IJC Heart & Vasculature 43 (2022) 101147

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature

Real-time analysis of heart rate variability during aerobic exercise in patients with cardiovascular disease

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ARTICLE INFO

Keywords:
Heart rate variability
Cardiac rehabilitation
Aerobic exercise
Ventilatory threshold

ABSTRACT

Background: Exercise therapy for cardiovascular disease (CVD) is mainly evaluated based on the heart rate (HR) or Borg scale. However, these indices can be unreliable depending on the patient's medication or their subjective decisions; thus, alternative methods are required for easier and safer implementation of aerobic exercise. Here, we examined whether real-time analysis of HR variability (HRV) can help maintain exercise intensity at the ventilatory threshold (VT) during exercise.

Methods: Twenty-eight patients with CVD treated at Keio University Hospital between August 2018 and March 2020 were enrolled. Initially, oxygen uptake (VO_2) and HR at the VT were determined using the cardiopulmonary exercise test. Patients then performed aerobic exercise on a stationary bicycle for 30 min while a parameter of HRV, the high-frequency (HF) component, was monitored in real time using an electrocardiograph. The work rate during exercise was adjusted every 2 min to maintain the HF range between 5 and 10. The VO_2 and HR values, recorded every 2 min during exercise, were compared with those at VT. The Bland–Altman method was used to confirm similarity.

Results: VO_2 and HR during exercise were closely correlated with those at VT (e.g., 19 min after exercise initiation; VO_2: $r = 0.647$, HR: $r = 0.534$). The Bland–Altman plot revealed no bias between the mean values (e.g., 19 min; VO_2: −0.22 mL/kg/min; HR: −0.07/min).

Conclusion: Real-time HRV analysis with electrocardiograph alone during exercise can provide continuous and non-invasive exercise intensity measurements at VT, promoting safer and effective exercise strategies.

1. Introduction

Adequate regular physical activity is paramount to maintaining good health [1,2] and preventing cardiovascular diseases (CVDs); the current clinical practice guidelines and expert statements recommend aerobic exercise for patients with CVD [3–5]. Currently, exercise therapy for CVD is performed mainly based on the heart rate (HR) or Borg scale. However, HR may be influenced by chronotropic effects and the use of beta-blockers [6,7], and the Borg scale is unreliable due to its dependence on patients' subjective decisions. Therefore, alternative methods are needed to allow health care providers to implement a simpler and safer aerobic exercise regimen in accordance with the day-to-day physical condition of the patient and to expand the use of exercise therapy to outpatient settings. To date, there have been several analyses of HR variability (HRV) during exercise. HRV is a widely used non-invasive assessment of cardiac autonomic activity and can be used to indicate mortality and morbidity in patients with CVD [8–10]. Moreover, several studies have shown that the ventilatory threshold (VT) can be determined by assessing HRV [11–13]. We previously demonstrated that a power spectral analysis of HRV using the maximum entropy method combined with automatic recordings and measurements of the elapsed time between two consecutive R waves in an electrocardiogram (RR interval) at 1000 Hz enabled instantaneous visualization of high frequency (HF; 0.15–0.4 Hz), low frequency (LF; 0.04–0.15 Hz), and

Abbreviations: BNP, brain natriuretic peptide; CPX, cardiopulmonary exercise test; CR, cardiac rehabilitation; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HF, high-frequency; HR, heart rate; HRV, heart rate variability; IQR, interquartile range; LVEF, left ventricular ejection fraction; VCO_2, carbon dioxide production; VE, expiratory ventilation; VO_2, oxygen uptake; VT, ventilatory threshold; WR, work rate.

