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Prognostic Value of Heart Rate Reserve in Exercise Treadmill Test after Coronary Revascularization

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Abstract

Objective: The aim of this study was to assess heart rate (HR) responses to exercise in the prediction of the major adverse cardiovascular events (MACE) in patients with revascularization.

Methods: We retrospectively analyzed 253 patients with successful revascularization and exercise treadmill test (ETT) 4 months later in asymptomatic status. MACE was defined as cardiac death, nonfatal myocardial infarction and revascularization. HR reserve as index of chronotropic response was calculated as (peak HR-baseline HR) ×100/(220-age-baseline HR). Impaired HR reserve was defined as achievement of <80% in patients without beta-blockers (BB) and <62% in patients with BB. HR recovery at 1minute (HRR 1min) was calculated as peak HR–HR at recovery 1minute. Impaired HRR 1min was defined as a decrease of ≤12bpm.

Results: HRR 1min and HR reserve were significantly lower in MACE group. In multivariate analysis, HRR 1min and HR reserve were independent predictors for the MACE. The odds ratios (OR) for the MACE in impaired HRR 1min was 4.7 with adjustment. In addition, the OR for the MACE in impaired HR reserve was 4.4 with adjustment. Moreover, the OR for the MACE in patients with both impaired HRR 1min and impaired HR reserve was 7.5 with adjustment.

Conclusions: Impaired HRR 1min and HR reserve to exercise could be associated with the MACE in the asymptomatic patients with successful revascularization.

Introduction

Percutaneous coronary intervention (PCI) for coronary revascularization is ecumenically performed to treat patients with coronary artery disease (CAD). However, major cardiac adverse event (MACE) in CAD has been reported at about 10% even though successful PCI with drug eluting stent (DES) [1]. There were several studies on prediction for the MACE after successful PCI. However, the studies about non-invasive tests have not been complete yet [2,3].

Exercise treadmill test (ETT) as representative test of a non-invasive test has provided a variety of prognostic information, including symptom assessment, functional capacity, and hemodynamic responses to exercise. To assist with clinical interpretation of the ETT, the Duke Treadmill Score (DTS) was developed [4,5]. However, the DTS fails to incorporate other important data from the ETT. Recent studies have demonstrated that impaired HR responses in the ETT were related to unfavourable prognosis in patient follow-up [6-9]. Vivekananthan et al. reported the relationship between impaired HR responses and higher atherosclerotic burden in patients referred for suspected CAD [7]. Furthermore, impaired HR responses might be associated with several risk factors for atherosclerosis [8].

The aim of this study was to evaluate the HR reserve in the ETT as a predictor of the MACE in patient underwent the PCI, by focusing on the correlation between HR responses and various parameters.

Materials and Methods

The study was approved by the institutional review board of Daegu Catholic University Medical Center (Daegu, Korea). From January 2008 to December 2013, we enrolled 253 asymptomatic patients to perform successful PCI with DES, ETT 4 month after PCI, and clinical follow-up more than 1 year at our center. Exclusion criteria included: 1) patients with angina symptom after successful PCI; 2) patients with contraindications to or an inability to perform the ETT because of an extracardiac condition; 3) congestive heart failure NYHA grade III/IV; 4) significant mitral and aortic valve disease; 5) pre-excitation; 6) Brady arrhythmias; 7) bundle branch block; 8) pacemaker placement.

Ethical approval

Ethical approval for our study was obtained from the Daegu Catholic University Medical Center Institutional Review Board and the study has been conducted according to the principles expressed in the Declaration of Helsinki. This consent procedure was approved by the ethic committee.

Echocardiography and coronary angiography

The patients underwent two-dimensional and M-mode echocardiography. Conventional Doppler echocardiography and tissue Doppler imaging (TDI) data were also obtained from all patients. Doppler echocardiographic and TDI recordings were measured during normal respiration. All measurements were performed by two independent experienced investigators (senior echocardiographer and attending cardiologist) who were blinded to the clinical data. Inter-observer variability was calculated as the difference between values obtained by the two independent investigators divided by the mean (coefficient: 0.97). To assess intra-observer variability, all measurements were repeated by one observer on the same day (coefficient: 0.98).

