[研究論文] Echocardiographically Measured Ejection Fraction Still is a Strong Prognostic Tool in Patients with Coronary Heart Disease: a Long-term Retrospective Cohort Study

-- Ejection Fraction as a Prognosticator--

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Abstract

Background: Echocardiographically determined left ventricular ejection fraction (LVEF) is a prognosticator of coronary artery disease (CAD). However, few studies have shown the superiority of LVEF to cineangiographic or cardiopulmonary exercise measurements as a long-term prognostic tool of CAD.
Methods and Results: We retrospectively followed up 204 consecutive patients with CAD. All underwent echocardiography, cineangiography, and cardiopulmonary exercise testing. There were 18 and 54 cardiac deaths during the first five-year and the entire 20-year follow-up period, respectively. Univariate Cox proportional regression analyses revealed that at 5 years from entry, the number of diseased vessels, LVEF, peak oxygen uptake (peak VO2), and the oxygen uptake efficiency slope (OUES), whilst at 20 years, age at entry, diagnosis (myocardial infarction), number of diseased vessels, LVEF, peak VO2, OUES, and the VE/VCO2 regression slope were proved to be significant prognosticators. However, multivariate Cox regression model revealed that only LVEF and OUES, and LVEF and peak VO2 were independent prognosticators after 5 years and 20 years, respectively.
Conclusion: Echocardiographically measured LVEF still is the most valid tool in evaluating long-term prognosis of patients with CAD.

Keywords: echocardiography, coronary artery disease, exercise testing, prognosis

1. INTRODUCTION

Coronary artery disease (CAD) is one of the leading causes of death in industrialized countries[1)]. Therefore, predicting the prognosis of patients with CAD and early treatment for high risk patients are essential. Several methods have been utilized to identify the prognosis of CAD. Left ventricular ejection fraction (LVEF) measured by M-mode echocardiogram or cineangiogram is one of the oldest prognosticators of patients with chronic heart failure[2-8)]. However, the information on the prognostic value of LVEF among patients with CAD irrespective of having heart failure is limited. The number of diseased vessels measured by cineangiogram is also known to affect the outcome of CAD[9-12)]. However, the long-term prognostic value of the measurement in CAD populations still remains to be elucidated. Measurements of cardiopulmonary exercise testing including peak oxygen uptake (peak VO2) [13-15)], the slope of the minute ventilation-carbon dioxide output relationship during incremental exercise (VE/VCO2 slope) [16-20)], and the oxygen uptake efficiency slope (OUES) [21-23)] are popular methods for evaluating the prognosis of patients with chronic heart failure. However, little is known as to the prognostic value of these measurements in CAD populations with various levels of exercise tolerance.

Therefore, the aim of the present study was to elucidate the long-term (20years) prognostic value of these measurements in Japanese patients with CAD irrespective of having chronic heart failure

2. MATERIALS AND METHODS

2.1 Study patients

We retrospectively studied 225 consecutive patients with IHD (defined by a presence of significant coronary stenosis≧75% reduction in luminal diameter) who had been sent to our exercise testing laboratory between August 1983 and February 1985. Patients with unstable angina, myocardial infarction within the last month, documented lung diseases, patients who could not walk on the treadmill, were excluded from the study.

Data on mortality were determined in May 2006 by examining medical records and/or conducting telephone interviews with the patients or their families. Data on 7 patients were missing because of changes in residence. Fourteen patients died of noncardiovascular-related diseases during the follow-up period. After excluding these 21 patients, data on the remaining 204 patients were used for analyses. The characteristics of the study subjects were listed in Table 1.

All were on medications that included digoxin, diuretics, isosorbide dinitrate, calcium channel blockers, ß-blockers, which were not discontinued prior to exercise testing. The investigation was approved by the Local Ethics Committee and therefore conformed with the principles outlined in the Declaration of Helsinki.

2.2 Treadmill exercise testing

Exercise tests were performed using a Marquette Case 2 computerized treadmill system (Marquette Electronics, Milwaukee, WI) according to a symptom-limited original or modified Bruce protocol.

