies. However, if not designed and conducted properly, it will be more susceptible to biases. Thus, studies conducted with a PROBE design using soft end points included in the primary end point require the participating physicians to adhere to the guidelines for PROBE studies more strictly.

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Prognostic Value of Heart Rate Profiles During Cardiopulmonary Exercise Testing in Patients With Cardiac Disease

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SUMMARY

Earlier studies have demonstrated that an impaired capacity to increase heart rate (HR) and a slowed HR recovery following exercise are both associated with cardiovascular mortality. We sought to determine whether HR profiles during exercise testing are superior to respiratory gas parameters in predicting mortality among patients with cardiac disease.

Five-hundred and fifty stable cardiac patients (63.4 ± 9.9 years) underwent a symptom-limited incremental exercise test. Measurements included peak VO_2, VE/VCO_2 slope, HR increase (HR difference from rest to peak exercise), and HR recovery (HR difference from peak to 2 minutes after exercise). Twenty-eight cardiovascular-deaths occurred during 4 years of prospective follow-up. In multivariate analysis, the CPX parameters were found to be significant predictors of cardiovascular-death; peak VO_2 (relative risk (RR), 3.44; 95% CI 1.37 to 8.62; $P = 0.008$), VE/VCO_2 slope (RR, 1.52; 95% CI 1.11 to 2.08; $P = 0.009$), while HR increase and HR recovery were determined not to be independent predictors.

Although HR profiles during exercise testing are easy to perform and useful as prognostic predictors in patients with cardiac disease, they are not superior to respiratory gas analysis. (Int Heart J 2009; 50: 59-71)

Key words: Cardiopulmonary exercise testing, Heart rate, Prognosis

PARAMETERS obtained from cardiopulmonary exercise testing (CPX) reflect the severity of heart disease and the activities of daily living in cardiac patients. The widely used CPX parameters are peak oxygen uptake (VO_2), gas exchange (anaerobic) threshold, ratio of the increase in VO_2 to the increase in work rate (WR) ($\Delta VO_2 / \Delta WR$), and the slope of the increase in ventilation (VE) to the

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increase in CO_2 output (VCO_2) (VE/VCO_2 slope). Landmark studies have established peak VO_2 as the key measure of exercise physiology, and low peak VO_2 is widely recognized as a predictor of poor prognosis.[1] Peak VO_2 is derived from the Fick equation, and most patients achieve comparable arterial-venous oxygen differences when they give maximal effort. Peak VO_2 thus serves as a noninvasive marker for peak cardiac output response and cardiac reserve. VE/VCO_2 slope, an index of ventilatory efficiency, also serves as a prognostic predictor.[2,3] The most meaningful determinants are the matching of ventilation and perfusion. The reliability of CPX parameters in predicting cardiovascular events and death is undisputable.

Recent research has revealed that the autonomic nervous system also plays a significant role in cardiac arrhythmia and prognosis. Studies of markers for vagal tone and autonomic imbalance have shown that an elevated resting heart rate (HR), impaired HR recovery from exercise, suppressed peak HR, low HR variability, decreased baroreflex, and decreased baroreflex sensitivity are all predictive of cardiovascular events.[4-7] HR profiles can be measured easily throughout ordinary exercise testing without respiratory gas analysis. It remains unclear, however, whether HR profiles have more prognostic value than the established CPX parameters. The aim of this study was to determine whether HR profile analysis during exercise testing is more predictive of cardiovascular death than the measurement of CPX parameters in cardiac patients.

Methods

Study patients: We prospectively studied 571 consecutive patients with cardiovascular disease who underwent CPX between February 2001 and August 2003. The exercise testing was performed to evaluate exercise capacity or cause of dyspnea. Patients with lung disease or cerebrovascular disease diagnosed by clinical documentation, patients with ischemic heart disease who stopped exercise testing due to chest pain or significant ST depression in exercise ECG, and patients with implanted pacemakers were excluded from the study. After excluding these patients, 550 patients remained and were included in the analysis.

The patient population consisted of 438 males and 112 females, with an average age of 63.4 ± 9.9 years. The mean left ventricular ejection fraction (LVEF) was 59.4 ± 16.0%. Seventy-three patients were in atrial fibrillation. The underlying heart diseases included ischemic heart disease with some treatment interventions in 339 patients, valvular heart disease in 156, idiopathic dilated cardiomyopathy in 32, hypertrophic cardiomyopathy in 21, and other cardiovascular diseases in 2.

Medications influencing hemodynamic variables included nitrates (pre-

scribed in 270 patients), calcium-channel blockers (250 patients), β-blockers (207 patients), diuretics (137 patients), angiotensin-receptor blockers (124 patients), angiotensin-converting enzyme inhibitors (99 patients), digitalis (70 patients), and spironolactone (54 patients).

The protocol and procedures for the exercise testing were approved by the Human Subjects Committee of each participating institution. Each patient provided informed consent to participate in the study after being given an explanation of the purposes and risks of the study.

