Journal of Arrhythmia 30 (2014) 173–179

Contents lists available at ScienceDirect

Journal of Arrhythmia

journal homepage: www.elsevier.com/locate/joa

Original Article

Relationship between cardiopulmonary exercise testing parameters and heart failure risk (H2ARDD score) in atrial fibrillation ☆

Shinya Suzuki, MD[a,*], Akira Koike, MD[b], Koichi Sagara, MD[a], Takayuki Otsuka, MD[a], Hiroto Kano, MD[a], Shunsuke Matsuno, MD[a], Hideaki Takai, MD[c], Tokuhisa Uejima, MD[a], Yuji Oikawa, MD[a], Kazuyuki Nagashima, MD[a], Hajime Kirigaya, MD[a], Junji Yajima, MD[a], Hiroaki Tanabe, MD[c], Hitoshi Sawada, MD[a], Tadanori Aizawa, MD[a], Takeshi Yamashita, MD[a]

[a] Department of Cardiovascular Medicine, The Cardiovascular Institute, 3-2-19 Nishiazabu, Minato-Ku, Tokyo 106 0031, Japan
[b] Faculty of Medicine, University of Tsukuba 1-1-1, Tennodai, Tsukuba, Ibaraki, 305-8575 Japan
[c] Department of Cardiovascular Surgery, The Cardiovascular Institute, 3-2-19 Nishiazabu, Minato-Ku, Tokyo, Japan

ARTICLE INFO

Article history:
Received 12 September 2013
Accepted 19 September 2013
Available online 15 November 2013

Keywords:
Atrial fibrillation
Heart failure
Cardiopulmonary exercise testing

ABSTRACT

Background: A novel risk scoring system (H2ARDD) for estimating the incidence of heart failure (HF) events in atrial fibrillation (AF) has been developed, which represents points assigned for organic heart disease (2 points), anemia (1 point), renal dysfunction (1 point), diabetes (1 point), and diuretic use (1 point). We aimed to clarify whether H2ARDD score is related to cardiopulmonary exercise testing (CPX) parameters in patients with AF.

Methods: The study population included 344 consecutive patients with AF who underwent CPX as initial screening between June 2004 and March 2012. The association between 4 CPX parameters and the incidence of HF events was analyzed by using multiple linear regression models.

Results: The peak O_2 uptake (peak $\dot{V}O_2$), anaerobic (gas exchange) threshold (AT), and ratio of the increase in $\dot{V}O_2$ to the increase in work rate ($\Delta\dot{V}O_2/\Delta WR$) were lower and the slope of the increase in ventilation to the increase in CO_2 output ($\dot{V}E$–$\dot{V}CO_2$ slope) was higher in patients with than in those without each H2ARDD score component. Accordingly, the parameters significantly increased or decreased according to H2ARDD score. With the multiple linear regression models, H2ARDD score was independently associated with each CPX parameter even after adjustment for various cofactors.

Conclusions: H2ARDD score was independently associated with the well-established CPX parameters in patients with AF, suggesting a potential pathophysiological basis for a risk stratification system for predicting HF events in patients with AF.

1. Introduction

Atrial fibrillation (AF) is the most common type of arrhythmia in developed countries. Its prevalence almost doubles with each decade of life [1], with a lifetime prevalence of 25% [2]. AF is also an important risk factor for mortality [3].

Along with stroke, heart failure (HF), which is a significant complication of AF, was identified as an independent predictor of mortality in patients with AF [4]. Our previous data suggested that HF remains an important target for the treatment of AF to improve patient prognosis [5]. To prevent hospital admission or death from HF, identifying the population with a high-risk for such HF events is mandatory. Therefore, we developed the H2ARDD scoring system to measure the risk for HF events in patients with AF by assigning points as follows: organic heart disease, 2 points; anemia (hemoglobin level < 11 g/dL), 1 point; renal dysfunction (estimated glomerular filtration rate [GFR] < 60 mL/min m^2), 1 point; diabetes mellitus (DM), 1 point; and diuretic use, 1 point [6]. Although it is a simple scoring system, it was a strong predictor of the risk of HF events (hospital admission or death from HF) in our AF patient population; the incidence rates of HF events in patients scoring 0 and 6 points were 0.2% and 40.8% per patient-year, respectively; C-statistic, 0.840 [6]. However, although the clinical implications of the H2ARDD score were statistically suggested, its pathophysiological basis has not been fully evaluated.

Cardiopulmonary exercise testing (CPX) is the criterion standard for assessing exercise capacity, with much evidence for the benefits of its use in the clinical setting, especially for patients

☆ *Grants*: This work was supported by grants from St. Luke's Life Science Institute (Tokyo, Japan) and the Health Promotion Foundation (Tokyo, Japan).
* Corresponding author. Tel.: +81 3 3408 2151; fax: +81 3 3408 2159.
E-mail address: sinsuz-tky@umin.ac.jp (S. Suzuki).