The 12-lead electrocardiogram and heart rate were monitored throughout the test. Cuff blood pressure was measured every minute with a manual manometer. Subjects were encouraged to continue the exercise until they perceived exhaustion. A supervising physician could stop the exercise testing on the following criteria: (1) development of a significant symptom, such as chest pain or dizziness; (2) marked systolic hypotension or hypertension (more than 250/120 mmHg or a decrease in systolic BP or heart rate in spite of increasing workload); (3) development of dangerous or potentially dangerous arrhythmias; or (4) ST-segment deviation (horizontal or downsloping depression > 80 ms from the J point) or elevation in non-Q wave leads of > 0.1 mV. We considered that an exercise test had reached maximum when at least two of the following three conditions were satisfied: 1) volitional exhaustion, 2) reaching predicted maximal heart rate (220-age), or 3) a respiratory exchange ratio (RER) >1.0.

2.3 Analysis of Expired Gas

Carbon dioxide production (VCO2, [ml/min, STPD]), oxygen uptake (VO2 [ml/min, STPD]), minute ventilation (VE [l/min, BTPS]), were measured continuously on a mixing chamber basis every 30s using a respiratory gas analyzer (System-5, AIC, Tokyo, Japan) equipped with Fleish pneumotachometer, a polarograph type oxygen sensor (RAS-31) and an infrared sensor for carbon dioxide detection (RAS-41). The flow, oxygen and carbon dioxide sensors were calibrated before each test.

The peak VO2 was calculated for each subject by averaging values obtained during the final 60 seconds of exercise. The RER was calculated at the same time point as peak VO2.

The VE/VCO2 slope was obtained by linear regression analyses of the relation between VE and VCO2 during the exercise test. The following equation was used to determine the relation between VO2 (ml/min/kg) and VE (l/min/kg) during an incremental exercise test:

$VO2 = a \times \log VE + b$

where the constant a was defined as the OUES[24).

2.4 Coronary Cineangiography

Cornary cineangiography was performed within a week after the treadmill exercise testing. The diagnosis of coronary artery diseases were made by a presence of significant coronary stenosis defined ≧75% reduction in luminal diameter.

2.5 Echocardiography

Echocardiography was performed within a week after the treadmill exercise testing using Toshiba SSH-160A. Resting left ventricular ejection fraction (LVEF) was measured by the Teichholz's method.

2.6 Statistical analysis

Data were presented as the mean ± SD. Intergroup differences for variables were compared with the unpaired t test or $\chi 2$ analysis, when appropriate. The prognostics value of the OUES and other clinical variables were assessed by the univariate and multivariate Cox proportional hazard regression model with potential confounders including age, sex, body mass index, diagnosis (angina pectoris or myocardial infarction), intervention (coronary artery bypass surgery or percutaneous coronary intervention), number of diseased vessels, peak VO2, OUES, VE/VCO2 slope, and LVEF. The patients were divided into 2 groups according to median value of the peak VO2, OUES, VE/VCO2 slope, and LVEF for the univariate analyses. A p value less than 0.05 was considered statistically significant. All analyses were performed using commercially available statistical software (StatView J-4.5, Abacus Concept, Tokyo Japan).

3. RESULTS

Among the 204 study subjects, there were 18 and 54 cardiac deaths during the first five-year and the entire 20-year follow-up period, respectively. Characteristics of the study subjects, as well as the comparisons between survivors and non-survivors are listed in Table 1. Results of univariate Cox proportional hazard regression analyses at 5 and 20 years are listed in Table 2. At 5 years from entry, the number of diseased vessels, LVEF, peak VO2, and OUES, whilst at 20 years, age, diagnosis (myocardial infarction), number of diseased vessels, LVEF, peak VO2, OUES, and VE/VCO2 slope were proved to be significant prognosticators (Table 2). However, multivariate model revealed that only LVEF and OUES were significantly related with prognosis after 5 years, whilst LVEF and peak VO2 were significant prognosticators at 20 years (Tables 3 and 4).

4. DISCUSSION

The present study has revealed that echocardiographically measured LVEF still is the most valid tool in evaluating long-term prognosis of patients with CAD. It is of interest considering that it is one of the oldest and simplest methods to obtain in the era of cineangiography and cardiopulmonary exercise testing.

Although not the sole determinant of the prognosis of CAD, LVEF has been considered to be a prognostic tool of CAD: a reduced LVEF is known to be related with poor outcome of chronic heart failure and increased risk of sudden cardiac death[2-8]. However, very few studies have shown the superiority of LVEF to cineangiographic or cardiopulmonary exercise measurements as a prognostic tool of CAD. To our knowledge, the present study is the first one that deals with this issue.

