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ORIGINAL ARTICLE

Right ventricular dysfunction is associated with exercise intolerance and poor prognosis in ischemic heart disease

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Abstract

Right ventricular (RV) function is a prognostic factor in ischemic heart disease (IHD) patients, although its correlations with exercise capacity and cardiac rehabilitation (CR) efficacy are unknown. We aimed to clarify how RV function was associated with exercise tolerance and efficacy of phase II CR in IHD patients. We retrospectively analyzed 301 consecutive IHD patients who underwent phase II CR. We defined RV dysfunction using a combination of RV fractional area change < 35%, tricuspid annular plane systolic excursion < 1.6 cm, and systolic velocity < 10 cm/s. Exercise capacity was assessed using cardiopulmonary testing. The relation between RV function and exercise capacity was analyzed. The all-cause death and major adverse cardiac events (MACE) were evaluated by survival curve. The RV dysfunction group ($n = 121$) showed impaired left ventricular (LV) systolic and diastolic function before CR contrary to the normal RV function group ($n = 180$). The presence of RV dysfunction significantly reduced %AT by 4% and %Peak$\dot{V}O_2$ by 9% before CR, but increases the degree of improvement in %Peak$\dot{V}O_2$ with CR, independent of LV systolic and diastolic function. Univariate analysis demonstrated that previous coronary artery bypass grafting (CABG) was negatively associated with all-cause deaths and MACE. Adjusted for previous CABG, poor prognosis correlated with coexisting LV and RV dysfunction (hazard ratio [HR] 3.91, 95% confidence interval [CI] 1.13–13.53, $P = 0.03$) and RV dysfunction alone (HR 3.08, 95% CI 1.01–9.37, $P = 0.05$). In IHD patients, RV dysfunction is associated with exercise intolerance before CR and increased MACE risk, independent of LV function. The CR was effective in patients with RV dysfunction.

Keywords Myocardial ischemia · Coronary artery disease · Right ventricular function · Left ventricular function · Exercise tolerance · Cardiac rehabilitation

Introduction

Right ventricular (RV) function has recently emerged as an important prognostic factor in addition to left ventricular (LV) function in patients with ischemic heart disease (IHD) and chronic heart failure [1, 2]. Furthermore, RV systolic dysfunction is a major independent risk factor for death, sudden death, heart failure, or stroke after myocardial infarction [3].

Right ventricular function is evaluated by RV fractional area change (RVFAC), tricuspid annular plane systolic excursion (TAPSE), and tissue Doppler maximal systolic velocity at the tricuspid annulus (s') [4]. Small cohort studies of chronic heart failure showed that RVFAC was associated with prognosis and the maximum rate of oxygen consumption (Peak$\dot{V}O_2$) [5], while no clinical significance of TAPSE was found in post-coronary artery bypass graft (CABG) patients [6]. Therefore, precise assessment of RV function and study of its correlation with exercise capacity are needed in IHD patients. Furthermore, the relation between RV function and efficacy of cardiac rehabilitation (CR) is unclear. In this study, we sought to evaluate the effects of RV function on exercise capacity and efficacy of recovery-phase (phase II) CR in IHD patients.

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Materials and methods

Population

We retrospectively reviewed clinical records of IHD patients who received phase II CR at the Sakakibara Heart Institute, Tokyo, Japan between April 2014 and April 2016. They underwent percutaneous coronary intervention (PCI) or off-pump CABG surgery following diagnosis of stable/unstable angina pectoris, acute/chronic myocardial infarction, or silent myocardial ischemia. Comorbidities were recorded when hypertension, diabetes mellitus, chronic kidney disease or dyslipidemia coexisted. Hematological examination and transthoracic echocardiography were performed before CR, and cardiopulmonary exercise testing (CPX) was performed before and after CR. Exclusion criteria were: (1) any valvular disease, (2) history of open-heart surgery, (3) any respiratory disorder, (4) the absence of echocardiographic findings before CR, (5) the absence of CPX findings before and after CR, or (6) dropout from CR. Spirometry assessment was performed to rule out respiratory disorders. Follow-up data were collected from clinical records or by contacting patients.