1880-4276/$ - see front matter © 2013 Japanese Heart Rhythm Society. Published by Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.joa.2013.09.002

with systolic HF [7–14]. That evidence has also been extended to patients with HF who have preserved left ventricular ejection fraction [15–17]. The most important measurements obtained from CPX include peak oxygen uptake (peak $\dot{V}O_2$) [7,8,15,16], anaerobic (gas exchange) threshold (AT) [9–11], increase rate in ventilation per unit increase in carbon dioxide production ($\dot{V}E$–$\dot{V}CO_2$ slope) [12,13,17], and the ratio of the increase in $\dot{V}O_2$ to the increase in work rate ($\Delta\dot{V}O_2/\Delta WR$) [14], all of which reflect heart disease severity and the ability of cardiac patients to perform activities of daily living. In the present study, we evaluated whether H2ARDD score is related to these 4 classic CPX parameters in patients with AF to clarify its pathophysiological implications.

2. Materials and methods

2.1. Study patients

The Shinken Database (*Shinken* is the Japanese abbreviated form of the name of the hospital) was established in June 2004 to document new patients who visit the Cardiovascular Institute in Tokyo, Japan. The principal aim of this hospital-based database is to survey the prevalence and prognosis of cardiovascular diseases in patients in an urban area of Japan [5,6]. Patients (except foreign travelers and those with active cancer) have been registered annually in the database since its inception.

Data from the Shinken Database recorded between June 2004 and March 2012 were used in the present study, including 17,517 newly admitted patients. From these patients, 344 consecutive patients with AF who underwent CPX for evaluation of exercise capacity and/or HF severity as initial screening at their initial visit were extracted as the study population of the present study.

2.2. Data collection at initial visit

For each patient, an electrocardiogram (ECG), a chest radiograph, and laboratory data were obtained, and cardiovascular status was evaluated by using echocardiography, CPX, and 24-h Holter recordings within 3 months after the initial visit, according to the discretion of the attending physician. Information regarding each patient's medications was obtained from the hospital database within 3 months after the initial visit [5,6].

2.3. Cardiopulmonary exercise testing

An incremental symptom-limited maximal exercise test was performed by using an upright, electromagnetically braked cycle ergometer (Corival 400, Lode BV, Groningen, the Netherlands). After a 4-min warm-up at 0 or 20 W at 60 revolutions per minute (rpm), the exercise load was increased incrementally by 1 W every 6 s (10 W/min). ECG was monitored continuously during the test (ML-6500 or ML-9000 system, Fukuda Denshi Co., Ltd., Tokyo, Japan). Cuff blood pressure was measured at rest on the cycle ergometer and then every minute during exercise testing with an automatic indirect manometer (STBP-780, Nippon Colin Co., Ltd., Aichi, Japan, or FB-300, Fukuda Denshi Co., Ltd.).

$\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}E$ were measured throughout the test with an Aeromonitor AE-300S (Minato Medical Science, Osaka, Japan) [18]. Before the parameters from the respiratory gas analysis were calculated, breath-by-breath data were interpolated to give second-by-second values, which were then calculated as successive 3-s averages that were converted to a 5-point moving average. Peak $\dot{V}O_2$ was defined as the average value obtained during the last 15 s of incremental exercise. $\Delta\dot{V}O_2/\Delta WR$ was calculated from the data recorded between 30 s after the start of incremental exercise to 30 s before the end of the exercise, by using least squares linear regression [14]. The $\dot{V}E$–$\dot{V}CO_2$ slope was calculated during incremental exercise by using least squares linear regression [14].

2.4. Definition of AF

In the present study, AF was diagnosed by using electrocardiographic recordings, including 12-lead surface electrocardiograms and 24-h Holter recordings performed within 3 months after the initial visit, and based on the medical history of AF from the patient's referring physicians. New-onset AF that occurred more than 3 months after the initial visit was not included in the diagnosis of AF in the present study.

2.5. H2ARDD score

The H2ARDD scoring system was developed for predicting the risk for future incidence of HF events (admission or death by HF) in patients with AF. The acronym *H2ARDD* represents organic heart disease (2 points), anemia (hemoglobin level < 11 g/dL, 1 point), renal dysfunction (estimated GFR < 60 mg/min m^2, 1 point), diabetes mellitus (hemoglobin A1c level [National Glycohemoglobin Standardization Program] $\geq 6.5\%$, or medical history of diabetes, 1 point), and diuretic use (1 point) [6]. For H2ARDD scoring, heart disease includes one or more of the following: (1) valvular heart disease with moderate or greater severity, left ventricular hypertrophy (intraventricular septal or posterior wall thickness $\geq$ 14 mm), or left ventricular dysfunction (ejection fraction $< 50\%$) on echocardiography; (2) previous diagnosis of coronary artery disease based on coronary angiography findings; (3) previous diagnosis of congenital heart disease; and (4) left ventricular noncompaction on echocardiogram [6].