Coronary angiographic data were obtained at the time of index PCI and included the number of vessels stenosed, the vessels that were subjected to PCI, characteristics of the lesions, diameter and length of DES, and generation of DES. In generation of DES, first generation DES was included sirolimus or paclitaxel eluting stent, and second generation DES was included everolimus or zotarolimus or biolimus eluting stent. Quantitative coronary angiography was used to assess the severity of stenosis before and after PCI. Procedural success was defined as residual stenosis <50% without a major clinical event (thrombus, side branch occlusion, or distal embolization).

Exercise treadmill test (ETT)

About 4 months after PCI, the patients in asymptomatic status underwent symptom-limited ETT using modified Bruce protocols. To record HR recovery, after achievement of peak exercise, all patients sat immediately on stopping exercise, and recorded HR at recovery 1minute after 1minute on stopping exercise. During each exercise stage, peak stage and recovery stage, symptoms, BP, HR, electrocardiogram (ECG) and metabolic equivalents (METs) were recorded. A 12-lead ECG was obtained every minute, and a 3-lead ECG was monitored continuously [10]. Exercise capacity in METs was estimated using standard tables [11]. The reasons for termination of the ETT, including dyspnea, fatigue, chest pain, ischemic ST changes, marked elevation in BP, or ventricular ectopy, were recorded. Achieving target HR alone was not used as a justification for terminating the ETT. Inadequate ETT of the patients who had not reached the reference standards established for age, sex, and weight were excluded from the analysis [10]. The DTS of the ETT was calculated using the following formula: Time (minutes) – 5 x (ST-segment depression mm) – 4 x (chest pain: 0 = no pain/ 1 = non-limiting pain/ 2 = limiting pain). The DTS was set as: low-risk DTS ≥ +5; intermediate-risk DTS between +4 to -10 and high-risk DTS ≤ -11. HR responses in ETT were included HR recovery (HRR) and HR reserve as index of chronotropic response. HRR 1min was defined as HRR at recovery 1minute, calculated as peak HR – HR at recovery 1minute. HR reserve was calculated as (peak HR - baseline HR) x 100/ (220–age-baseline HR).

Impaired HRR 1min was defined as a decrease of ≤12bpm from peak HR at recovery 1minute [12]. Impaired HR reserve was defined as achievement of <80% of a patient's HR reserve. Because BB medication can alter HR reserve, and previous studies have indicated that achieving <62% of HR reserve was predictive of the adverse events among patients taking BB [13].

Major cardiac adverse events (MACE)

Clinical follow-up was obtained via review of electronic medical records and telephone contact by a dedicated physician or research nurse. The primary end-point was the occurrence of the MACE, defined as cardiac death, nonfatal myocardial infarction (MI), revascularization in target lesion and/or new lesion. Cardiac death defined as death caused by acute MI, ventricular arrhythmias, or refractory heart failure. Nonfatal MI defined as typical chest pain with elevated cardiac enzyme levels and typical ST-segment changes on the ECG.

Revascularization in target lesion was defined as diameter stenosis of <50% at follow-up. Revascularization in new lesion was defined as significant diameter stenosis of >50% at follow-up without diameter stenosis at initial PCI.

Statistical analysis

All statistical analyses were conducted using the SPSS package for Windows version 17.0 (SPSS Inc., Chicago, IL, USA). The levels of normally distributed continuous variables were expressed as mean ± standard deviation. Differences in frequencies were analyzed using chi-square test. Differences in continuous variables between two groups were examined using the independent t-test. Univariate linear relationships between key variables were tested using Pearson's correlation coefficient. Potential independent predictors of outcome were identified using univariate analysis. All univariate predictors were then entered in a stepwise manner into a multivariate model. The best cut-off for predicting the MACE in our study was defined as that yielding the highest sensitivity and specificity in receiver-operating characteristic (ROC) curve. Survival was plotted according to the Kaplan-Meier method, and event rates were compared using log-rank test. P<0.05 was considered statistically significant.

Results

Major cardiac adverse events (MACE)

The mean follow-up duration after the PCI was 25.6±13.5 months. The incidence of the MACE in all patients was 19 (7.5%) patients. The incidence of cardiac death, non-fatal MI, revascularization were 2 (0.8%), 6 (2.4%) and 11 (4.3%) patients, respectively.