The extent of coronary artery disease, i.e. the number of diseased vessels determined by coronary cineangiogram has been demonstrated to be useful as a short- or medium-term prognostic tool of CAD[9-12].However, its long-term ability of prognostication has not been established. Results of the present study show the limitation of the measurement as a long-term prognostic tool of CAD, as the multivariate Cox proportional regression model did not prove it to be a significant prognosticator. This would be a great problem, as it is an invasive test and is not suitable for repeated measurements.

The prognostic usefulness of cardiopulmonary exercise testing in patients with chronic heart failure has been well established and widely used. Peak VO2 is the gold standard of exericise tolerance[13-15]. The VE/VCO2 slope has been used to estimate the prognosis of chronic heart failure[21-23]. OUES is a relatively new index of exercise tolerance[25-34] and is a prognostic tool for chronic heart failure[21-23]. However, patients with CAD show various degrees of exercise tolerance from severely limited daily activities to normal exercise tolerance. Very few studies have been published using populations with such heterogeneous exercise tolerance to elucidate the prognosis of patients with CAD. In the present study, only OUES and peak VO2 are adopted as independent prognostic tools of CAD at 5 years and 20 years, respectively. This may be accounted for by the fact that the measurements of cardiopulmonary exercise testing can only explain mortalities caused by heart failure, not by arrhythmias.

The present study revealed that the LVEF, an old, non-invasive and the simplest method still is the most powerful prognostic tool of CAD. Of course, the authors admit that there are several shortcomings in the LVEF. Its prognostic usefulness is limited in patients with heart failure who have preserved left ventricular systolic function3,4 or in the very elderly[3].However, its measurements are very easy to obtain and can be measured repeatedly. Combining other more elaborate indices would enable more precise prognostic information.

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Table 1. Characteristics of the study subjects

	Total	5years			20years		
	(n=204)	Survivors (n=186)	Nonsurvivors (n=18)	p value	Survivors (n=150)	Nonsurvivors (n=54)	p value
Age (yr)	54.8±7.7	54.6±7.6	56.9±9.1	0.23	54.3±7.4	56.6±8.1	0.06
Male/Female	180/24	163/23	17/1	0.39	129/21	Mar-51	0.17
BMI	23.3±2.5	23.3±2.4	23.6±3.9	0.47	23.0±2.8	23.4±2.4	0.35
Diagnosis (AP/MI)	80/124	74/112	6/12	0.61	69/81	11/43	$<$0.001
No. of diseased vessels	1.8±0.8	1.7±0.8	2.3±0.8	0.003	1.7±0.8	2.1±0.9	0.003
PCI/CABG/N	20/80/104	18/74/94	2002/6/10	0.64	16/60/74	4/20/30	0.33
LVEF (%)	59.5±13.1	60.7±12.5	47.0±12.5	$<$0.001	63.0±11.4	49.9±12.8	$<$0.001
LVEF$<$40% (%)	6.8	4.8	27.7	$<$0.001	1.3	20.4	$<$0.001
peak VO_2 (ml/kg/min)	22.0±7.9	22.7±7.7	15.0±5.3	$<$0.001	23.5±7.8	17.8±6.5	$<$0.001
OUES	33.8±7.8	34.6±7.5	26.6±8.3	$<$0.001	34.9±7.5	30.9±8.2	0.001
VE/VCO_2 slope	31.1±6.3	31.1±6.1	31.8±8.3	0.65	30.9±6.3	31.9±6.4	0.32
Smoking (%)	45.1	44.1	55.6	0.35	42.7	51.9	0.24
Hypertension (%)	54.9	54.8	55.6	0.95	52	63	0.17
Hyperlipidemia (%)	22.5	22	27.8	0.58	22	24.1	0.75
Diabetes mellitus (%)	10.3	9.7	16.7	0.35	8.7	14.8	0.2
Digitalis (%)	15.7	14.1	33.3	0.03	14	22.2	0.16
β blocker (%)	11.3	10.8	16.7	0.45	11.3	11.1	0.96

Numerical data are expressed as mean±SD.
Abbreviations: AP=angina pectoris; CABG=coronary arterial bypass graft;
BMI=body mass index; LVEF=left ventricular ejection fraction; MI=myocardial infarction;
N=normal; OUES=oxygen uptake efficiency slope; PCI=percutaneous coronary intervention;
VE/VCO_2 slope=the regression slope of minute ventilation-carbon dioxide production; VO_2=oxygen uptake.