Exercise testing: An incremental symptom-limited exercise test was performed using an upright, electromagnetically braked cycle ergometer (Corival 400; Lode; Groningen, Holland) according to the Ramp protocol. The test consisted of a 4-minute resting period, followed by 4 minutes of warm-up at an ergometer setting of 0 W or 20 W (60 rpm), followed by testing with a 1 W increase in exercise load every 6 seconds (10 W/minute). After achieving peak workload, all the patients spent at least 1 minute in cool-down at 0 W. During recovery, the subjects remained in the upright position on the cycle ergometer until the end of the 6th minute. ECG was monitored continuously during the test (System ML-6500; Fukuda Denshi Co. Ltd., Tokyo). Cuff blood pressure was measured at rest on the cycle ergometer, once every minute during the test, and once every minute after the completion of the test up to the 6th minute of recovery, using an automatic indirect manometer (STBP-780; Nippon Colin Co. Ltd.; Aichi, Japan).[8]

HR profiles: We examined data on the subjects' resting HR, the increase in HR from rest to peak exercise (HR increase), and the decrease in HR from peak exercise to 2 minutes after the termination of exercise (HR recovery). The resting HR was the average HR during the 4-minute resting period. HR increase was determined as the difference from resting HR to peak HR, and HR recovery was determined as a difference from peak HR to HR at 2 minutes after exercise.

Respiratory gas analysis: VO_2, VCO_2, and VE were measured throughout the test using an Aeromonitor AE-300S (Minato Medical Science; Osaka, Japan).[9,10] Prior to calculating the parameters from respiratory gas analysis, a 5-point moving average of the breath-by-breath data was obtained. Peak VO_2 was defined as the average value obtained during the last 15 seconds of incremental exercise. $\Delta VO_2 / \Delta WR$ was calculated from the data recorded between 30 seconds after the start of incremental exercise to 30 seconds before the end of exercise, by least squares linear regression.[11] VE/VCO_2 slope was calculated from the start of incremental exercise to the respiratory compensation point, by least squares linear regression as previously described.[11,12]

Endpoint: The primary endpoint was death due to a cardiovascular cause. Vital status was assessed by investigation of the hospital information system.

Statistics: Clinical and exercise variables for survivors and nonsurvivors were compared through the use of χ^2 tests (categorical variables) and unpaired *t* tests (continuous variables). HR measurements were nonnormally distributed, and thus were compared by the Mann-Whitney U test.

Lower peak VO_2, lower ΔVO_2 / ΔWR, lower HR increase, lower HR recovery, and lower LVEF have been associated with a poor prognosis in a previous study, so cut-off values were based on 25th percentiles. In the same way, a higher VE/VCO_2 slope and higher age have been related to a poor prognosis, therefore, the cut-off value was based on 75th percentiles, as appropriate (Cut-off values; peak VO_2:14.5 mL/minute/kg, VE/VCO_2 slope: 35.8, ΔVO_2 / ΔWR: 8 mL/minute/W, HR increase: 35 bpm, HR recovery: 22 bpm, LVEF: 50%, age: 70 years old). The relationships between the tertiles of HR increase, HR recovery, peak VO_2, and VE/VCO_2 slope with mortality were evaluated by Kaplan-Meier analysis. Patients who died of cancer were excluded from the survival analyses.

The association between the variables and mortality was assessed using Cox proportional hazards models for both categorical and continuous values. All continuous variables were standardized and included as such in Cox survival analyses to avoid artifacts of dichotomization. The hazard ratios are reported for a 1-SD increase or decrease in each variable.

All analyses were performed using the SPSS statistical package, version 11.0 (SPSS Inc., Chicago). Statistical comparisons were considered significant when the probability values were less than 0.05.

Results

Baseline characteristics: After 1,392 ± 637 days (3.8 years) of prospective follow-up, 28 cardiovascular deaths and 1 cancer death had occurred. The causes of cardiovascular death included progressive heart failure in 13 patients, sudden cardiac death in 13, acute myocardial infarction in 1, and cerebrovascular disease in 1.

Among the patients with coronary artery disease, 53 received percutaneous coronary intervention and 5 underwent coronary artery bypass graft surgery during the follow-up period. Twenty-five of the patients with valvular disease underwent cardiac valve replacement and/or repair during the follow-up. Two of the patients with coronary artery disease underwent cardioverter-defibrillator implantation.

Table I shows a comparison of the clinical characteristics between survivors and nonsurvivors. Nonsurvivors were significantly older, and had a significantly lower LVEF and higher incidence of atrial fibrillation than survivors.