The study was approved by the Research Ethics Board of the Sakakibara Heart Institute and complied with the Declaration of Helsinki. We obtained written informed consent from all the participants.

Echocardiography

Systolic and diastolic LV function and RV function were evaluated using resting transthoracic echocardiography before CR, measuring LVEF, peak early diastolic mitral inflow velocity (*E*), peak late diastolic mitral inflow velocity (*A*), peak early diastolic mitral annular velocity (*e′*), RVFAC, TAPSE and *s′*. Based on the American Society of Echocardiography guidelines [4], LV dysfunction was defined as LVEF < 50%. To accurately detect RV dysfunction, we defined RV dysfunction by two or more of the following criteria: (1) RVFAC < 35%, (2) TAPSE < 1.6 cm, or (3) *s′* < 10 cm/s.

Cardiopulmonary exercise test (CPX)

Cardiopulmonary exercise test was performed on a bicycle ergometer Strength Ergo 8 (Mitsubishi Electric Engineering Co. Ltd., Tokyo, Japan) with 10 W/min workload increments until the subjects achieved the criteria for test termination (e.g., exhaustion, angina, drop in blood pressure, ST change, and arrhythmias) [7]. Continuous measurement of Peak$\dot{V}O_2$, CO_2 production, and minute ventilation was performed using the ML-9000 (Fukuda denshi Co. Ltd., Tokyo, Japan) [8]. Anaerobic threshold (AT), peak$\dot{V}O_2$, ventilator equivalent for carbon dioxide ($\dot{V}E/\dot{V}CO_2$), and end-tidal carbon dioxide tension ($PetCO_2$) were measured. For $\dot{V}E/\dot{V}CO_2$ measurement, we used the $\dot{V}E/\dot{V}CO_2$ slope. AT and Peak$\dot{V}O_2$ were age- and sex-corrected (%AT and % Peak$\dot{V}O_2$, respectively) using Itoh's predictive equations [9].

Phase II cardiac rehabilitation

The study subjects, participated in phase I (acute-phase) CR at bedside a few days after revascularization, proceeded to in-hospital phase II (recovery-phase) CR in a rehabilitation room for 1–2 weeks, and then were shifted to outpatient phase II CR according to the Japanese Circulation Society 2012 guidelines [10]. AT-level exercise on treadmill or bicycle ergometer with or without resistance training lasted for 1 h under the supervision of medical staff with ECG monitoring as necessary. The recovery-phase CR program typically lasted for 3 months, up to a maximum of 5 months.

Outcomes

The study endpoint was a composite of all-cause death and major adverse cardiovascular events (MACE) including myocardial infarction, revascularization with re-PCI/CABG, stroke, or hospitalization for heart failure.

Statistical analysis

Continuous and categorical data were expressed as mean ± standard deviation, median, or number (%). Continuous variables such as age, laboratory data, echocardiographic measurements, and CPX measurements were compared using unpaired Student's *t* test and one-way ANOVA. Categorical variables such as number of males, comorbidities, medications, and history of CABG were compared using Fisher's exact test. Pearson's correlation was performed between indices of RV function and CPX measurements. The correlation of LV and RV function with CPX measurements was evaluated by univariable and multivariable linear regression analysis. Associations with event-free survival were evaluated using univariate and multivariate Cox proportional regression models to calculate hazard ratio (HR) and 95% confidence interval (CI). A *P* value of < 0.05 was considered statistically significant. All statistical analyses were performed using the software SPSS ver. 24.0 (SPSS, Inc., Chicago, IL, USA).