Baseline characteristics of patient

The baseline characteristics showed in Table 1. In clinical characteristics, the overall patients had 213 men (84.2%) and 40 women (15.8%) and mean age of 57.1 years. Among them, the incidence of acute coronary syndrome (ACS) was 79.1%. All patients received dual anti-platelet agents after PCI. BB was used in 89.7%, and CCB was used in 17.4%. There were no differences in clinical characteristics including the CAD associated risk factors and medication history between non-MACE group and MACE group. Also, laboratory characteristics like left ventricular ejection fraction (LVEF), renal function and lipid profiles were not different between both groups.

In angiographic characteristics, there were no differences in location and severity of lesion between non-MACE and MACE group. In addition, there were no differences in diameter and length of DES in both groups. However, the proportion of first generation DES was significantly higher in MACE group compared to non-MACE group.

Parameters	All subjects	Non-MACE	MACE	p value
	(n=253)	(n=234, 92.5%)	(n=19, 7.5%)	
Clinical characteristics				
Age (years)	57.1 ± 9.9	57.0 ± 9.8	58.3 ± 11.5	0.607
Male (n, %)	213 (84.2%)	196 (83.6%)	17 (89.5%)	0.746
Hypertension (n, %)	98 (38.7%)	91 (38.9%)	7 (36.8%)	0.86
Diabetes (n, %)	45 (17.8%)	43 (18.4%)	2 (10.5%)	0.308
Smoking (n, %)	76 (30.0%)	69 (29.5%)	7 (36.8%)	0.501
Hyperlipidemia (n, %)	77 (30.6%)	71 (30.5%)	6 (31.6%)	0.92
ACS (n, %)	200 (79.1%)	184 (78.6%)	16 (84.2%)	0.408
AMI (n, %)	150 (59.3%)	138 (59.0%)	12 (63.2%)	0.721
Dual anti-platelet agent (n, %)	253 (100.0%)	234 (100.0%)	19 (100.0%)	1
ACEI or ARB (n, %)	226 (89.3%)	210 (89.7%)	16 (84.2%)	0.33
BB (n, %)	226 (89.3%)	210 (89.7%)	16 (84.2%)	0.33
CCB (n, %)	44 (17.4%)	40 (17.1%)	4 (21.1%)	0.428
Statin (n, %)	194 (77.6%)	179 (77.2%)	15 (83.3%)	0.395
Laboratory characteristics				
LVEF (%)	60.1 ± 8.1	59.5 ± 9.3	60.3 ± 11.0	0.724
Hemoglobin (g/dl)	13.3 ± 1.7	13.3 ± 1.7	13.3 ± 1.9	0.876
eGFR (mL/min/1.73m)	70.5 ± 30.2	70.8 ± 30.4	66.5 ± 27.9	0.554
Fasting glucose (mg/dl)	118.1 ± 60.4	117.3 ± 61.5	126.8 ± 48.0	0.654
Total cholesterol (mg/dl)	179.0 ± 37.3	178.7 ± 37.5	183.2 ± 36.0	0.628
Triglyceride (mg/dl)	143.2 ± 88.3	143.5 ± 91.0	140.4 ± 43.5	0.889
HDL-C (mg/dl)	47.5 ± 13.6	47.8 ± 13.7	43.1 ± 11.3	0.17
LDL-C (mg/dl)	118.2 ± 35.3	117.4 ± 36.1	125.4 ± 26.9	0.367
hs-CRP (mg/L)	3.2 ± 4.2	3.2 ± 4.1	4.0 ± 5.7	0.497
Angiographic characteristics				
Multi-vessel disease (n, %)	101 (40.1%)	91 (39.1%)	10 (52.6%)	0.246
Complex lesion (n, %)	153 (60.5%)	141 (60.3%)	12 (63.2%)	0.91
LM (n, %)	3 (1.2%)	2 (0.9%)	1 (5.3%)	0.21
LAD (n, %)	124 (49.0%)	116 (49.6%)	8 (42.1%)	0.531
LCX (n, %)	56 (22.1%)	51 (21.8%)	5 (26.3%)	0.415
RCA (n, %)	70 (27.7%)	65 (27.8%)	5 (26.3%)	0.891
DES diameter (mm)	3.12 ± 0.46	3.11 ± 0.46	3.24 ± 0.43	0.279
DES length (mm)	26.8 ± 13.9	26.9 ± 13.5	25.4 ± 18.2	0.656
DS after PCI (%)	15.1 ± 7.8	15.0 ± 7.9	15.6 ± 5.9	0.789