HR responses: The HR responses to exercise according to outcome are de-

Table I. Baseline Characteristics

Characteristic	All Patients ($n = 549$)	Survivors ($n = 521$)	Nonsurvivors ($n = 28$)	P
Age (years)	63.4 ± 9.9	63.2 ± 10.6	67.7 ± 9.3	0.028
Male/female	437/112	413/108	24/4	0.411
HT (cm)	163.4 ± 8.0	163.5 ± 8.0	161.0 ± 8.1	0.102
BW (kg)	62.1 ± 10.8	62.3 ± 10.8	58.0 ± 9.9	0.040
BMI	23.2 ± 3.1	23.2 ± 3.1	22.3 ± 2.9	0.132
Etiology				
Ischemic heart disease	338 (62%)	324 (62%)	14 (50%)	0.175
Valvular heart disease	156 (28%)	145 (28%)	11 (39%)	0.167
Idiopathic dilated cardiomyopathy	32 (6%)	31 (6%)	1 (4%)	0.485
Hypertrophic cardiomyopathy	21 (4%)	19 (4%)	2 (7%)	0.305
Other cardiovascular disease	2 (0.4%)	2 (0.4%)	0	0.897
Presence of atrial fibrillation	73 (13.3%)	63 (12.1%)	10 (35.7%)	0.002
Medication				
Nitrates	269 (49%)	254 (48%)	15 (54%)	0.429
Calcium-channel blockers	249 (45%)	241 (46%)	8 (29%)	< 0.001
β-Blockers	206 (38%)	195 (37%)	11 (39%)	0.713
Diuretics	137 (25%)	121 (23%)	16 (57%)	0.002
Angiotensin-receptor blockers	134 (24%)	124 (24%)	10 (36%)	0.008
Angiotensin-converting enzyme inhibitors	104 (19%)	99 (19%)	5 (18%)	0.960
Digitalis	70 (13%)	64 (12%)	6 (21%)	0.012
Spironolactone	54 (10%)	46 (9%)	8 (29%)	< 0.001
LVEF (%)	59.3 ± 16.0	60.4 ± 14.7	40.9 ± 22.0	< 0.001

Data presented are the mean value ± SD. HT indicates height, BW, body weight, BMI, body mass index; and LVEF, left ventricular ejection fraction.

Table II. HR at Rest and Changes During and After Exercise

Variable	All Patients ($n = 549$)	Survivors ($n = 521$)	Nonsurvivors ($n = 28$)	P
Rest HR (bpm)	76.5 ± 14.1	76.5 ± 14.2	76.6 ± 12.6	0.976
Peak HR (bpm)	128.7 ± 23.8	129.5 ± 23.6	113.8 ± 21.6	0.001
HR increase (bpm)	52.2 ± 22.2	53.1 ± 22.0	37.2 ± 20.6	< 0.001
HR recovery (bpm)	32.6 ± 14.8	33.0 ± 14.7	24.3 ± 14.8	0.002
Rest SBP (mmHg)	125.7 ± 19.8	126.0 ± 24.9	120.8 ± 24.9	0.180
Rest DBP (mmHg)	71.3 ± 11.4	71.7 ± 11.3	64.8 ± 11.6	0.002
Peak SBP (mmHg)	186.2 ± 34.5	187.9 ± 33.9	155.3 ± 31.0	< 0.001
Peak DBP (mmHg)	86.3 ± 16.6	86.7 ± 16.7	78.6 ± 14.3	0.012

Data presented are the mean value ± SD.
HR indicates heart rate; SBP, systolic blood pressure; and DBP, diastolic blood pressure.

scribed in Table II. Peak HR, HR increase, HR recovery, and peak SBP were significantly lower in nonsurvivors than in survivors.

Exercise test response: Table III presents the exercise test responses according to outcome status. Nonsurvivors had significantly lower peak VO_2, higher VE/VCO_2 slope, lower $\Delta VO_2/\Delta WR$, and lower peak WR than survivors. The respiratory exchange ratio (ie, VCO_2/VO_2) in nonsurvivors was similar to that in

Table III. Respiratory Gas Parameters

Variable	All Patients ($n = 549$)	Survivors ($n = 521$)	Nonsurvivors ($n = 28$)	P
Peak VO_2 (mL/minute/kg)	18.2 ± 5.3	18.5 ± 5.2	12.3 ± 3.5	< 0.001
Δ VO_2/ Δ WR, (mL/minute/W)	9.1 ± 2.3	9.2 ± 2.2	6.8 ± 2.2	< 0.001
VE/VCO_2 slope	32.7 ± 8.0	32.2 ± 7.3	43.1 ± 11.9	< 0.001
Peak WR (W)	89.3 ± 32.0	90.9 ± 31.6	58.9 ± 22.5	< 0.001
Peak R	1.090 ± 0.092	1.090 ± 0.093	1.079 ± 0.085	0.496

Data presented are the mean value ± SD.
VO_2 indicates O_2 uptake; WR, work rate; VE, ventilation; VCO_2, CO_2 output; and R, respiratory exchange ratio.