Results

Population characteristics

During the study period, 571 consecutive subjects with IHD attended phase II CR. In total, 52 patients dropped out from CR; 26 due to comorbidities, 15 due to exercise at home or other rehabilitation facilities, 6 due to no time to commit to CR, 3 due to social/family reasons, and 2 due to unwillingness to exercise. Moreover, 218 patients were excluded because echocardiographic or CPX measurements were unavailable. Finally, 301 patients were included in the analysis. Of the study population, 179 patients underwent PCI and other 122 patients underwent CABG. Clinical, demographic and echocardiographic findings are shown in Table 1. Acute coronary syndrome (ACS), triple vessel disease, or history of CABG surgery and LV dysfunction (both systolic and diastolic dysfunction) was more frequent and NT-proBNP was higher in the RV dysfunction group [RVdys(+)] than in the normal RV function group [RVdys(−)]. RV systolic pressure (RVSP) was within the normal range in both the groups.

Exercise intolerance in the RV dysfunction group

Cardiopulmonary exercise testing indices of the study subjects are shown in Table 2. Before CR, RV dysfunction related to high HR at rest and low HR at peak exercise, although rest HR of the RVdys(+) group decreased to the same level of the RVdys(−) group. AT and Peak$\dot{V}O_2$ were lower in the RVdys(+) group than in the RVdys(−) group

Table 1 Clinical characteristics of the study subjects

	Total ($n=301$)	RVdys(−) ($n=180$)	RVdys(+) ($n=121$)	P value
Age, years old	68 ± 10	68 ± 10	68 ± 9	0.99
Male, *n* (%)	241 (79)	139 (77)	102 (84)	0.14
ACS, *n* (%)	123 (40)	84 (47)	39 (32)	0.02
No. of diseased vessels				< 0.001
3VD	140 (47)	50 (28)	90 (74)	
2VD	80 (27)	59 (33)	21 (17)	
1VD	80 (27)	70 (39)	10 (8)	
History of smoking	126 (42)	74 (41)	52 (43)	0.81
HT, *n* (%)	203 (67)	126 (70)	77 (64)	0.26
DM, *n* (%)	76 (25)	40 (22)	36 (30)	0.18
DL, *n* (%)	234 (77)	142 (79)	89 (74)	0.33
CKD, *n* (%)	67 (22)	41 (23)	26 (22)	0.89
Beta blocker, *n* (%)	240 (80)	129 (72)	111 (92)	< 0.001
RAAS inhibitor, *n* (%)	145 (47)	101 (56)	41 (34)	< 0.001
CCB, *n* (%)	90 (30)	49 (27)	40 (33)	0.30
Diuretics, *n* (%)	39 (13)	14 (8)	25 (21)	< 0.01
CABG, *n* (%)	132 (44)	30 (16.7)	101 (84)	< 0.001
Hospitalization period (days)	11 ± 7	8 ± 6	15 ± 7	< 0.001
NT-proBNP, pg/mL	665 ± 802	540 ± 818	867 ± 736	< 0.01
LVEF, %	58 ± 8	59 ± 6	55 ± 10	< 0.001
E/*A*	1.0 ± 0.3	0.9 ± 0.3	1.0 ± 0.4	0.05
E/*e′*	15 ± 6	14 ± 5	16 ± 8	< 0.01
RVFAC, %	41 ± 6	42 ± 4	39 ± 6	< 0.001
TAPSE, cm	1.7 ± 0.6	2.0 ± 0.4	1.1 ± 0.3	< 0.001
s′, cm/s	10 ± 3	11 ± 3	7 ± 2	< 0.001
RVSP, mmHg	26 ± 7	26 ± 7	26 ± 6	0.34

Δ = Value (final) − Value (initial)

RVdys right ventricular dysfunction, *ACS* acute coronary syndrome, *VD* vessel disease, *HT* hypertension, *DM* diabetes mellitus, *DL* dyslipidemia, *CKD* chronic kidney disease, *RAAS* renin–angiotensin–aldosterone system, *CCB* calcium channel blocker, *CABG* coronary artery bypass graft, *NT-proBNP* N-terminal prohormone of brain natriuretic peptide, *LVEF* left ventricular ejection fraction, *E* peak early diastolic mitral inflow velocity, *A* peak late diastolic mitral inflow velocity, *e′* peak early diastolic mitral annular velocity, *RVFAC* right ventricular fractional area change, *TAPSE* tricuspid annular plane systolic excursion, *s′* maximal systolic velocity at the tricuspid annulus, *RVSP* right ventricular systolic pressure