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https://doi.org/10.1016/j.ijcha.2022.101147
Received 27 July 2022; Received in revised form 10 September 2022; Accepted 4 November 2022

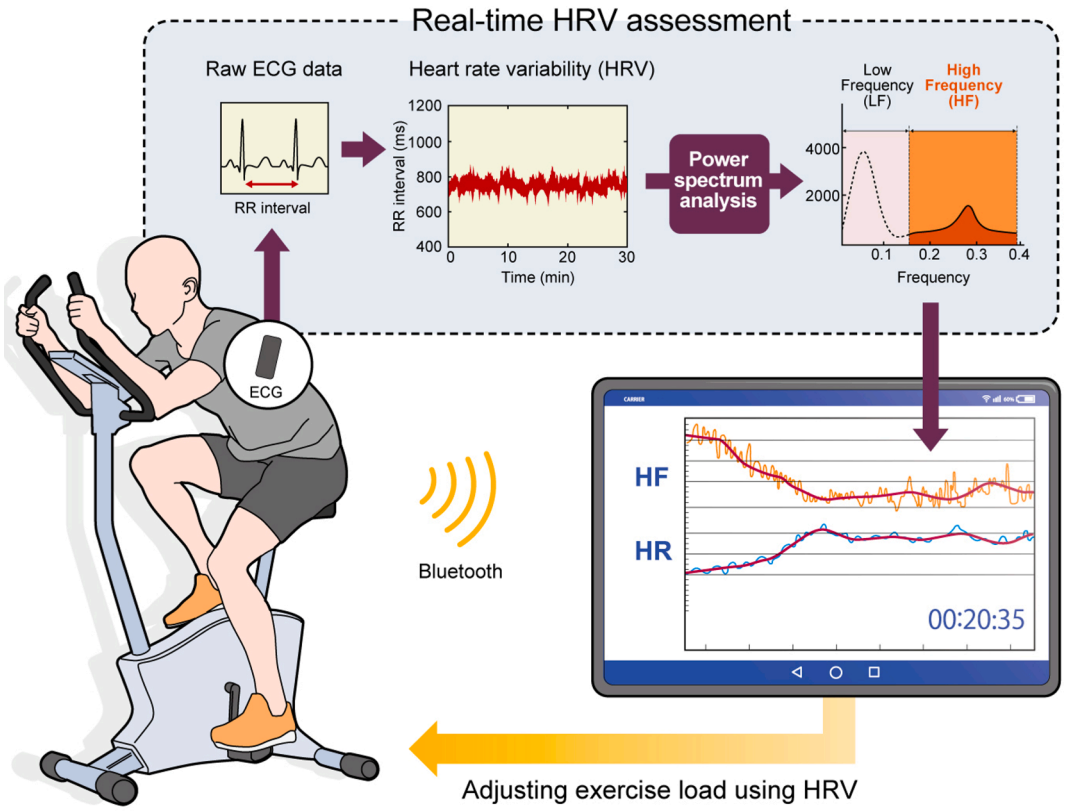

Fig. 1. Experimental procedure. HRV is continuously recorded, and WR is adjusted based on the high frequency (HF) component during the exercise (target HF: 5–10). ECG: electrocardiogram; HR: heart rate; HRV: heart rate variability; WR: work rate.

ratio of LF to HF (L/H) during incremental exercise. Further, a real-time evaluation of HRV with a single-lead electrocardiograph (ECG) during incremental exercise could be helpful for determining the aerobic exercise threshold [14]. These findings suggest that continuous monitoring of HRV during exercise aids the immediate clinical determination of VT, which is considered clinically equivalent to that in aerobic exercise.

This study aimed to identify the concerns of health care providers regarding the implementation of exercise therapy for CVD and to investigate whether continuous HRV monitoring through a wireless ECG data transfer system during exercise can provide continuous measurement of exercise intensity at VT in patients with CVD. Therefore, we designed an exercise protocol in which the work rate (WR) was adjusted based on the HF value and the VO_2, HR, and WR were quantitatively compared during exercise with those at VT determined by the cardiopulmonary exercise test (CPX).