First generation DES (n,%)	50 (19.8%)	41 (17.5%)	9 (47.4%)	0.004

Values are n (%) or mean ± SD. MACE: Major Cardiac Adverse Event; ACS: Acute Coronary Syndrome; AMI: Acute Myocardial Infarction; ACEI: Angiotensin Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; BB: Beta Blocker; CCB: Calcium Channel Blocker; LVEF: Left Ventricular Ejection Fraction; eGFR: Estimated Glomerular Filtration Rate; HDL-C: High Density Lipoprotein-Cholesterol; LDL-C: Low Density Lipoprotein-Cholesterol; hs-CRP: high sensitivity C-Reactive Protein; LM: Left Main Coronary Artery; LAD: Left Anterior Descending Coronary artery; LCX: Left Circumflex Coronary Artery; RCA: Right Coronary Artery; DES: Drug Eluting Stent

Table 1: Baseline Characteristics in the Study Patients.

Exercise treadmill test (ETT) of patient

ETT characteristics showed in Table 2. Systolic blood pressure (BP) and diastolic BP at baseline, peak and recovery stage were not different between non-MACE and MACE group. There was no difference in baseline HR between both groups. However, HR in peak stage was significantly lower in MACE group compared to non-MACE group. In addition, HR reserve was significantly lower in MACE group compared to non-MACE group. HR at recovery 1minute was tended to decrease in MACE group. According to decrease of HR at recovery 1minute, HRR 1min was significantly lower in MACE group compared to non-MACE group. There was no difference in exercise capacity and time and DTS between both groups. Most patients were included in low-risk DTS.

Parameters	All subjects (n=190)	Non-MACE (n=171, 90.0%)	MACE (n=19, 10.0%)	P value
Baseline SBP (mmHg)	115.4 ± 18.3	115.5 ± 18.6	113.5 ± 14.3	0.653
Baseline DBP (mmHg)	66.3 ± 12.1	66.5 ± 12.3	64.4 ± 8.6	0.479
SBP at peak stage (mmHg)	163.0 ± 27.3	163.5 ± 27.3	156.6 ± 27.2	0.291
DBP at peak stage (mmHg)	78.2 ± 13.9	78.1 ± 13.8	79.5 ± 14.5	0.675
SBP at recovery 1min (mmHg)	161.2 ± 27.3	161.6 ± 26.7	158.3 ± 32.7	0.096
DBP at recovery 1min (mmHg)	77.2 ± 12.4	77.5 ± 12.0	74.5 ± 15.6	0.6
Baseline HR (bpm)	68.5 ± 12.8	68.8 ± 12.9	65.3 ± 9.4	0.146
HR at peak stage (bpm)	136.9 ± 20.3	138.1 ± 19.7	121.9 ± 21.2	0.001
HR at recovery 1min (bpm)	113.1 ± 18.9	113.5 ± 18.8	107.5 ± 19.4	0.186
HRR 1min (bpm)	23.8 ± 10.4	24.6 ± 10.3	14.4 ± 6.8	<0.001
HR reserve (%)	72.8 ± 18.6	74.0 ± 18.1	58.8 ± 18.2	0.001
Exercise capacity (METs)	9.7 ± 2.3	9.7 ± 2.3	9.7 ± 1.9	0.952
Exercise time (minutes)	14.0 ± 2.2	14.0 ± 2.3	14.2 ± 1.6	0.748
DTS	13.0 ± 3.7	13.1 ± 3.7	12.4 ± 4.1	0.41
- Low risk in DTS	239 (94.5%)	222 (94.9%)	17 (89.5%)	0.283
- Intermediate risk in DTS	14 (5.5%)	12 (5.1%)	2 (10.5%)	

Values are n (%) or mean ± SD. MACE: Major Cardiac Cdverse Event; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HR: Heart Rate; HRR 1min: HR Recovery at 1minute; HR reserve: Heart Rate reserve; DTS: Duke Treadmill Score (low-risk in DTS: ≥ +5, intermediate-risk in DTS: between +4 to -10)

Table 2: ETT Characteristics of Study Population

Prognostic value of HR responses for the MACE

As described earlier, impaired HRR 1min was defined as ≤12bpm and impaired HR reserve was defined as <62% in patients with BB medication and <80% in patients without BB medication. In multivariate analysis for the MACE, impaired HRR 1min and impaired HR reserve were identified as significant and independent predictors for the MACE after adjustment of several factors including age, HR related medication history like BB and CCB, generation of DES (Table 3).