Table 2 Cardiopulmonary indices of the study subjects

	Total ($n=301$)	RVdys(−) ($n=180$)	RVdys(+) ($n=121$)	P value
HR at rest (initial), bpm	71 ± 12	69 ± 11	74 ± 12	< 0.001
HR at rest (final), bpm	68 ± 11	68 ± 10	69 ± 11	0.49
HR at peak (initial), bpm	126 ± 21	130 ± 21	120 ± 20	< 0.001
HR at peak (final), bpm	131 ± 22	133 ± 22	128 ± 22	0.28
AT (initial), mL/min/kg	12 ± 3	12 ± 3	11 ± 2	< 0.001
AT (final), mL/min/kg	13 ± 3	14 ± 3	13 ± 3	0.01
ΔAT, mL/min/kg	1 ± 2	1 ± 2	2 ± 2	0.14
%AT (initial), %	78 ± 17	80 ± 17	73 ± 17	< 0.001
%AT (final), %	86 ± 19	88 ± 18	84 ± 20	0.05
Δ %AT, %	9 ± 17	8 ± 17	10 ± 18	0.24
Peak$\dot{V}O_2$ (initial), mL/min/kg	19 ± 6	20 ± 5	18 ± 8	< 0.01
Peak$\dot{V}O_2$ (final), mL/min/kg	22 ± 6	22 ± 7	21 ± 5	0.02
Δpeak$\dot{V}O_2$, mL/min/kg	2 ± 6	2 ± 6	3 ± 7	0.53
%Peak$\dot{V}O_2$ (initial), %	80 ± 20	85 ± 20	73 ± 18	< 0.001
%Peak$\dot{V}O_2$ (final), %	90 ± 21	93 ± 21	87 ± 20	0.03
Δ%peak$\dot{V}O_2$	10 ± 17	8 ± 17	15 ± 15	< 0.001
$\dot{V}E/\dot{V}CO_2$ slope (initial)	34 ± 7	32 ± 6	36 ± 8	< 0.001
$\dot{V}E/\dot{V}CO_2$ slope (final)	31 ± 5	31 ± 5	31 ± 6	0.20
Δ$\dot{V}E/\dot{V}CO_2$ slope	−3 ± 7	−1 ± 6	−5 ± 8	< 0.001
$PetCO_2$ at rest (initial), mmHg	35 ± 3	36 ± 3	34 ± 4	< 0.01
$PetCO_2$ as rest (final), mmHg	36 ± 3	36 ± 3	36 ± 3	0.77
$PetCO_2$ at AT (initial), mmHg	40 ± 4	41 ± 4	38 ± 4	< 0.001
$PetCO_2$ at AT (final), mmHg	42 ± 4	42 ± 4	41 ± 4	0.39
$PetCO_2$ at peak (initial), mmHg	36 ± 5	36 ± 5	34 ± 5	< 0.001
$PetCO_2$ at peak (final), mmHg	37 ± 4	37 ± 4	37 ± 4	0.31

Δ = Value (final) − Value (initial)

RVdys right ventricular dysfunction, *HR* heart rate, *AT* the rate of oxygen consumption at anaerobic threshold, *Peak*$\dot{V}O_2$ the maximum rate of oxygen consumption, $\dot{V}E/\dot{V}CO_2$ ventilator equivalent for carbon dioxide, $PetCO_2$ end-tidal carbon dioxide tension

both before and after CR. However, the RVdys(+) group exhibited greater improvement in Peak$\dot{V}O_2$ with CR than the RVdys(−) group. $PetCO_2$ was lower in the RVdys(+) group than in the RVdys(−) group at rest, AT and peak exercise before CR, while it was not different between the groups at any point of CPX after CR. When analyzing the exercise tolerance of PCI and CABG group separately, we found no significant difference in any CPX measurements between the RVdys(+) and RVdys(−) subgroups both before and after CR.