2. Methods

2.1. Study sample and ethics approval

Twenty-eight patients with CVD (heart failure, cardiomyopathy, or coronary artery disease) who performed exercise therapy from August 2018 to February 2020 at our facility were enrolled. Patients with frequent ectopic beats, atrial fibrillation, 2- or 3-degree conduction blocks, or an HF component of HRV < 10 at rest were excluded. The study protocol was approved by the Institutional Review Board of Keio University School of Medicine [permission number: 20140023], and the study was conducted in accordance with the guidelines of the Declaration of Helsinki. All patients provided written informed consent.

2.2. Experimental procedure/exercise protocol

All patients performed CPX with the RAMP protocol for measurement of VO_2, HR, and WR at VT. WR at VT was defined as WR 1 min before VT, as is often followed in daily practice, considering the delay in physiological response. Within a week after the test, the patients exercised in the upright position on an electronically braked ergometer (Strength Ergo 8; Mitsubishi Electric Engineering Company, Tokyo, Japan). VO_2, HR, and HF were continuously recorded during the exercise (Fig. 1). The exercise protocol was as follows: for the first 5 min, the initial WR was half of WR at VT. For the subsequent 2 min, WR increased by three-quarters of WR at VT. Then, WR increased or decreased every 2 min by around 1/15th of the WR at VT using HRV, and the exercise lasted for a total of 25 min. We previously reported that an HF value of < 5 indicated exercising above the VT value [14]. WR was adjusted

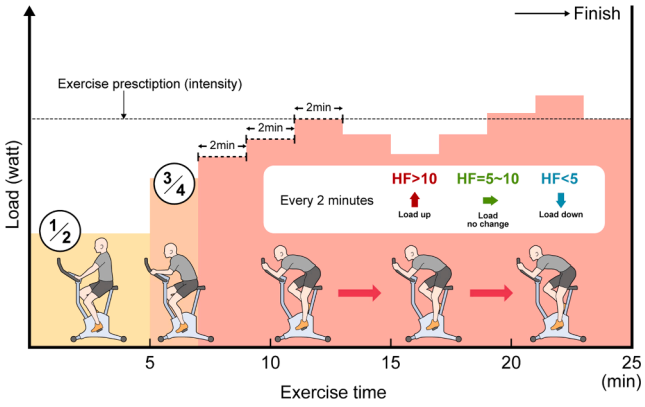

Fig. 2. Exercise protocol. WR increased or decreased by approximately 1/15th of WR at VT every 2 min. If HF is > 10, WR tends to increase. If HF is < 5, WR tends to decrease. The exercise lasted>25 min. HF: high frequency; WR: work rate.

using HF every 2 min, and the target HF was defined as 5–10 (Fig. 2). We compared VO_2, HR, and WR during the second half of the exercise with those at VT (VT-VO_2, VT-HR, and VT-WR) determined by CPX.

2.3. Exercise testing protocol

CPX was performed 1–3 h after a meal, and the intake of caffeinated beverages was restricted 3 h before exercise. An incremental cycle exercise was performed in a quiet room maintained at a constant temperature (22 °C–24 °C). The patients performed the test in the upright position on an electronically braked ergometer (Strength Ergo 8; Mitsubishi Electric Engineering Company, Tokyo, Japan). At first, the patients rested for 2 min on the ergometer. Following the 2-min rest, the patients performed a 2-min warm-up, pedaling at 0 W and then exercised at a progressively increasing intensity until they could no longer maintain the pedaling rate (volitional exhaustion). The intensity was increased with a RAMP protocol ergometer (10–15 W/min), depending on the exercise capacity of each patient. After the exercise tests were terminated, the patients were instructed to stop pedaling and to stay on the ergometer for 3 min (recovery phase). Single-lead and 12-lead electrocardiograms were continuously recorded. Blood pressure was measured every minute with an indirect automatic manometer.