2.6. Ethical considerations

The ethics committee at the Cardiovascular Institute granted permission for our database (2006/12/25, No. 95; 2011/4/8, No. 169), and all patients provided written informed consent. The study was performed in accordance with the Declaration of Helsinki.

2.7. Statistical analysis

Categorical and consecutive data pertaining to the patients' background characteristics were presented as number (percentage) and mean $\pm$ standard deviation, respectively.

Differences in the distribution of CPX parameters according to H2ARDD score and its components were first identified. The Student *t* test and one-way analysis of variance were used for group comparisons of the CPX parameters between the presence and absence of each H2ARDD score component and between the H2ARDD score categories, respectively.

To evaluate the relationship between H2ARDD score with the CPX parameters, simple and multiple linear regression analyses were then performed. First, simple linear regression analysis was performed by calculating the coefficients of correlation between the CPX parameters and various clinical variables, including H2ARDD score, H2ARDD score components (organic heart disease, anemia, renal dysfunction, diabetes mellitus, and diuretic use), consecutive variables related to the H2ARDD score components (B-type natriuretic peptide [BNP] level, left ventricular ejection fraction [LVEF], hemoglobin level, estimated GFR, and hemoglobin A1c level), and other clinical variables (sex, age, resting heart rate, body mass index, body height, chronic AF, hypertension, and use of β-blockers, renin–angiotensin system inhibitors, and statins). Next, to evaluate the independent relationship between the

H2ARDD score with the CPX parameters, the following 3 adjusted multiple linear regression analysis models were performed: H2ARDD score+components of H2ARDD score (model 1), H2ARDD score+consecutive variables related to components of H2ARDD score (model 2), and variables in model 2+other clinical variables (model 3). Variables in each multivariate model were selected in a forward stepwise method.

The analyses were performed by using SPSS version 19.0 software (SPSS Inc., Chicago, Illinois) for Windows (Microsoft Corporation, Redmond, Washington). Statistical significance was set at 2-sided $p < 0.05$.

3. Results

3.1. Patient characteristics

The characteristics of the study patients (i.e., those with AF, $n=344$) are shown in Table 1. The patients with AF in the present study included 266 men (77.3%) with a mean age of 62.7 years. Organic heart disease and comorbidities of renal dysfunction, diabetes mellitus, and anemia were observed in 167 (48.5%), and in 103 (29.9%), 48 (14.0%), and 13 (3.8%) of the patients with AF, respectively. β-Blockers, diuretics, anticoagulants, and antiplatelet drugs were prescribed for 48.3%, 44.5%, 61.0%, and 54.7% of the patients with AF, respectively.

3.2. Distribution of the CPX parameters according to H2ARRD score

The CPX parameters (peak $\dot{V}O_2$, AT, $\dot{V}E$–$\dot{V}CO_2$ slope, and $\Delta\dot{V}O_2/\Delta WR$) were worse in the patients with than in those without each of the H2ARDD score components (Table 2). The only exception was the association between $\dot{V}E$–$\dot{V}CO_2$ slope and anemia, which showed an insignificant difference ($p=0.243$). Accordingly, as these components accumulated, significant differences were found between low (0 point) and high (6 points) H2ARDD scores in peak $\dot{V}O_2$ (22.8 vs. 9.1 mL/min kg), AT (14.1 vs. 7.2 mL/min kg), $\dot{V}E$–$\dot{V}CO_2$ slope (29.2 vs. 42.1), and $\Delta\dot{V}O_2/\Delta WR$ (10.3 vs. 6.5 mL/min W), respectively (Fig. 1).

3.3. Relationship between CPX parameters and H2ARDD score

The coefficients of correlation between the CPX parameters and the various clinical variables are shown in Table 3. H2ARDD score was significantly associated with all the CPX parameters ($r=-0.568$, -0.544, 0.457, and -0.474 for peak $\dot{V}O_2$, AT, $\dot{V}E$–$\dot{V}CO_2$ slope, and $\Delta\dot{V}O_2/\Delta WR$, respectively; all $p<0.001$). Notably, the consecutive variables related to the H2ARDD score components (BNP level, LVEF, hemoglobin level, estimated GFR, and hemoglobin A1c level) were all significantly related to all of the CPX parameters, with the exception of the hemoglobin A1c level for peak $\dot{V}O_2$, $\dot{V}E$–$\dot{V}CO_2$ slope, and $\Delta\dot{V}O_2/\Delta WR$.

Next, to identify the independent effects of the H2ARDD score on the CPX parameters, the 3 adjusted multiple linear regression analysis models were performed (Table 4). In model 1, the effects of the H2ARDD score on the CPX parameters remained independent after adjustment for the H2ARDD score components, with attenuation of the effect of each component, suggesting that the scoring system could work better for the accumulated parameters than for the individual components. In model 2, the effects of the H2ARDD score on the CPX parameters remained independent after adjustment for consecutive variables related to the H2ARDD score components. Moreover, in model 3, the effects of the H2ARDD score on the CPX parameters remained independent even after adjustment for other clinical variables, adding to the consecutive variables in model 2.