We assessed the association of echocardiographic values of RV function with CPX parameters before CR (Table 3). TAPSE and s' were weakly correlated with %AT, % Peak$\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ slope. RVFAC was weakly correlated with

Table 3 Correlation between indices of RV function and exercise capacity before CR

	RVFAC		TAPSE		s'	
	r	P value	r	P value	R	P value
%AT	0.04	0.48	0.23	< 0.001	0.13	0.02
%Peak$\dot{V}O_2$	0.09	0.14	0.31	< 0.001	0.22	< 0.001
$\dot{V}E/\dot{V}CO_2$ slope	−0.12	0.05	−0.35	< 0.001	−0.25	< 0.001
$PetCO_2$ at rest	0.20	< 0.001	0.19	< 0.01	0.09	0.12

RVFAC right ventricular fractional area change, *TAPSE* tricuspid annular plane systolic excursion, s' maximal systolic velocity at the tricuspid annulus, *AT* the rate of oxygen consumption at anaerobic threshold, *Peak*$\dot{V}O_2$ the maximum rate of oxygen consumption, $\dot{V}E/\dot{V}CO_2$ ventilator equivalent for carbon dioxide, $PetCO_2$ end-tidal carbon dioxide tension

$\dot{V}E/\dot{V}CO_2$ slope and $PetCO_2$ at rest. Interestingly, $PetCO_2$, an indicator of pulmonary hypertension, had no significant relationship to RVSP ($r = -0.10$, $P = 0.08$).

Even though LV systolic and diastolic function were strongly correlated with RV function as previously explained, RV dysfunction had a significant association with exercise intolerance before CR, independently of LV systolic and diastolic function. Multiple regression analysis demonstrated that RV dysfunction reduced %AT by 4% and reduced %Peak$\dot{V}O_2$ by 9% before CR, independently of LVEF < 50% and $E/e' > 15$, which were indicators of LV systolic and diastolic function, respectively (Table 4). The presence of RV dysfunction increases the degree of improvement in %Peak$\dot{V}O_2$ (Δ%Peak$\dot{V}O_2$) with CR, whereas LV systolic or diastolic function had no association with the improvement of exercise tolerance.

Incidence of all-cause death, MACE and repeat revascularization

The average follow-up period was 706 ± 254 (interquartile range 531–917) days, after which the study endpoints were assessed. A patient died of pneumonia, 36 patients developed IHD requiring revascularization (23 cases of silent ischemic cardiomyopathy, 7 of stable angina pectoris, 3 of unstable angina pectoris, 2 of acute myocardial infarction, and one of coronary spastic angina), three had heart failure, two had abdominal aortic aneurysms, and one had aortic dissection. Univariate analysis of event-free survival showed a history of CABG as a strong predictive factor (HR 0.35, 95% CI 0.18–0.72, $P < 0.01$), while LV dysfunction and RV dysfunction had no significant association (Table 5). When adjusted for a history of CABG, adverse events were likely to occur in the presence of LV dysfunction (HR 2.04, 95% CI 0.94–4.45, $P = 0.07$) and RV dysfunction (HR 2.02, 95% CI 0.92–4.44, $P = 0.08$) (Fig. 1). The Cox proportional hazard regression model adjusted for a history of CABG demonstrated that occurrence of events increased in the LVdys(+)-RVdys(+) group (HR 3.91, 95% CI 1.13–13.53, $P = 0.03$) and the LVdys(+)-RVdys(−) group (HR 3.08, 95% CI 1.01–9.37, $P = 0.05$) compared to the LVdys(−)-RVdys(−) group (Fig. 2). The LVdys(−)-RVdys(+) group also tended to be at higher risk for adverse events (HR 2.33, 95% CI 0.95–5.73, $P = 0.07$).