Table IV. Univariate Predictors of Death

Variable	Relative Risk	95% CI	Chi-square	P
Peak VO_2	4.79	2.92-7.91	38.50	< 0.0001
VE/VCO_2 slope	2.24	1.81-2.77	53.74	< 0.0001
HR increase	2.42	1.53-3.77	14.89	< 0.0001
HR recovery	2.04	1.33-3.17	10.43	0.001
Peak WR	3.95	2.48-6.54	31.48	< 0.0001
Δ VO_2/ Δ WR	2.44	1.87-3.18	44.11	< 0.0001
LVEF	2.69	1.95-3.67	37.26	< 0.0001
Peak SBP	2.76	1.87-4.24	23.67	< 0.0001
Atrial fibrillation	3.35	1.56-7.20	9.55	0.002
Rest HR	1.00	0.69-1.43	0.01	0.977
Rest SBP	1.35	0.91-1.98	2.06	0.151
Age	1.56	1.04-2.35	4.57	0.033
Male	1.46	0.51-4.20	0.49	0.486
BMI	1.37	0.93-2.01	2.53	0.112
β Blocker use	1.09	0.51-2.33	0.05	0.825
Ischemic heart disease	1.56	0.81-3.48	1.80	0.643

Except for the variables male, atrial fibrillation, β blocker use, and ischemic heart disease, the relative risks were calculated for a change of 1-SD.
CI indicates confidence interval; VO_2, O_2 uptake; VE, ventilation; VCO_2, CO_2 output; WR, work rate; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; HR, heart rate; SBP, systolic blood pressure; and BMI, body mass index.

survivors.

Outcome: Univariate analyses. Table IV presents the univariate predictors of death. The prognostic significance of the measurements was assessed by testing variables as continuous values using Cox regression analysis. When evaluating as univariate predictors, peak VO_2 (relative risk (RR), 4.79; 95% CI 2.92 to 7.91; $P < 0.0001$) had the highest significance, followed by VE/VCO_2 slope (RR, 2.24; 95% CI 1.81 to 2.77; $P < 0.0001$), ΔVO_2 / ΔWR (RR, 2.44; 95% CI 1.87 to 3.18; $P < 0.0001$), peak WR (RR, 3.95; 95% CI 2.48 to 6.54; $P < 0.0001$), HR increase (RR, 2.42; 95% CI 1.53 to 3.77; $P < 0.0001$), HR recovery (RR, 2.04; 95% CI 1.33 to 3.17; $P = 0.001$), LVEF (RR, 2.69; 95% CI 1.95 to 3.67; $P < 0.0001$), peak SBP (RR, 2.76; 95% CI 1.87 to 4.24; $P < 0.0001$), presence of

Table V. Multivariate Predictors of Death

Variable	Relative Risk	95% CI	Chi-square	*P*
Model 1 (continuous variables)				
LVEF	2.16	1.52-3.03	19.47	< 0.0001
Peak VO_2	3.44	1.37-8.62	6.93	0.008
VE/VCO_2 slope	1.52	1.11-2.08	6.92	0.009
$\Delta VO_2/\Delta$ WR	1.43	0.90-2.27	2.33	0.127
HR increase	1.05	0.43-2.60	0.01	0.908
HR recovery	1.41	0.66-3.07	0.76	0.383
Atrial fibrillation	1.67	0.65-4.29	1.13	0.287
Age	1.76	0.85-3.63	2.34	0.126
Model 2 (categorical variables)				
Low LVEF (≤ 50%)	7.47	3.26-17.11	22.58	< 0.0001
Low Peak VO_2 (< 14.5 mL/minute/kg)	2.75	1.01-7.50	3.89	0.049
High VE/VCO_2 slope (> 35.8)	4.43	1.70-11.52	9.29	0.002
Low $\Delta VO_2/\Delta$ WR (< 8 mL/minute/W)	1.87	0.78-4.50	1.95	0.162
Low HR increase (< 35 bpm)	2.87	0.97-8.47	3.65	0.056
Low HR recovery (< 22 bpm)	1.22	0.48-3.14	0.17	0.677
Atrial fibrillation	2.33	0.94-5.81	3.31	0.069
High age (> 70 years old)	1.58	0.70-3.57	1.21	0.271

Relative risks and CIs in Model 1 were calculated for a change of 1-SD.
CI indicates confidence interval; VO_2, O_2 uptake; VE, ventilation; VCO_2, CO_2 output; WR, work rate; LVEF, left ventricular ejection fraction; and HR, heart rate.

atrial fibrillation (RR, 3.35; 95% CI 1.56 to 7.20; $P < 0.0001$), and age (RR, 1.56; 95% CI 1.04 to 2.35; $P = 0.033$).

Multivariate analyses. Although several variables were found to be associated with higher mortality in our study, the background characteristics of the patients might affect the outcome as confounding factors. To determine the independent effects of these variables on the prognosis, multivariate analysis was performed. The results of the multivariate analysis, using both continuous and categorical models, are shown in Table V.