Table 1
Background characteristics of the study patients with atrial fibrillation.

Variable	Total ($n=344$)
Male sex	266 (77.3)
Age (years)	62.7 ± 10.6
Body mass index (kg/m^2)	23.9 ± 3.6
Paroxysmal atrial fibrillation	136 (39.5)
Chronic atrial fibrillation	208 (60.5)
Coexistence of organic heart disease	167 (48.5)
Valvular heart disease	124 (36.0)
Coronary heart disease	41 (11.9)
Myocardial infarction	17 (4.9)
Hypertrophic cardiomyopathy	6 (1.8)
Dilated cardiomyopathy	19 (5.5)
Others	0 (0.0)
New York Heart Association Class	
I	225 (65.4)
II	84 (24.4)
III	28 (8.1)
IV	7 (2.0)
≥ II	119 (34.6)
Comorbidities	
Hypertension	138 (40.1)
Renal dysfunction	103 (29.9)
Dyslipidemia	88 (25.6)
Diabetes mellitus	48 (14.0)
Anemia	13 (3.8)
Cardiac indices and laboratory data	
Resting heart rate (beats/min)	73.3 ± 17.8
Left ventricular ejection fraction (%)	58.1 ± 15.6
Brain natriuretic peptide (pg/mL)	258.3 ± 327.9
Hemoglobin (g/dL)	14.1 ± 1.6
Estimated GFR (mL/min m^2)	67.0 ± 15.7
Hemoglobin A1c (%)	6.0 ± 0.8
H2ARDD score	
0	111 (32.3)
1	50 (14.5)
2	40 (11.6)
3	67 (19.5)
4	63 (18.3)
5	11 (3.2)
6	2 (0.6)
Medications	
β-Blockers	166 (48.3)
Renin–angiotensin system inhibitors	152 (44.2)
Angiotensin-converting enzyme inhibitors	52 (15.1)
Angiotensin II receptor blockers	122 (35.5)
Diuretics	153 (44.5)
Loop diuretics	145 (42.2)
Thiazides	21 (6.1)
Potassium-sparing diuretics	117 (34.0)
Antiarrhythmic drug other than β-blockers	
Class I antiarrhythmic drug	53 (15.4)
Class III antiarrhythmic drug	19 (5.5)
Class IV antiarrhythmic drug	62 (18.0)
Digitalis	86 (25.0)
Antithrombotic drugs	
Anticoagulants	210 (61.0)
Antiplatelet drugs	188 (54.7)

Categorical and consecutive data are presented as number (percentage) and mean ± standard deviation, respectively.

4. Discussion

4.1. Major findings

We investigated the association between 4 CPX parameters (peak $\dot{V}O_2$, AT, $\dot{V}E$–$\dot{V}CO_2$ slope, and $\Delta\dot{V}O_2/\Delta WR$) and a novel scoring system for the estimation of the risk for HF events in patients with AF (the H2ARDD scoring system) and its components. Our findings were as follows: (1) The CPX parameters were significantly worse

Table 2
Differences in cardiopulmonary exercise testing parameters according to each H2ARDD score component.

H2ARDD score components	Peak $\dot{V}O_2$ (mL/min kg)	AT (mL/min kg)	$\dot{V}E$–$\dot{V}CO_2$ slope	$\Delta\dot{V}O_2/\Delta WR$ (mL/min W)
Organic heart disease				
Yes ($n=167$)	16.0 ± 5.3	10.7 ± 2.9	36.0 ± 8.7	8.5 ± 2.0
No ($n=177$)	21.6 ± 5.8	13.5 ± 3.0	30.2 ± 5.8	10.0 ± 1.8
p Value	< 0.001	< 0.001	< 0.001	< 0.001
Anemia				
Yes ($n=13$)	13.4 ± 5.1	9.6 ± 2.9	35.5 ± 7.1	7.3 ± 1.6
No ($n=331$)	19.1 ± 6.2	12.2 ± 3.2	32.9 ± 7.9	9.4 ± 2.0
p Value	0.001	0.004	0.243	< 0.001
Renal dysfunction				
Yes ($n=103$)	16.1 ± 5.8	10.7 ± 3.1	36.4 ± 9.5	8.4 ± 2.1
No ($n=241$)	20.1 ± 6.0	12.7 ± 3.1	31.6 ± 6.6	9.7 ± 1.8
p Value	< 0.001	< 0.001	< 0.001	< 0.001
Diabetes mellitus				
Yes ($n=48$)	15.6 ± 4.7	10.7 ± 2.7	35.3 ± 8.4	8.7 ± 2.2
No ($n=296$)	19.4 ± 6.3	12.3 ± 3.2	32.7 ± 7.7	9.4 ± 1.9
p Value	< 0.001	< 0.001	0.033	0.027
Diuretics use				
Yes ($n=153$)	15.4 ± 5.3	10.4 ± 2.9	36.6 ± 8.8	8.3 ± 2.1
No ($n=191$)	21.6 ± 5.5	13.5 ± 2.8	30.2 ± 5.6	10.0 ± 1.6
p Value	< 0.001	< 0.001	< 0.001	< 0.001

The parameter data are presented as mean ± standard deviation.