Discussion

The present study is the first large-scale, long-term study closely evaluating the association between RV function and exercise capacity in IHD patients. Our findings suggest that RV function is a significant factor determining exercise capacity in IHD patients before CR, in addition to LV function. RV dysfunction also tended to increase the risk of MACE by twofold. These results provide new evidence for the importance of RV function in IHD patients.

As TAPSE and s' are independently related to exercise capacity in healthy subjects [11], RV function can also be associated with exercise capacity in patients with cardiovascular disease. In heart failure patients, RV dysfunction is responsible for poor prognosis [12] but its relationship to exercise capacity is unexplained [13]. As for IHD patients, there are little data on the relationship between RV function

Table 4 Associations between cardiac function and exercise tolerance, results from univariate and multivariable regression analysis

	Univariable		Multivariable	
	Coefficient (β)	R^2	Coefficient (B)	R^2
%AT (initial)				0.09
LVEF < 50%	−8**	0.02	−8**	
$E/e' > 15$	−8***	0.06	−8***	
RV dysfunction	−7***	0.03	−4*	
%AT (final)				0.07
LVEF < 50%	−12***	0.04	−13***	
$E/e' > 15$	−7**	0.03	−8***	
RV dysfunction	−4*	0.01	–	
Δ%AT				
LVEF < 50%	−4	0.002	–	
$E/e' > 15$	1	−0.002	–	
RV dysfunction	2	0.001	–	
%Peak$\dot{V}O_2$ (initial)				0.15
LVEF < 50%	−8*	0.01	−7*	
$E/e' > 15$	−12***	0.08	−11***	
RV dysfunction	−12***	0.08	−9***	
%Peak$\dot{V}O_2$ (final)				0.09
LVEF < 50%	−9**	0.02	−11**	
$E/e' > 15$	−11***	0.06	−12***	
RV dysfunction	−5*	0.01	–	
Δ%Peak$\dot{V}O_2$				0.03
LVEF < 50%	−1	−0.003	–	
$E/e' > 15$	1	−0.003	–	
RV dysfunction	7***	0.04	7***	

Results from univariable regression $Y = \beta * X + \varepsilon$, and multivariable regression $Y = B * X + \varepsilon$ of %AT (initial), %AT (final), Δ%AT, %Peak$\dot{V}O_2$ (initial), %Peak$\dot{V}O_2$ (final), and Δ%Peak$\dot{V}O_2$. Results are presented as estimated partial regression coefficient β and B, respectively, in univariable and multivariable model, with P values (*$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$) for each parameter. ε represents the error-term in the model. R^2 represents adjusted determination coefficient

Δ = Value (final) − Value (initial)

LVEF left ventricular ejection fraction, *E* peak early diastolic mitral inflow velocity, *e′* peak early diastolic mitral annular velocity, *RV* right ventricle, *AT* the rate of oxygen consumption at anaerobic threshold, *Peak*$\dot{V}O_2$ the maximum rate of oxygen consumption

Table 5 Results of univariate Cox regression analysis of event-free survival

	HR	95% CI
Age > 75 years	0.71	[0.35, 1.43]
Male	1.12	[0.52, 2.42]
HT	0.81	[0.44, 1.51]
DM	0.46	[0.20, 1.09]
DL	1.37	[0.64, 2.96]
CKD	0.91	[0.44, 2.03]
CABG	0.36	[0.16, 0.72]
NT-proBNP > 125 pg/mL	0.92	[0.42, 2.03]
E/*e'* > 15	0.95	[0.51, 1.75]
LV dysfunction	1.67	[0.78, 3.61]
RV dysfunction	0.77	[0.41, 1.45]

HR hazard ratio, *CI* confidence interval, *HT* hypertension, *DM* diabetes mellitus, *DL* dyslipidemia, *CKD* chronic kidney disease, *CABG* coronary artery bypass graft, *NT-proBNP* N-terminal prohormone of brain natriuretic peptide, *E* peak early diastolic mitral inflow velocity, *e'* peak early diastolic mitral annular velocity, *LV* left ventricle, *RV* right ventricle