Analyzing the variables as continuous, peak VO_2 (RR, 3.44; 95% CI 1.37 to 8.62; $P = 0.008$), VE/VCO_2 slope (RR, 1.52; 95% CI 1.11 to 2.08; $P = 0.009$), and LVEF (RR, 2.16; 95% CI 1.52 to 3.03; $P < 0.0001$) were determined to be strong independent predictors of survival. However, HR increase and HR recovery were determined to not be independent predictors.

In the same way, analyzing the variables as categorical, using cut-off values, a low peak VO_2 (RR, 2.75; 95% CI 1.01 to 7.50; $P = 0.049$), high VE/VCO_2 slope (RR, 4.43; 95% CI 1.70 to 11.52; $P = 0.002$), and low LVEF (RR, 7.47; 95% CI 3.26 to 17.11; $P < 0.0001$) were found to be strong independent predictors of survival. However, HR increase and HR recovery were determined not to be independent predictors.

The results of Kaplan-Meier analysis of the relationships of peak VO_2, VE/VCO_2 slope, HR increase, HR recovery, and LVEF with cardiovascular mortality

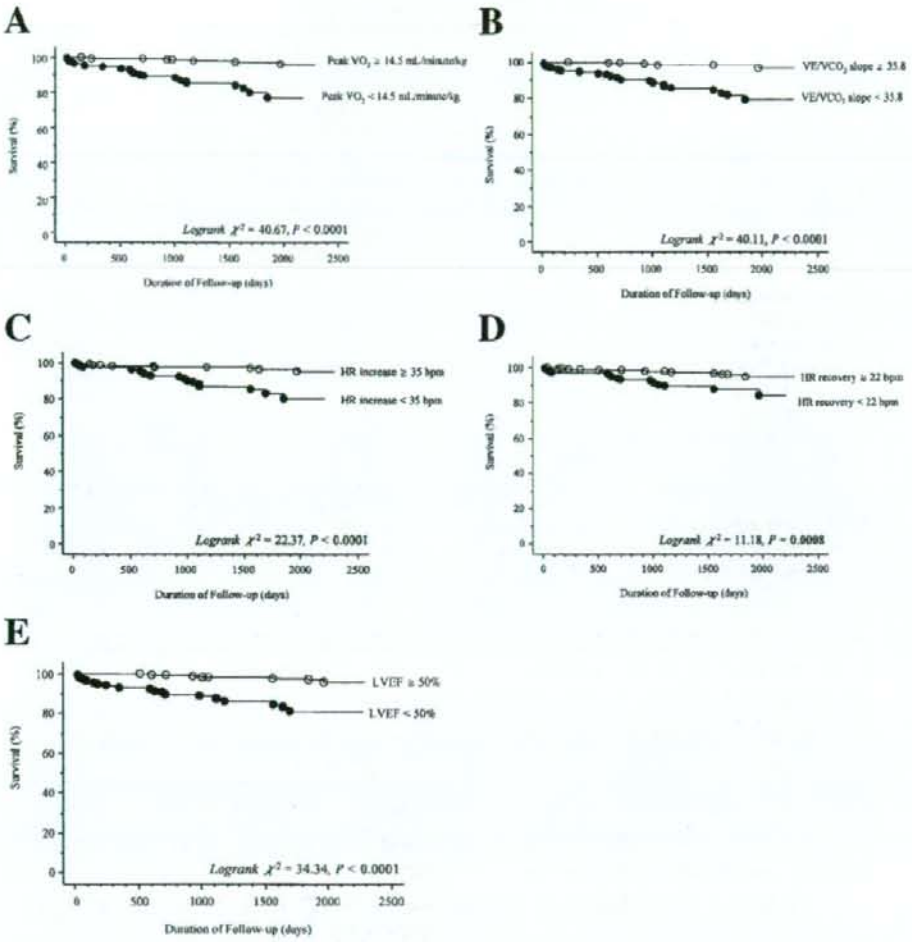

Figure. Kaplan-Meier plot relating survival peak VO_2 (**A**), VE/VCO_2 slope (**B**), HR increase (**C**), HR recovery (**D**), and LVEF (**E**).

are shown in Figure. There were significant associations between the tertiles of these parameters and mortality.

Discussion

The results of the present study indicate that both CPX parameters and HR profiles provide valuable prognostic information in cardiac patients.