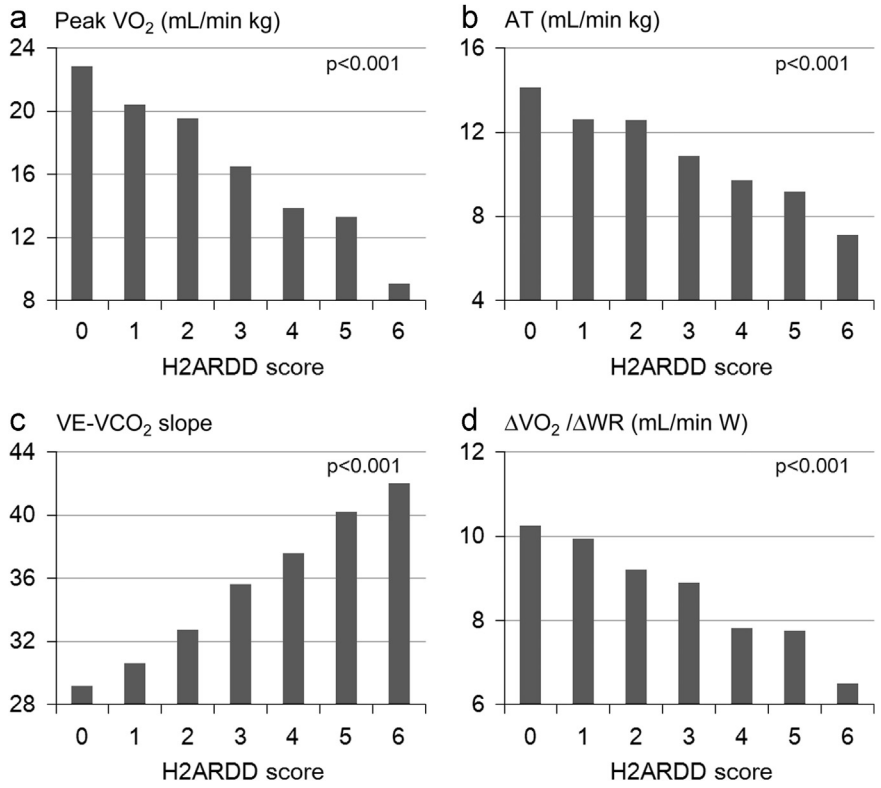

Fig. 1. Cardiopulmonary exercise testing parameters in the AF patients according to H2ARDD score.

in the patients with than in those without each of H2ARDD score compared with those without them. (2) Accordingly, the CPX parameters were significantly different between the low and high H2ARDD scores, which seemed to reflect the cumulative effect of each H2ARDD score component. Finally, (3) the H2ARDD score was independently associated with all the 4 CPX parameters even after adjustment for various clinical covariates.

4.2. Clinical implications

HF is a complication of AF that significantly affects the patients' mortality [4]. The incidence rate of HF in patients with AF has been reported to be approximately 1–10% per year [4,6,19–21], although the figure is widely distributed according to patient backgrounds. The first, crucial step in preventing the development of HF in

Table 3
Coefficient of correlation between the cardiopulmonary exercise testing parameters and various clinical variables.

Variables	Peak $\dot{V}O_2$	AT	$\dot{V}E$–$\dot{V}CO_2$ slope	$\Delta\dot{V}O_2/\Delta WR$
H2ARDD score	−0.568***	−0.544***	0.457***	−0.474***
Components of H2ARDD score				
Organic heart disease	−0.452***	−0.433***	0.373***	−0.356***
Anemia	−0.173**	−0.155**	0.063	−0.199***
Renal dysfunction	−0.294***	−0.287***	0.282***	−0.302***
Diabetes mellitus	−0.214***	−0.181***	0.115*	−0.120*
Diuretic use	−0.495***	−0.486***	0.407***	−0.424***
Consecutive variables related to components of H2ARDD score				
Brain natriuretic peptide (pg/mL)	−0.357***	−0.347***	0.424***	−0.332***
Left ventricular ejection fraction (%)	0.216***	0.250***	−0.190***	0.200***
Hemoglobin (g/dL)	0.358***	0.305***	−0.225***	0.379***
Estimated GFR (mL/min m^2)	0.293***	0.270***	−0.265***	0.310***
Hemoglobin A1c (%)	−0.130	−0.150*	0.104	−0.028
Other clinical variables				
Male sex	0.277***	0.221***	−0.107*	0.286***
Age (years)	−0.429***	−0.271***	0.302***	−0.292***
Resting heart rate (beats/min)	−0.214***	−0.214***	0.124*	−0.223***
Body mass index (kg/m^2)	0.038	−0.035	−0.172**	0.272***
Body height (cm)	0.342***	0.241***	−0.196***	0.346***
Chronic form of atrial fibrillation	−0.064	−0.017	0.141**	−0.076
Hypertension	−0.181***	−0.120*	−0.052	−0.101
β-Blocker use	−0.291***	−0.325***	0.173**	−0.311***
Renin–angiotensin system inhibitor use	−0.458***	−0.442***	0.239***	−0.345***
Statin use	−0.230***	−0.220***	0.086	−0.086