The incidence of MACE according to impaired HRR 1min and HR reserve demonstrated in Table 4. The incidence of cardiac death was significantly higher both impaired HRR 1min. The incidence of non-fatal MI was significantly higher both impaired HRR 1min and HR reserve. However, the incidence of revascularization tended to increase in MACE group. Stratifying the patients by the impaired HRR 1min

and HR reserve, Kaplan-Meier curves showed Figure 1. In Kaplan-Meier curves, impaired HRR 1min and HR reserve showed significant prognostic value for the MACE.

	Uni-variate analysis			Multi-variate analysis		
	OR	95% CI	p value	OR	95% CI	p value
Age > 65 years	1.992	0.747-5.314	0.133	1.117	0.372-3.352	0.844
Female	0.607	0.131-2.735	0.395			
Hypertension	0.917	0.348-2.414	0.86			
Diabetes	0.523	0.116-2.347	0.308			
ACS	1.449	0.406-5.172	0.408			
ACEI or ARB	0.61	0.166-2.244	0.33			
BB	0.61	0.166-2.244	0.33	0.926	0.219-3.918	0.917
CCB	1.293	0.408-4.102	0.428	0.833	0.240-2.894	0.774
LVEF < 50%	0.916	0.196-4.279	0.635			
Intermediate risk in DTS	2.176	0.450-10.526	0.283			
First generation DES	3.654	1.568-8.512	0.004	4.106	1.384-12.182	0.011
HRR 1min ≤ 12bpm	7.775	2.815-21.472	<0.001	4.662	1.506-14.430	0.008
HR reserve < 62%[*]	5.494	1.910-15.801	0.001	4.444	1.450-13.623	0.009

MACE: Major Cardiac Adverse event; OR: Odds Ratio; CI: Confidence Interval; BB: Beta Blocker; LVEF: Left Ventricular Ejection Fraction; DTS: Duke Treadmill Score (intermediate-risk in DTS: between +4 to -10); DES: Drug Eluting Stent; HRR 1min: Heart Rate Recovery at 1minute; HR reserve: Heart Rate Reserve

[*]Stratifying the patients by 62% of HR reserve in patient with beta-blocker and by 80% of HR reserve in patient without beta-blocker

Table 3: Univariate and Multivariate Analysis for the MACE

	HRR 1min	HRR 1min		HR reserve	HR reserve	
	> 12bpm	≤ 12bpm	p value	≥ 62%*	< 62%*	p value
	(n=220, 84.7%)	(n=33, 15.3%)		(n=160, 63.2%)	(n=93, 36.8%)	
Non-MACE (n=234, 92.5%)	208 (94.5%)	26 (78.8%)	<0.001	155 (96.9%)	79 (84.9%)	0.001
MACE (n=19, 7.5%)	12 (5.5%)	7 (21.2%)		5 (3.1%)	14 (15.1%)	
-Cardiac death (n=2, 0.8%)	0 (0.0%)	2 (6.1%)	0.017	0 (0.0%)	2 (2.2%)	0.134
-Non-fatal MI (n=6, 2.4%)	3 (1.4%)	3 (9.1%)	0.031	0 (0.0%)	6 (6.5%)	0.002
-Revascularization (n=11, 4.3%)	9 (4.1%)	2 (6.1%)	0.433	5 (3.1%)	6 (6.5%)	0.175

MACE: Major Cardiac Adverse Event; HRR 1min: Heart Rate Recovery at 1minute; HR reserve: Heart Rate reserve; MI: Myocardial Infarction; OR: Odds Ratio; CI: Confidence Interval

*Stratifying the patients by 62% of HR reserve in patient with beta-blocker and by 80% of HR reserve in patient without beta-blocker

Table 4: Prediction for the MACE according to HRR 1min and HR reserve

Prognostic value of HRR 1min and HR reserve in predicting the MACE

We tried to assess the clinical value of HRR 1min and HR reserve in predicting the MACE. Based on these results, the patients was classified the four group according to presence and absence of the impaired HRR 1min and HR reserve; Group 1 consisted of patients with normal HRR 1min and HR reserve (HRR 1min > 12bpm and HR reserve ≥62%); Group 2 consisted of patients with impaired HRR 1min and normal HR reserve (HRR 1min ≤12bpm and HR reserve ≥62%); Group 3 consisted of patients with normal HRR 1min and impaired HR reserve (HRR 1min > 12bpm and HR reserve<62%); Group 4