2.4. Respiratory gas analysis

Expired gas flows were measured using a breath-by-breath automated system (Vmax®, Nihon Koden, Tokyo, Japan). Respiratory gas exchange, including expiratory ventilation (VE), oxygen uptake (VO_2), and carbon dioxide production (VCO_2), was monitored continuously and measured using a 10-s average. This system was subjected to a three-way calibration process, involving a flow volume sensor, gas analyzer, and delay time calibration. The peak VO_2 was calculated as the average oxygen consumption during the last 30 s of exercise. The ventilation/carbon dioxide (ventilator efficiency) slope (VE-VCO_2 slope) was calculated based on data collected from the onset of exercise to the respiratory compensation point, and was obtained by a linear regression analysis of data acquired throughout the entire period of exercise. Resting HR was defined as the average of the HR values recorded in the sitting position for 2 min before the exercise.

2.5. HRV measurement

ECG data were recorded using a wearable electrograph, Duranta® (Zaiken, Tokyo, Japan), and stored with a sampling rate of 1000 Hz. The Reflex Meijin® (Crosswell, Yokohama, Japan) was used to measure the RR intervals (beat-to-beat fluctuations in the HR) of the patients at 1000 Hz during the exercise. The RR interval data were instantaneously stored for real-time analyses. Based on these data, the power spectral densities were computed continuously by the maximum entropy method analyzing the RR intervals for 30 s using the Reflex Meijin®. After storing the RR interval data for the first 30 s at rest, the power continued to be quantified in terms of HF and LF, with data being updated for every heartbeat. With continuous analyses of every heartbeat, the power spectrum, including HF, LF, and L/H, was projected on the screen in real time during the exercise [14].

2.6. VT determination

VT was determined using the procedure described previously by Gaskill et al., using the ventilatory equivalent, excess carbon dioxide, and modified V-slope methods [15]. VT was evaluated as the point at which VE/VCO_2 was unchanged or decreased but VE/VO_2 increased, whereas $FETCO_2$ was unchanged or decreased but $FETO_2$ increased, and a plot of the production of CO_2 over VO_2 use showed an increase in the gradient of the slope from < 1 to > 1.

Table 1
Baseline characteristics of 28 patients with cardiovascular disease.

Demographic and anthropometric data	
Age, years	65.5 ± 8.0
Male, n (%)	25 (89)
Height, cm	169.2 ± 7.0
Weight, kg	70.1 ± 11.9
BMI, kg/m^2	24.2 ± 3.2
ICM, n (%)	22 (79)
DCM, n (%)	4 (14)
HCM, n (%)	2 (7)
Hypertension, n (%)	12 (43)
Diabetes mellitus, n (%)	11 (39)
Dyslipidemia, n (%)	23 (82)
Medication	
β-Blocker, n (%)	26 (93)
ACEi or ARB, n (%)	25 (89)
Antiplatelet drug, n (%)	22 (79)
Statin, n (%)	24 (86)
Laboratory data	
eGFR, mL/min per 1.73 m^2	62.4 ± 11.4
HbA1c, %	6.3 ± 0.8
BNP, pg/mL (IQR)	224.1 (34.5–282.2)
Echocardiography data	
LVEF (Simpson), %	48.8 ± 14.4
E/e'	10.3 ± 3.2

Data represented as n (%), mean ± standard deviation or median (IQR). BMI: body mass index; ICM: ischemic cardiomyopathy; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; ACEi: angiotensin converting enzyme inhibitors; ARB: angiotensin II receptor blocker; eGFR: estimated glomerular filtration rate; BNP: brain natriuretic peptide; IQR: inter quartile range; LVEF: left ventricular ejection fraction.

2.7. Demographic, anthropometric, and metabolic data

Clinical data regarding patient age, sex, anthropometry (height, body weight, and body mass index), past history, medications, and CVD type were collected. Creatinine levels, HbA1c values, serum brain natriuretic peptide (BNP) levels, and lipid profiles were obtained at baseline. The metabolic data at baseline, including BNP levels, were assessed on the day before CPX. The estimated glomerular filtration rate (eGFR) (mL/min/1.73 m^2) was calculated using the following equation: $eGFR = 186 \times (Cr / 88.4) - 1.154 \times (age)\text{-}0.203 \times (0.742 \text{ for women})$.