CPX parameters: Since the 1980s, CPX has been applied to patients with heart

disease to objectively assess exercise capacity, to risk stratify patients, and to assess responses to therapeutic interventions.[12,13] In 1991, Mancini, *et al* proposed that cardiac transplantation could be safely deferred in ambulatory patients with severe left ventricular dysfunction when the peak VO_2 was > 14 mL/min/kg.[1] Since then, peak VO_2 has been considered a key index to list for cardiac transplantation. Other investigators have also reported that peak VO_2 measurement is advantageous for predicting prognosis.[14,15] Chua, *et al* examined the relationship between mortality and ventilatory response during symptom-limited exercise over a 2-year follow-up period in cardiac patients.[2] Their data indicated that the VE/VCO_2 slope correlated with the severity of the heart failure. They also found that the VE/VCO_2 slope was an independent prognostic marker in their cardiac patients. Several studies since then have demonstrated the strong predictive value of peak VO_2 and VE/VCO_2 slope.[3,16-21] Most patients achieve comparable arterial-venous oxygen differences when they give maximal effort. Peak VO_2 has thus served as a noninvasive marker for peak cardiac output response and cardiac reserve. Yet cardiac output response is not the only factor influencing peak VO_2: limited skeletal muscle mass and perfusion also have affects. Ventilatory efficiency, meanwhile, depends on pulmonary hemodynamics and related parameters such as ventilation-perfusion mismatch, skeletal muscle ergoreceptor and peripheral chemoreceptor sensitivity, and heightened sympathetic activity. Most reports characterize the VE/VCO_2 slope as prognostically superior to peak VO_2, and thus underscore the clinical importance of assessing ventilatory efficiency.[2,16,18,19] Because CPX parameters are closely related to hemodynamics and peripheral function, they can predict cardiovascular death.

HR profiles: There have been many reports on prognoses estimated from HR response during exercise. In the early 1970s, Ellestad, *et al* described chronotropic incompetence during exercise testing as a marker of poor prognosis.[22] Since then, chronotropic incompetence has been proved to be a poor predictor of survival among healthy cohorts and patients with coronary artery disease and heart failure.[23-28] Chronotropic incompetence might have been more meaningful as a marker for autonomic dysfunction in those studies. HR recovery, an index of parasympathetic activity, has been reported as another significant prognostic predictor in healthy subjects and patients with coronary artery disease and heart failure.[29-38] In 1999, Cole, *et al* noted that HR recovery was a strong and significant predictor of prognosis among 2,428 adults with no history of CHF or coronary revascularization.[5]

HR profiles are related not only to vagal tone and autonomic imbalance but also to exercise tolerance. Patients with lower exercise tolerance tend to exhibit a lower HR increase and lower HR recovery. Autonomic imbalance, a term used to indicate a relative or absolute decrease in vagal activity or an increase in

sympathetic activity, has been associated with an increased risk of death from cardiac and arrhythmic causes.[7] The limited number of cases of sudden death in the present study prevents us from discussing the prediction of sudden death in our subjects. HR profiles may be more useful for the prediction of sudden death than CPX parameters.

CPX parameters versus HR profiles: Robbins, *et al* examined how mortality related to chronotropic response and CPX parameters, especially ventilatory response, during symptom-limited exercise testing conducted by the Naughton protocol in heart failure patients, over a 1.5-year follow-up period.[39] Ventilatory response and chronotropic response were more powerful independent predictors of cardiovascular death than peak VO_2 in their study. In a study with heart failure patients by Arena, *et al*, HR recovery and VE/VCO_2 slope during symptom-limited exercise testing according to the treadmill Ramp protocol were both predictive of prognosis over a 1-year follow-up period.[40] Nanas, *et al* noted that HR recovery in heart failure patients was a better predictor than peak VO_2 or ventilatory response during symptom-limited exercise testing according to the Bruce or modified Naughton protocol, over a 2-year follow-up period.[41]

These three studies concluded that HR profiles were comparable or superior to CPX as predictors of prognosis. Though HR profiles can easily be assessed as valuable markers in clinical practice, the HR profiles in our study were not superior to peak VO_2 or VE/VCO_2 slope. The discrepancy between these earlier results and our own study might be attributable to the observation period or exercise protocol. While CPX parameters closely reflect cardiac function and peripheral function, HR profiles are more closely related to cardiac function, vagal tone, and autonomic imbalance. Peak VO_2 is derived from the Fick equation, as follows: VO_2 = cardiac output x arterial-mixed venous O_2 content difference ((C (a-v) O_2) diff). Cardiac output equals heart rate times stroke volume. This equation implies that HR can be treated as a determinant of VO_2. If this is so, CPX parameters might be superior to HR profiles.

Limitations: CPX parameters are known to integrate cardiac function and lung function with oxygen delivery and use in exercising muscles. Although the prognostic power of the parameters may at least partly depend on the etiology and severity of heart disease, there were too few subjects in the present study to bring out any disease-specific characteristics of the prognostic parameters individually.

In general, many studies have failed to show a significant link between exercise capacity (peak VO_2) and LVEF in patients with chronic heart failure,[42] and it has been reported that peak VO_2 is superior to LVEF as a prognostic predictor. However, in this study population, because averaged LVEF was about 60% and several patients with preserved LVEF were included, it seemed that

LVEF was the strongest prognostic parameter.