consisted of patients with impaired HRR 1min and HR reserve (HRR 1min ≤12bpm and HR reserve <62%). The incidence of MACE according to Group demonstrated in Table 5. The incidence of MACE was significant higher in Group 3 and 4 compared to Group 1. In Group 2 compared to Group 1, the incidence of MACE tended to increase. The incidence of cardiac death and non-fatal MI were significantly higher in Group 4 compared to Group 1. And, the

incidence of revascularization tended to increase in Group 2 and 3 compared to Group 1. Stratifying the patients according to group, Kaplan-Meier curves showed Figure 2. Kaplan-Meier curves in patients with both of impaired HRR 1min and HR reserve showed significant prognostic value for the MACE. Like this, the combined HRR 1min and HR reserve gave us greater information in the prognostic value than either parameter alone.

	Group 1 (n=143, 56.5%)	Group 2 (n=17, 6.7%)	Group 3 (n=77, 30.4%)	Group 4 (n=16, 6.3%)	
Non-MACE (n=234, 92.5%)	140 (97.9%)	15 (88.2%)	68 (88.3%)	11 (68.8%)	
MACE (n=19, 7.5%)	3 (2.1%)	2 (11.8%)	9 (11.7%)†	5 (31.3%)†	
-Cardiac death (n=2, 0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (12.5%)†	
-Non-fatal MI (n=6, 2.4%)	0 (0.0%)	0 (0.0%)	3 (3.9%)†	3 (18.8%)†	
-Revascularization (n=11, 4.3%)	3 (2.1%)	2 (11.8%)	6 (7.8%)	0 (0.0%)	
	Unadjusted			**Adjusted**		
	OR	95% CI	p value	OR	95% CI	p value
Group 1	1.0	-	—	1	—	—
Group 2	2.311	0.473-11.288	0.265			
Group 3	4.103	1.326-12.698	0.012	5.405	1.381-21.155	0.015
Group 4	7.24	2.209-23.730	0.004	7.515	2.156-26.188	0.002

MACE: Major Cardiac Adverse Event; MI: Myocardial Infarction; OR: Odds Ratio; CI: Confidence Interval

*Stratifying the patients by 62% of HR reserve in patient with beta-blocker and by 80% of HR reserve in patient without beta-blocker.

Group 1 indicates HRR 1min > 12 bpm and HR reserve ≥ 62%*; Group 2: HRR 1min ≤ 12 bpm and HR reserve ≥ 62%*; Group 3: HRR 1min > 12 bpm and HR reserve < 62%*; Group 4: HRR 1min ≤ 12 bpm and HR reserve < 62%*. †Significant when compared to Group 1

Table 5: Prediction for the MACE in Groups based on HRR 1min and HR reserve
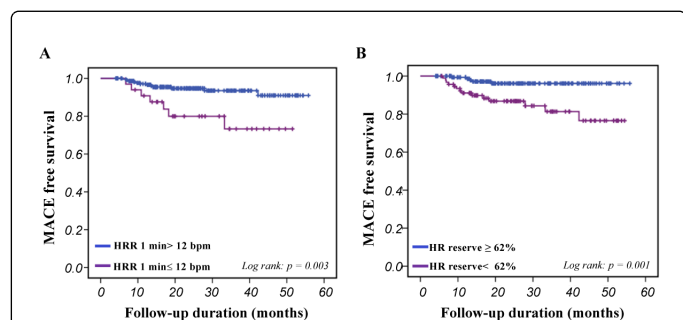
Figure 1: Kaplan-Meier survival curve. Kaplan-Meier survival curve in stratifying the patients by 12 bpm of HRR 1min. (A) Kaplan-Meier survival curve in stratifying the patients by 62%* of HR reserve (B)*Stratifying the patients by 62% of HR reserve in patient with beta-blocker and by 80% of HR reserve in patient without beta-blocker. HRR 1min: Heart Rate Recovery at 1minute; HR reserve: Heart Rate Reserve.
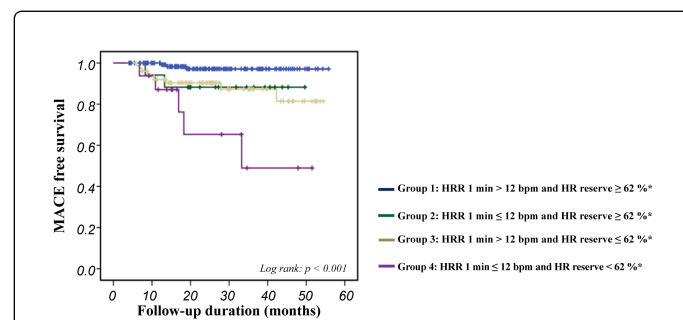
Figure 2: Kaplan-Meier survival curve. Kaplan-Meier survival curve in stratifying the patients by 12 bpm of HRR 1min and 62%* of HR reserve. *Stratifying the patients by 62% of HR reserve in patient with beta-blocker and by 80% of HR reserve in patient without beta-blocker. HRR 1min: Heart Rate Recovery at 1minute; HR reserve: Heart Rate reserve.