Peak $\dot{V}O_2$, peak O_2 uptake; AT, anaerobic (gas exchange) threshold; $\dot{V}E$–$\dot{V}CO_2$ slope, slope of the increase in ventilation to the increase in CO_2 output; $\Delta\dot{V}O_2/\Delta WR$, ratio of the increase in $\dot{V}O_2$ to the increase in work rate.

*** $p < 0.001$.
** $p < 0.01$.
* $p < 0.05$.

patients with AF is to identify high-risk patients. We therefore previously focused on the risk of hospitalization or death from HF, without distinguishing histories of HF, and developed a novel risk-scoring system, the H2ARDD scoring system [6].

CPX is a recognized modality for assessing exercise capacity. Classic CPX parameters, including peak $\dot{V}O_2$, AT, $\dot{V}E$–$\dot{V}CO_2$ slope, and $\Delta\dot{V}O_2/\Delta WR$, all reflect heart disease severity and the ability of cardiac patients to perform activities of daily living [7–17]. The peak $\dot{V}O_2$ in cardiac patients generally reflects maximal cardiac output, or the pumping reserve of the heart. The $\dot{V}E$–$\dot{V}CO_2$ slope, which ranges from approximately 24–34 in healthy subjects, becomes steeper in cardiac patients according to heart failure severity [22]. Theoretically, a steep $\dot{V}E$–$\dot{V}CO_2$ slope during exercise is assumed to relate to ventilation/perfusion mismatch such as an increased ratio of pulmonary dead space to tidal volume. Lactic acidosis from exercise occurs at lower intensities as heart disease worsens, which is reflected by a lower AT. $\Delta\dot{V}O_2/\Delta WR$ reflects the rate of increase in cardiac output during incremental exercise [23] and decreases with heart disease severity.

In the present study, we evaluated whether H2ARDD score is related to the 4 classic CPX parameters to clarify the pathophysiological basis of the risk-scoring system and found that the H2ARDD score was significantly associated with all of the CPX parameters. Moreover, the association is independent even after adjustment for various clinical covariates. These results provide a potential pathophysiological basis for the H2ARDD score as a risk-scoring system for predicting HF events in patients with AF.

4.3. Pathophysiological link between the H2ARDD score components and the CPX parameters

Here we discuss why H2ARDD score might be related to the CPX parameters. Oxygen uptake increases during incremental exercise, with peak $\dot{V}O_2$ representing the highest rate of oxygen uptake achieved. A reduction in its level may result from a variety of factors [24], including limited cardiac output, poor peripheral blood flow, impaired skeletal muscle metabolism, or early termination of the test because of cardiac-related or other symptoms. A similar relationship existed between the H2ARDD score in our study and AT because AT and peak $\dot{V}O_2$ were similarly affected by HF severity or the patients' backgrounds, including age [10].

In patients with organic heart disease, limited cardiac output, either from reduced systolic [13] or impaired diastolic function [16], is the main cause of reductions in peak $\dot{V}O_2$, AT, and $\Delta\dot{V}O_2/\Delta WR$ and an increase in $\dot{V}E$–$\dot{V}CO_2$ slope.

Patients with diabetes mellitus, either type 1 or 2, exhibit exercise intolerance [25,26]. This may be explained in part by myocardial contractile dysfunction resulting from exposure to high blood glucose levels via mitochondrial dysfunction or extracellular matrix remodeling, linking to advanced glycation end products (AGEs) [27]. The exercise intolerance seen in patients with DM may also be explained by systemic problems, including impaired bioenergetic capacity of skeletal muscle mitochondria [28], impaired capillary recruitment in exercising muscles [29], or impaired chronotropic response to exercise.

The role of anemia in exercise intolerance can be understood simply as reduced oxygen delivery to the exercising muscles. Anemia is more prevalent in severe HF and is known to worsen patient prognosis in HF [30]. The potential mechanisms by which anemia can worsen HF include exacerbation of myocardial and peripheral hypoxia, increased venous return and cardiac work, and consequent left ventricular hypertrophy. Hypoxia can also potentially lead to activation of neurohormones and cytokines. In turn, cytokines can exacerbate the anemia, leading to a vicious cycle, the so-called cardiorenal anemia syndrome [31]. Peak $\dot{V}O_2$ and exercise duration were reported to be significantly improved by

Table 4
Multiple linear regression models for predicting cardiopulmonary exercise testing parameters by using the H2ARDD score, its components, and other clinical variables.