β-Blockers have been found to improve the survival of heart failure patients in several studies. Yet β-blockers reduce resting and peak HR. The equipoise on the effect of β-blockers on HR is unresolved.[43,44] A small number of patients included in our study (37.7%) received β-blocker treatment during the study period. There was no difference between the numbers of nonsurvivors and survivors who received β-blockers. In univariate Cox proportional analyses, β-blocker use had no significance as a predictor of prognosis in earlier studies. β-Blocker use also lacked prognostic significance in our study.

Conclusions: Although heart rate profiles during exercise testing are easy to perform and useful as prognostic predictors in patients with cardiac disease, they are not superior to respiratory gas analysis.

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Demographics and Changes in Medical/Interventional Treatment of Coronary Artery Disease Patients Over a 3.5-Year Period in Japan

— The Japanese Coronary Artery Disease Study: Trend Examination —

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Background Cardiovascular medicine has undergone rapid changes in recent years, but there are insufficient reports using large cohorts regarding these changes for Japanese coronary artery disease (CAD) patients. Hence, a large-scale prospective observational study was needed.

Methods and Results A total of 36,298 patients were registered over 6 periods. Patients with hypertension, hyperlipidemia, obesity, and impaired glucose tolerance increased in number, while those with old myocardial infarction (MI), smoking habit, and family history of CAD decreased. Regarding the trends in interventional procedures, stent use increased in both the whole cohort and the acute MI subgroup, while the use of only medical control decreased. Regarding prescription trends, angiotensin-receptor blockers increased while nitrates decreased.

Conclusions In a period of 3.5 years, significant changes were observed for both interventional procedures and medication, which might be related to the well-timed compliance of physicians with published evidence. However, these changes were not related to changes in the event rates, at least over the short term. Although careful attention should be paid in interpreting the results, because this is an observational study and the background of patients in each cohort might have been heterogeneous, such investigations should be constantly conducted for evidence-based practice. (*Circ J* 2008; **72:** 1397–1402)

Key Words: Coronary artery disease; Evidence-based practice; Medicine; Percutaneous intervention; Trends

Among the vascular-related diseases in Japanese, cerebrovascular diseases have demonstrated a constant decline[1,2] partly because of the decrease in sodium intake[3] and the resultant decrease in blood pressure.[4] However, cardiovascular diseases in Japanese have not decreased substantially over several decades[5] so they are of relatively greater clinical concern. In general, interventional cardiology has progressed rapidly over the past decades[6,7] and ample scientific evidence with regard to the appropriate medication to be administered in various situations has also accumulated. This evidence has been generated through a number of clinical researches, and many clinical guidelines are based on these studies; however, there are insufficient reports regarding the actual practice of cardiovascular medicine in Japan, which prompted us to conduct a large-scale observational study with patients suffering from significant coronary artery disease (CAD, Japanese coronary artery disease (JCAD) study).[8] The JCAD study has 2 arms: a follow-up arm and a trend-only arm. We previously reported the results of the follow-up arm, in which patients were followed-up for a mean of 2.7 years.[9]

In order to elucidate the changes in medication or interventional procedures in Japanese cardiology practice, as well as the angiographic findings in JCAD patients, we analyzed the data of the trend-only group, together with that of the follow-up group, at the time of registration.

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Methods

Patients

The protocol of this study has been published elsewhere.[8] Briefly, consecutive patients who underwent coronary angiography (CAG) and who were diagnosed as having 75% or higher stenosis, based on the classification of the American Heart Association (AHA),[10] in at least 1 branch of a coronary artery were registered for the study. All CAG were performed after obtaining written informed consent from the patients. Patients in the first cohort were enrolled from April 2000 until March 2001. Initially, 15,628 patients were registered and 13,812 of them were followed up. Subsequently, consecutive patients were enrolled every 6 months over 5 periods until September 2003; 22,486 patients were registered with complete initial data, and 18,641 of them were followed up.