Discussion

In our study, we demonstrated a close relationship between the impaired HR responses in the ETT and the MACE in patients with the CAD to perform the PCI. In addition, impaired HRR 1min and HR reserve were identified as independent predictor for the MACE after the PCI. In the prediction of the MACE, the patients with impaired HR reserve or impaired HRR 1min were 4.7-fold or 4.4-fold higher than those with normal HR response after adjustment of several factors, respectively. In addition, the patients with both impaired HR reserve and impaired HRR 1min were 7.5-fold higher than those with normal HR response after adjustment of several factors. On the basis of these results, impaired HRR 1min and impaired HR reserve in ETT could be associated with the MACE in the patients with the CAD to perform the PCI.

Although several prior studies have combined various ETT parameters for the diagnosis and risk classification of the CAD [12], little has known about the relation between the MACE after the PCI and HR responses in ETT. Recent studies found a significant association between impaired HR responses and cardiovascular mortality [9]. However, the studies did not provide the information on the MACE after the PCI. Our study expands on these findings by demonstrating the association between the HR responses in the ETT and the MACE after the PCI. In addition, we provide a clinically useful value of HR reserve and HRR 1min in the ETT for the MACE after the PCI. The results of this study provide important additional insight into the role of HR reserve and HRR 1min for prognosis among the ETT in the patients with the CAD to perform the PCI.

Impaired HR responses in ETT have been demonstrated to independently predict adverse cardiac outcomes [14]. HR responses in ETT were caused by the changes of balance between the sympathetic and parasympathetic nervous systems [15]. Initial HR increase in the ETT was caused by parasympathetic withdrawal, while sympathetic activation was responsible for increased HR above 100bpm. In the cold period to define the first minute following termination of the ETT, the rapid decrease in HR was principally determined by parasympathetic reactivation [16]. The prognostic importance of impaired HR responses by the imbalance between the sympathetic and parasympathetic nervous systems in the ETT has been established [17,18].

HRR 1min appears to measure the capacity of the cardiovascular system to reverse the vagal withdrawal that occurs during exercise [18,19]. Impaired HRR 1min is associated with mortality in asymptomatic patients, patients with undergoing coronary angiography, patients undergoing stress echocardiography, and patients undergoing nuclear perfusion imaging [20]. However, the underlying pathophysiology and mechanism that link these relationships have not yet known [20]. Recent study of asymptomatic patients demonstrated that impaired HRR 1min was a stronger predictor of sudden cardiac death, as compared to other modes of death [20,21]. The most commonly used cut-off value in HRR 1min is 12bpm [12]. In our study, the sensitivity and specificity in 12bpm of cut-off value were 88.9% and 36.8% (AUC: 0.799, p<0.001). However, in some studies, the optimal cut-off value of HRR 1min, related with cardiac event, suggested 18bpm [22,23]. In our study, the sensitivity and specificity in 18bpm of cut-off value were 68.8% and 84.2%. In addition, left ventricular systolic dysfunction is more likely associated with impaired HRR 1min. Also, advancing age is strongly associated with impaired HRR 1min [22,24]. In our study, most patients had preserved left ventricular systolic dysfunction with the mean value of

LVEF in 60.1%. These findings may be associated with the gradual dysfunction in the autonomic regulation of HR according to the systolic dysfunction and aging process. Although several prior studies have various impaired HRR 1min for the MACE, only impaired HRR 1min was insufficient in the prediction of the MACE. Therefore, other impaired HR response for the prediction of the MACE was needed.