Variables	Peak $\dot{V}O_2$	AT	$\dot{V}E$–$\dot{V}CO_2$ slope	$\Delta\dot{V}O_2/\Delta WR$
Model 1				
H2ARDD score	−0.735**	−0.422**	0.457***	−0.820**
Organic heart disease	0.191*	NS	NS	0.348**
Anemia	NS	NS	NS	NS
Renal dysfunction	NS	NS	NS	NS
Diabetes mellitus	NS	NS	NS	0.123*
Diuretic use	NS	−0.155*	NS	NS
Model 2				
H2ARDD score	−0.444**	−0.399**	0.280**	−0.299**
Brain natriuretic peptide (pg/mL)	−0.192**	−0.206**	0.320**	−0.193**
Left ventricular ejection fraction (%)	NS	NS	NS	NS
Hemoglobin (g/dL)	NS	NS	NS	0.159*
Estimated GFR (mL/min m^2)	NS	NS	NS	NS
Hemoglobin A1c (%)	NS	NS	NS	NS
Model 3				
H2ARDD score	−0.370**	−0.321**	0.190*	−0.253**
Brain natriuretic peptide (pg/mL)	NS	−0.145*	0.276**	NS
Left ventricular ejection fraction (%)	NS	NS	NS	NS
Hemoglobin (g/dL)	NS	NS	NS	NS
Estimated GFR (mL/min m^2)	NS	NS	NS	NS
Hemoglobin A1c (%)	NS	NS	NS	NS
Male sex	NS	0.142*	NS	NS
Age (years)	−0.391**	−0.228**	0.215**	−0.237**
Resting heart rate (beats/min)	NS	NS	NS	−0.178**
Body mass index (kg/m^2)	−0.244**	−0.247**	NS	NS
Body height (cm)	NS	NS	NS	0.163*
Chronic form of atrial fibrillation	−0.191**	NS	0.242**	−0.214**
Hypertension	NS	NS	NS	NS
Beta blocker use	−0.284**	−0.245**	0.148*	−0.272**
Renin–angiotensin system inhibitor use	NS	NS	NS	NS
Statin use	NS	NS	NS	NS

Peak $\dot{V}O_2$, peak O_2 uptake; AT, anaerobic (gas exchange) threshold; $\dot{V}E$–$\dot{V}CO_2$ slope, slope of the increase in ventilation to the increase in CO_2 output; $\Delta\dot{V}O_2/\Delta WR$, ratio of the increase in $\dot{V}O_2$ to the increase in work rate.

*** $p < 0.001$.
** $p < 0.01$.
* $p < 0.05$.

normalization of hemoglobin concentration by erythropoietin administration in patients with HF [32], demonstrating the significant role of hemoglobin concentration in exercise capacity.

However, the role of renal dysfunction in exercise intolerance is less easily understood. One possible explanation is an indirect link via the coexistence of atherosclerotic disease. Factors associated with renal dysfunction, including oxidative stress, inflammation, and conditions promoting coagulation, are known to promote atherosclerosis and impair endothelial function [33]. Thus, renal dysfunction is strongly associated with ischemic heart disease [34]. Renal dysfunction can also be exacerbated by reduced renal perfusion as a consequence of left ventricular dysfunction.

Diuretic use indicates that a patient is in a state of diuretic-dependent HF and, as such, is merely a marker for a particular HF state. However, it is independently statistically associated with all the 4 classic CPX parameters in the present study.

4.4. Study limitations

CPX was performed for patients with particular indications for evaluating exercise capacity and/or HF severity. Thus, the subjects in the present study may not represent the general AF patient population. In addition, our database consisted of a cohort of patients from a single cardiovascular hospital in Japan, and the study population included only Japanese patients. Therefore, the results should be carefully interpreted when applied to different populations.

5. Conclusions

In this study, the H2ARDD score was independently associated with the well-established CPX parameters in our patients with AF. This result provides a potential pathophysiological basis for the H2ARDD scoring system as a method of risk stratification to predict HF events in patients with AF.

Conflict of interest

None.

Acknowledgments

We thank Shiro Ueda and Nobuko Ueda at Medical Edge Co., Ltd., for assembling the database by using the Clinical Study Supporting System (CliSSS). We also thank Ineko Hayakawa, Hiroaki Arai, and Hiroshi Aoki for the data management and system administration.

References

[1] Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. J Am Med Assoc 2001;285:2370–5.