Table 2. Univariate Cox proportional Hazard Regression Analysis at 5 and 20 years.

	5 years		20 years	
	$\chi 2$	p value	$\chi 2$	p value
Age	2.43	0.119	5.34	0.021
Sex (Male)	0.01	0.915	2.08	0.15
BMI (≧23.1)	1.94	0.164	2.05	0.153
Diagnosis (AP)	2.68	0.102	11.74	0.001
No. of diseased vessels	10.3	<0.001	18.97	<0.001
Treatment (PCI)	0.07	0.786	0.69	0.406
(CABG)	0.08	0.771	0.22	0.637
LVEF (<60%)	21.63	<0.001	52.82	<0.001
Peak VO_2 (<21.6ml/kg/min))	15.54	<0.001	35.68	<0.001
OUES (<34/kg)	22.23	<0.001	24.33	<0.001
VE/VCO_2 slope (≧30.2)	0.76	0.384	4.36	0.037

Abbreviations:
CABG=coronary arterial bypass graft; BMI=body mass index;
LVEF=left ventricular ejection fraction; MI=myocardial infarction; OUES=oxygen uptake efficiency slope;
PCI=percutaneous coronary intervention;
VE/VCO_2 slope=the regression slope of minute ventilation-carbon dioxide production;
VO_2=oxygen uptake.

Table 3. Multivariate Cox Proportional Hazard Regression Analysis at 5 years

	Regression coefficient	Standard error	Hazard Ratio (95% CI)	p value
Age	-0.007	0.038	0.993 (0.921-1.070)	0.848
Sex (Male)	-0.215	0.791	0.807 (0.171-3.804)	0.786
BMI	0.141	0.083	1.151 (0.978-1.355)	0.091
Diagnosis (AP)	0.152	0.64	1.164 (0.332-4.081)	0.813
No. of diseased vessels	0.407	0.444	1.502 (0.629-3.585)	0.36
Treatment (PCI)	1.315	0.926	3.724 (0.606-22.86)	0.156
(CABG)	0.662	0.686	1.939 (0.505-7.438)	0.334
LVEF	-0.057	0.028	0.945 (0.894-0.998)	0.044
Peak VO_2	-0.099	0.058	0.906 (0.808-1.015)	0.09
OUES	-0.149	0.051	0.861 (0.779-0.953)	0.004
VE/VCO_2 slope	-0.082	0.042	0.921 (0.848-1.001)	0.053

Abbreviations:
CABG=coronary arterial bypass graft; BMI=body mass index;
LVEF=left ventricular ejection fraction; MI=myocardial infarction;
OUES=oxygen uptake efficiency slope; PCI=percutaneous coronary intervention;
VE/VCO_2 slope=the regression slope of minute ventilation-carbon dioxide production;
VO_2=oxygen uptake.

Table 4. Multivariate Cox Proportional Hazard Regression Analysis at 20 years

	Regression coefficient	Standard error	Hazard Ratio (95% CI)	p value
Age	-0.001	0.022	0.999 (0.957-1.043)	0.965
Sex (Male)	0.654	0.617	1.923 (0.574-6.449)	0.289
BMI	-0.054	0.068	0.948 (0.830-1.082)	0.428
Diagnosis (MI)	-0.311	0.372	0.733 (0.353-1.520)	0.404
No. of diseased vessels	0.141	0.205	1.151 (0.771-1.720)	0.491
Treatment (PCI)	0.185	0.632	1.203 (0.348-4.156)	0.77
(CABG)	0.04	0.333	1.040 (0.542-1.997)	0.905
LVEF	-0.046	0.014	0.955 (0.930-0.981)	0.001
peak VO_2	-0.08	0.027	0.924 (0.875-0.974)	0.004
OUES	-0.043	0.028	0.958 (0.907-1.012)	0.127
VE/VCO_2 slope	-0.014	0.025	0.986 (0.940-1.035)	0.579

Abbreviations:
CABG=coronary arterial bypass graft; BMI=body mass index;
LVEF=left ventricular ejection fraction; MI=myocardial infarction;
OUES=oxygen uptake efficiency slope; PCI=percutaneous coronary intervention;
VE/VCO_2 slope=the regression slope of minute ventilation-carbon dioxide production;
VO_2=oxygen uptake.