Table 1 Background Characteristics of Patients at the Time of Registration

Drugs	T1 (n=15,628)	T2 (n=5,277)	T3 (n=4,554)	T4 (n=3,738)	T5 (n=3,664)	T6 (n=3,437)	p value
No. of males and age							
Male	11,979 (76.7%)	4,058 (76.9%)	3,409 (74.9%)	2,834 (75.8%)	2,816 (76.9%)	2,660 (77.4%)	0.891
Age (years)	65.6±9.8	65.9±9.9	66.0±9.8	66.1±10.0	66.5±10.1	66.6±10.0	<0.001
Diagnosis at the time of registration							
AMI	3,274 (20.9%)	1,092 (20.7%)	1,061 (23.3%)	783 (20.9%)	831 (22.7%)	718 (20.9%)	0.145
Old myocardial infarction	4,399 (28.1%)	1,485 (28.1%)	1,194 (26.2%)	992 (26.5%)	877 (23.9%)	885 (25.7%)	<0.001
Unstable AP	2,330 (14.9%)	751 (14.2%)	673 (14.8%)	600 (16.1%)	605 (16.5%)	507 (14.8%)	0.089
Stable AP	4,530 (29.0%)	1,586 (30.1%)	1,312 (28.8%)	1,088 (29.1%)	1,103 (30.1%)	1,036 (30.1%)	0.176
Other	1,095 (7.0%)	363 (6.9%)	314 (6.9%)	275 (7.4%)	248 (6.8%)	291 (8.5%)	0.046
Risk factors							
Hyperlipidemia	8,462 (54.1%)	2,892 (54.8%)	2,506 (55.0%)	2,099 (56.2%)	2,131 (58.2%)	2,021 (58.8%)	<0.001
IGT	6,262 (40.1%)	2,011 (38.1%)	1,789 (39.3%)	1,542 (41.3%)	1,517 (41.4%)	1,531 (44.5%)	<0.001
Hypertension	8,994 (57.6%)	3,064 (58.1%)	2,789 (61.2%)	2,281 (61.0%)	2,306 (62.9%)	2,191 (63.7%)	<0.001
Obesity	5,081 (32.5%)	1,744 (33.0%)	1,579 (34.7%)	1,290 (34.5%)	1,259 (34.4%)	1,143 (33.3%)	0.015
Smoking	6,075 (38.9%)	2,029 (38.4%)	1,645 (36.1%)	1,325 (35.4%)	1,316 (35.9%)	1,273 (37.0%)	<0.001
Family history of CAD	2,563 (16.4%)	748 (14.2%)	758 (16.6%)	560 (15.0%)	542 (14.8%)	449 (13.1%)	<0.001

T1 to T6, 6 cohorts in chronological order.
P value for age was calculated using the Kruskal-Wallis test. All other p values for trend were calculated using the Cochran-Armitage test.
AMI, acute myocardial infarction; AP, angina pectoris; IGT, impaired glucose tolerance; CAD, coronary artery disease.

Data Registration and Accumulation

All data were registered electronically as described previously[8,11] Briefly, a central database server was set up and the clinical information was transmitted to a central computer through a Web-based interface. Diagnosis of CAD at the time of registration was made by the attending physician based on the information provided in a manual that was distributed prior to the start of the study. The trade names and dosages of all the drugs that the patients were taking were registered by the attending physician. Medication data at the time of discharge was considered in the present analysis. The definition of each risk factor was as follows: hyperlipidemia=serum total cholesterol ≥220 mg/dl and/or low-density lipoprotein-cholesterol ≥140 mg/dl and/or triglyceride ≥150 mg/dl; impaired glucose tolerance (IGT), including diabetes mellitus=fasting blood glucose ≥110 mg/dl; hypertension=systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg; obesity=body mass index ≥25 kg/m^2; smoking=at least one episode of smoking in the 2 years before registration; familial history=CAD in any first-degree relative. These data were obtained from each patient by the attending physician. Careful attention was paid to data security.

Angiographic Findings

According to the AHA classification, coronary arteries were classified into 15 segments. When at least 1 segment of an artery (right coronary artery: segments #1–#4; left main trunk (LMT): segment #5; left anterior descending artery (LAD): segments #6–#10; and left circumflex artery: segments #11–#15) had 75% or more stenosis or occlusion, it was classified as diseased. Data were analyzed only for patients with no history of interventional procedures, because previously corrected arteries that did not demonstrate significant restenosis were not registered as diseased. These patients were termed 'de novo' patients.

Investigations

The endpoint was a composite of all-cause death and cardiovascular events and was defined as the occurrence of fatal or nonfatal myocardial infarction (MI), fatal or nonfatal strokes, other cardiovascular events, and death from any cause as the first event. All events were evaluated and registered by the attending physicians. Percutaneous coronary intervention performed against restenosis without clinical symptoms was explicitly excluded as an event.

Ethical Considerations

The institutional review board of each participating institution reviewed and approved the study protocol and other documents. Further, each attending physician explained the study to each candidate patient, who provided voluntary written informed consent prior to enrollment.

Statistical Analysis

Absolute numbers and percentages were computed to describe the patient population. The Kruskal-Wallis test was used to analyze the differences among cohorts with regard to continuous numbers. The Cochran-Armitage test was used to analyze trends over time. P values <0.05 were considered significant. All p values were the result of 2-tailed tests. Statistical analysis was performed using SAS version 9.1 (SAS Institute Inc, Cary, NC, USA).

Results

Background Characteristics

The background characteristics of the patients are shown in Table 1. Statistically significant increasing trends were observed for the risk factors hyperlipidemia, IGT, hypertension, and obesity. Significant decreasing trends were observed for old MI (OMI), smoking habit, and family history of CAD.

Angiographic Findings

Table 2 shows the trend in the angiographic findings for patients without prior coronary intervention. No trend of increase or decrease was observed with regard to the site of stenosis or occlusion in the coronary arteries. When examining for single-vessel disease, the LAD artery was the most frequently detected as diseased; 59.4% of the total de novo patients in this study cohort had a diseased LAD (Table 3). LMT involvement was calculated to be 7.6% (n=755).