[2] Lloyd-Jones DM, Wang TJ, Leip EP, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation 2004;110:1042–6.
[3] Benjamin EJ, Wolf PA, D'Agostino RB, et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998;98:946–52.
[4] Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. Circulation 2003;107:2920–5.
[5] Suzuki S, Yamashita T, Otsuka T, et al. Recent mortality of Japanese patients with atrial fibrillation in an urban city of Tokyo. J Cardiol 2011;58:116–23.
[6] Suzuki S, Sagara K, Otsuka T, et al. A new scoring system for evaluating the risk of heart failure events in Japanese patients with atrial fibrillation. Am J Cardiol 2012;110:678–82.
[7] Mancini DM, Eisen H, Kussmaul W, et al. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation 1991;83:778–86.
[8] Poggio R, Arazi HC, Giorgi M, et al. Prediction of severe cardiovascular events by VE/VCO_2 slope versus peak VO_2 in systolic heart failure: a meta-analysis of the published literature. Am Heart J 2010;160:1004–14.
[9] Weber KT, Janicki JS, McElroy PA. Determination of aerobic capacity and the severity of chronic cardiac and circulatory failure. Circulation 1987;76: VI40–VI45.
[10] Itoh H, Koike A, Taniguchi K, et al. Severity and pathophysiology of heart failure on the basis of anaerobic threshold (AT) and related parameters. Jpn Circ J 1989;53:146–54.
[11] Koike A, Itoh H, Taniguchi K, et al. Detecting abnormalities in left ventricular function during exercise by respiratory measurement. Circulation 1989;80: 1737–46.
[12] Clark AL, Volterrani M, Swan JW, et al. The increased ventilatory response to exercise in chronic heart failure: relation to pulmonary pathology. Heart 1997 138–46.
[13] Francis DP, Shamim W, Davies LC, et al. Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuous and independent prognostic value from VE/VCO(2)slope and peak VO(2). Eur Heart J 2000;21:154–61.
[14] Koike A, Itoh H, Kato M, et al. Prognostic power of ventilatory responses during submaximal exercise in patients with chronic heart disease. Chest 2002;121:1581–8.
[15] Guazzi M, Myers J, Peberdy MA, et al. Cardiopulmonary exercise testing variables reflect the degree of diastolic dysfunction in patients with heart failure-normal ejection fraction. J Cardiopulm Rehabil Prev 2010;30:165–72.
[16] Kitzman DW, Higginbotham MB, Cobb FR, et al. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank–Starling mechanism. J Am Coll Cardiol 1991;17:1065–72.
[17] Guazzi M, Myers J, Arena R. Cardiopulmonary exercise testing in the clinical and prognostic assessment of diastolic heart failure. J Am Coll Cardiol 2005;46:1883–90.
[18] Koike A, Hiroe M, Adachi H, et al. Oxygen uptake kinetics are determined by cardiac function at onset of exercise rather than peak exercise in patients with prior myocardial infarction. Circulation 1994;90:2324–32.
[19] Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med 2008;358:2667–77.
[20] Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med 2002;347:1834–40.
[21] Yusuf S, Healey JS, Pogue J, et al. Irbesartan in patients with atrial fibrillation. N Engl J Med 2011;364:928–38.
[22] Chua TP, Ponikowski P, Harrington D, et al. Clinical correlates and prognostic significance of the ventilatory response to exercise in chronic heart failure. J Am Coll Cardiol 1997;29:1585–90.
[23] Hansen JE, Sue DY, Oren A, et al. Relation of oxygen uptake to work rate in normal men and men with circulatory disorders. Am J Cardiol 1987;59:669–74.
[24] Harrington D, Anker SD, Chua TP, et al. Skeletal muscle function and its relation to exercise tolerance in chronic heart failure. J Am Coll Cardiol 1997;30:1758–64.
[25] Bottini P, Tantucci C, Scionti L, et al. Cardiovascular response to exercise in diabetic patients: influence of autonomic neuropathy of different severity. Diabetologia 1995;38:244–50.
[26] Estacio RO, Regensteiner JG, Wolfel EE, et al. The association between diabetic complications and exercise capacity in NIDDM patients. Diabetes Care 1998;21:291–5.
[27] Willemsen S, Hartog JWL, Hummel YM, et al. Tissue advanced glycation end products are associated with diastolic function and aerobic exercise capacity in diabetic heart failure patients. Eur J Heart Failure 2011;13:76–82.
[28] Kelley DE, He J, Menshikova EV, et al. Dysfunction of mitochondria in human skeletal muscle in type 2 diabetes. Diabetes 2002;51:2944–50.
[29] Womack L, Peters D, Barrett EJ, et al. Abnormal skeletal muscle capillary recruitment during exercise in patients with type 2 diabetes mellitus and microvascular complications. J Am Coll Cardiol 2009;53:2175–83.
[30] Al-Ahmad A, Rand WM, Manjunath G, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. J Am Coll Cardiol 2001;38:955–62.
[31] Silverberg DS, Iaina A, Wexler D, et al. The pathological consequences of anaemia. Clin Lab Haematol 2001;23:1–6.
[32] Mancini DM, Katz SD, Lang CC, et al. Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. Circulation 2003;107:294–9.
[33] Foley RN, Parfrey PS, Sarnak MJ. Epidemiology of cardiovascular disease in chronic renal disease. J Am Soc Nephrol 1998;9:S16–23.
[34] Anavekar NS, McMurray JJV, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med 2004;351:1285–95.