2.8. Survey questionnaire

Surveillance of exercise therapy for heart diseases was conducted at seven major cardiac rehabilitation (CR) centers in Japan. A total of 40 physicians and physical therapists responded to the survey. First, they were asked to rate their anxiety during exercise therapy with one of two choices; "yes" or "no." Second, they were asked to select the indicators that they used as a guide during exercise therapy from the following list: HR, blood pressure, Borg scale, exercise load, respiratory rate, and body weight. They were also asked to mention indicators they trusted the most. Finally, if they did have any concerns, they were asked to select the reasons for their concerns from the following: (1) anxiety about how much load should be applied, (2) fear of worsening heart failure, (3) difficulty gauging patient condition, (4) unreliable HR measurements, and (5) difficulties in expired gas analysis.

2.9. Statistical analyses

Results are represented as mean ± standard deviation or median with an interquartile range (IQR) for continuous variables and as percentages for categorical variables. The relationship between VO_2, HR, or WR every 2 min and that at the VT determined by the CPX were investigated by the Pearson correlation coefficient test. In addition, the Bland and Altman technique was applied to verify the similarities [16]. This comparison was a graphical representation of the difference

Table 2
Cardiopulmonary exercise test (CPX) results of 28 patients with cardiovascular disease.

Cardiopulmonary exercise test (CPX) results				
Variable	**Rest**	**Warm-up**	**VT**	**Peak**
HR, bpm	70 ± 12	76 ± 11	92 ± 14	117 ± 20
SBP, mmHg	124 ± 18	135 ± 27	144 ± 29	172 ± 45
DBP, mmHg	77 ± 13	81 ± 15	81 ± 14	82 ± 15
VO_2, mL/kg per minute	3.7 ± 0.6	6.1 ± 1.3	12.2 ± 2.2	18.4 ± 3.8
WR, watt	–	0	54 ± 10	100 ± 27
RQ	–	–	0.9 ± 0.1	1.2 ± 0.1
VE-VCO_2 slope	30.1 ± 4.6			

Data represented as mean ± standard deviation. VT: ventilatory threshold; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; VO_2: volume of oxygen uptake; WR: work rate; RQ: respiratory quotient; VE: expiratory ventilation; VCO_2: volume of carbon dioxide.

between the methods and the average of these methods. All probability values were two-tailed, and p-values of < 0.05 were considered statistically significant. All statistical analyses were performed with the SPSS version 25.0 software (SPSS Inc., Chicago, Illinois, USA).

3. Results

3.1. Patient characteristics

Table 1 shows the baseline clinical characteristics of the study cohort. Overall, the patients were predominantly male (89.0%), and the mean body mass index was 24.2 ± 3.2 kg/m^2, with a mean age and left ventricular ejection fraction (LVEF) of 65.5 ± 8.0 years and 48.8% ± 14.4%, respectively. Twenty-three (93%) patients were using beta-blockers. Past medical history included ischemic cardiomyopathy (79.0%), dilated cardiomyopathy (14.0%), and hypertrophic cardiomyopathy (7.0%). The CPX results are presented in Table 2. All patients completed the exercise tests without any complications, and the test was stopped when the patient could no longer maintain the desired pedal rate. Among the CPX variables, the peak VO_2, peak HR, and VE/VCO_2 slope were 18.4 ± 3.8 mL/kg/min, 117 ± 20/min, and 30.1 ± 4.6, respectively.