Impaired HR reserve may indicate disruptions in autonomic balance and an inability of the cardiovascular system to appropriately respond to the sympathetic discharge and parasympathetic withdrawal that occurs during exercise [25]. Some studies have suggested that impaired HR reserve serves as a protective response in the presence of the CAD to avoid excessively high HR and its associated demands for coronary artery flow [26]. In the patients with BB of our study, the sensitivity and specificity in 62% of cut-off value were 69.5% and 68.7% like result of previous studies (AUC: 0.721, p=0.003).

In our study, both of HRR 1min as value after exercise and HR reserve as value during exercise was associated with the MACE. In addition, HRR 1min as value after exercise was correlation with HR reserve as value during exercise (r=0.360, p<0.001). Desai et al. reported that HR recovery after exercise is strongly dependent upon chronotropic response [27]. An impaired HR recovery after exercise, to a great extent, can be explained by chronotropic incompetence. They pointed that chronotropic response during exercise and heart rate recovery after exercise can be similar phenomenon. On the basis of this report, in our study, both of impaired HRR 1min and impaired HR recovery could be associated with the MACE. In addition, the OR for the MACE in patient with both of impaired HRR 1min and impaired HR recovery was higher than in patient with one of impaired HRR 1min and impaired HR recovery.

Several studies have mostly reported the DTS and the result of ETT in the evaluation of the MACE [28,29]. However, the DTS was not correlated with the MACE in our study. As the reason of this result, the patients in our study were mostly in the low-risk DTS patients (94.5%). The relation between the MACE and impaired HR responses in low-risk DTS patients supported the importance of impaired HR responses in assessing the MACE. Maddox et al. demonstrated that 5.7% of low-risk DTS patients with impairment of both HRR and CR died or had a nonfatal MI, in comparison to only 3.0% of intermediate-risk DTS patients with normal HRR and CR [30]. The higher MACE rate in these low-risk DTS patients compared to intermediate-risk DTS patients could suggest the new classification of patient risk based on these study. Therefore, impaired HR responses in low-risk DTS patients could be suggested prognostic information for the MACE. In our study results, impaired HR reserve and HRR 1min could be suggested as the prognostic marker of the MACE rather than the DTS in low-risk DTS patients.

On the basis of our study results, we need to closely follow up the patients with impaired HR response at ETT to reduce the MACE. The HR reserve with HR recovery could help us to predict the exercise performance in the patients with heart failure with severe depressed LV systolic function as well as CAD. Also, we might predict the improvement of LV systolic function in the patients with acute MI with depressed LV systolic function through the assessment of the regulation of the autonomic nerve function.

Study Limitations

There are several limitations in this study. First, the number of patient population is limited because of the single center study and the

inclusion and exclusion criteria we used. Although our patient population was homogeneous, it represents a very small percentage of the patients with the CAD to perform the PCI. Thus, the effectiveness of clinical usage is relatively limited. Second, because of the retrospective design of the study, some important clinical characteristics were not recorded and it is possible that some of the MACE may not have been recorded because of a review of electronic medical records and telephone contact. In addition, the design was not inclusive of all the related factors that are associated with MACE in the patients with the CAD to perform the PCI. These problems may be resolved by doing a prospective study. Third, because of the small number of cardiac death and nonfatal MI in our study, we could not determine the association of HR reserve with cardiac related mortality and nonfatal MI. However, in overall MACE included cardiac death, nonfatal MI and revascularization, we could determine important prognosis for the patients. Forth, our population was generally healthy, as indicated by the predominance of low-risk DTS. Thus, we cannot generalize our results to the patients in intermediate-risk or high-risk DTS in the ETT. However, the results provided by our study analysis should have applicability to most patients undergoing the ETT, because optimal clinical management is less clear for low-risk DTS patients, as compared to intermediate-risk or high-risk DTS patients. In addition, our results demonstrated that HR reserve were especially valuable among low-risk DTS patients. Fifth, HR responses in the ETT are closely related to the intensity of exercise, body temperature, and cardiovascular conditioning [31,32]. In addition, normal reference value of in the HR responses containing HR reserve, HRR 1min in the ETT has not yet known. Influence of extracardiac condition and normal reference value in HR response should be verified by further investigation.

Conclusion

Up to our knowledge, our study is the first report to find out the association between HR responses and the MACE after successful PCI in the CAD patients. The HR recovery and HR reserve could provide us important information of the MACE in asymptomatic patients to perform the PCI. Therefore, HRR 1min and HR reserve could be suggested as the clinically useful value of the MACE.

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