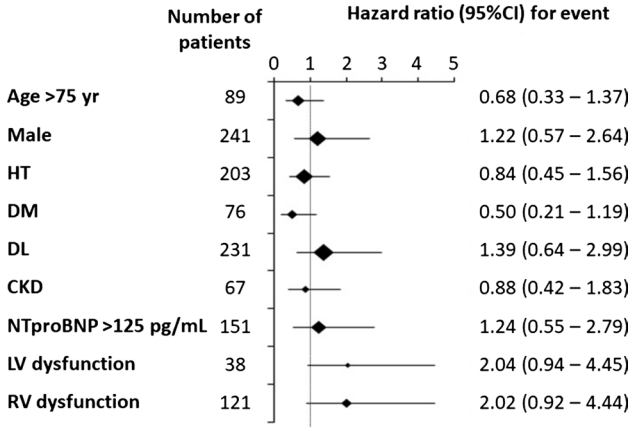

Fig. 1 Univariate Cox regression hazard ratio of potential factors for events adjusted for history of CABG. Univariate Cox regression analysis adjusted for history of coronary artery bypass graft (CABG), which was a strong predictive factor for events (hazard ratio [HR] 0.35, 95% confidence interval [CI] 0.18–0.72, $P < 0.01$), showed that occurrence of adverse events was likely to be associated with left ventricular (LV) dysfunction (HR 2.04, 95% CI 0.94–4.45, $P = 0.07$) and right ventricular (RV) dysfunction (HR 2.02, 95% CI 0.92–4.44, $P = 0.08$)

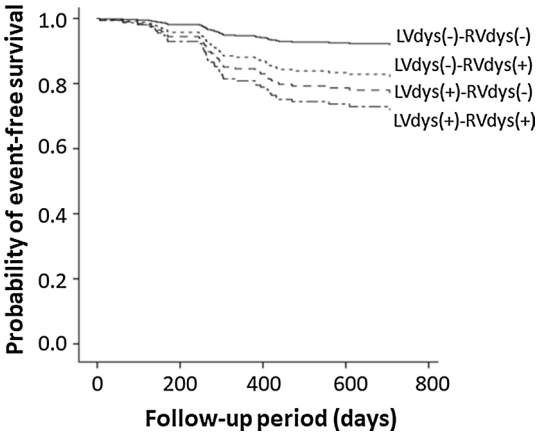

Fig. 2 Cox proportional hazard regression model of event-free survival. After adjusting for a history of coronary artery bypass graft (CABG), event-free survival in the four subgroups divided based on left ventricular dysfunction (LVdys) and right ventricular dysfunction (RVdys) was analyzed using a Cox proportional hazard regression model. Comparing with the LVdys(−)-RVdys(−) group, occurrence of events increased in the LVdys(+)-RVdys(+) group (hazard ratio [HR] 3.91, 95% confidence interval [CI] 1.13–13.53, $P = 0.03$) and the LVdys(+)-RVdys(−) group (HR 3.08, 95% CI 1.01–9.37, $P = 0.05$). The LVdys(−)-RVdys(+) group also tended to be at higher risk for events (HR 2.33, 95% CI 0.95–5.73, $P = 0.07$)

and exercise capacity. Kim et al. reported that regional LV ischemia of the inferior and lateral wall was involved in RV dysfunction and decreased effort tolerance, but they did not provide detailed analysis of exercise capacity such as AT and Peak$\dot{V}O_2$ measurements [14]. This study revealed the weak, but significant association of RV dysfunction with exercise intolerance before CR by close monitoring of cardiopulmonary functions. Since RV dysfunction also related to many coronary stenosis lesions, unrepaired RV scars caused by the large extent of coronary lesions may lead to severe ischemic cardiomyopathy, reduced exercise capacity, and poor prognosis.

Consistently with previous studies [2, 15], this study also showed poor prognosis in IHD patients with RV dysfunction, especially in those who underwent PCI. Typically, temporary worsening of RV function is observed immediately after CABG surgery, though it recovers to the preoperative level within 6 months [16, 17]. In this study, RV function would be also temporarily, but not fundamentally, impaired in post-CABG patients when echocardiographic findings were obtained. Thus, RV dysfunction would have the higher clinical importance in IHD patients who underwent PCI than in those who underwent CABG. To confirm this hypothesis, RV function after revascularization needs to be followed up and compared between PCI and CABG groups in the further study.

Another notable result of our study is that IHD patients with RV dysfunction experienced significant improvement in exercise capacity after CR. In general, LV dysfunction involves in exercise intolerance [18, 19], but CR in IHD patients with reduced LV function is considered as effective and safe as in those with preserved LV function [20]. On the other hand, the influence of RV function on efficacy of CR has been unclear in IHD patients before. This is the first study to prove the clinical significance of CR in IHD patients with RV dysfunction.

We also noticed the reactive pulmonary hypertension induced by exercise in RV dysfunction before CR, which is suggested by low $PetCO_2$ during exercise. Low $PetCO_2$ would reflect reduced cardiac output, directly regulating pulmonary blood flow. Similar to the report of Lim HS et al. that reactive pulmonary hypertension was caused by exercise in heart failure with reduced EF [21], this study also revealed that such exercise-induced pulmonary hypertension occurred in IHD patients with decreased cardiac function and could be ameliorated by CR. Moreover, our results also highlight the significance of CR in the improvement of cardiac sympathetic nerve overactivity. Before CR, RV dysfunction was involved in high HR at rest and low HR at peak exercise, which, respectively, indicated cardiac sympathetic hyperactivity and exercise intolerance. After CR, however, RV dysfunction also related to large decline in rest HR, suggesting normalization of cardiac sympathetic nerve activity. Similar to the report of Mimura et al. that exercise training improved baroreflex sensitivity in patients with acute myocardial infarction [22], this study also demonstrates the effectiveness of CR against cardiac sympathetic hyperactivity in IHD patients with reduced cardiac function. Since abnormality in cardiac autonomic nerve activity is recognized as a risk factor for adverse cardiac events [23], we can expect the improvement the prognosis of IHD patients with RV dysfunction through the correction of cardiac sympathetic hyperactivity by CR.

This study had several limitations. First, selection bias could have occurred due to its retrospective design. However, analysis of consecutive patients would minimize the consequent influence on results. Although 218 of 519 subjects were excluded because of the lack of echocardiographic or CPX data, there was no significant difference in patients' background, such as age, sex, history of CABG, between the finally analyzed population consisted of 301 subjects and the original population consisted of 519 subjects. Therefore, exclusion of subjects due to the lack of data would have little influence on the outcome of this study. Second, it is difficult to accurately assess RV function in general, particularly in post-CABG patients. We defined RV dysfunction by a combination of RVFAC, TAPSE, and s', which are individually used as indices of RV function, for more precise detection in this study. Third, cardiovascular endpoint was detected at preplanned follow-up invasive coronary angiography (CAG), mostly performed 8–12 months after the ischemic cardiac event. According to our hospital's policy, we do not plan revascularization on just morphological coronary stenosis without ischemic change. Consequently, all the patients who received re-revascularization after the follow-up CAG had already presented with angina or had evidence of myocardial ischemia detected by exercise ECG or myocardial scintigraphy. This policy may minimize the bias of re-revascularization as endpoint after preplanned CAG.

Conclusion

Right ventricular dysfunction in IHD patients is associated with lower exercise intolerance before CR and an increased risk of MACE, independently of LV function. The $\%Peak\dot{V}O_2$ was improved after CR in patients with RV dysfunction.

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Compliance with ethical standards

Conflict of interest There are no conflicts of interest to declare.

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