3.2. Relationship between VO_2 during exercise and VO_2 at VT

We compared VO_2 during the second half of the exercise with VT-VO_2 determined by CPX, to investigate whether continuous monitoring of HRV during exercise provides the exercise intensity at VT (Supplementary Table S1). First, the mean percentages of VO_2 during the exercise in relation to VT-VO_2 are shown in the Fig. 3a. VO_2 was maintained at 96%–100% of VT-VO_2 at 13–25 min after exercise initiation. The relationship between VO_2 during exercise and VT-VO_2 showed a good correlation, with a coefficient in the range of 0.5–0.7 (Fig. 3b, Supplementary Fig. 1, Supplementary Table S2). The Bland–Altman plot revealed that there were very small mean differences ranging from −0.09 to −0.54 mL/kg/min, and no biases between the mean values, which indicated strong agreements (Fig. 3b, Supplementary Figure S1, Supplementary Table S2).

3.3. Relationship between HR during exercise and HR at VT

Next, we compared the HR during the second half of exercise with the VT-HR determined by CPX (Supplementary Table S1). The mean

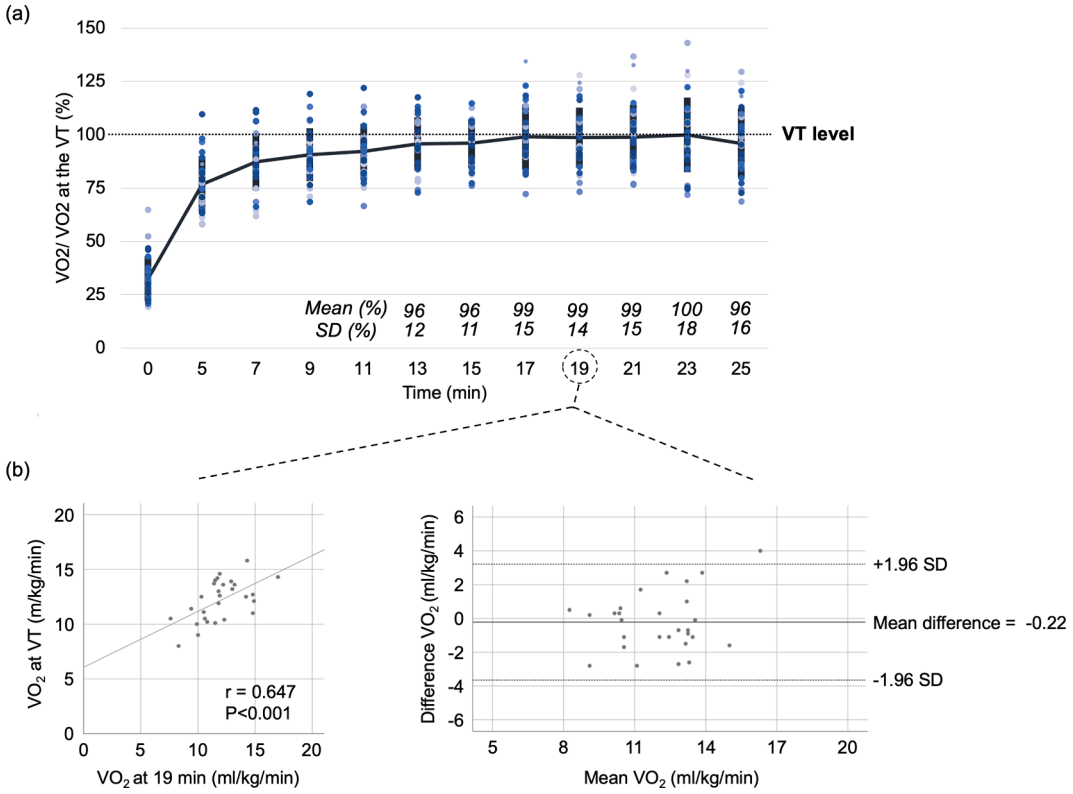

Fig. 3. Oxygen uptake (VO_2) during exercise based on heart rate variability. (a) Individual patient data regarding the mean percentage of the VO_2 during exercise to the VO_2 at the ventilatory threshold (VT). The mean ± SD values for each time point are shown at the bottom. "100%" on the vertical axis indicates VO_2 at VT. (b) The graphs on the left show the relationship between VO_2 at VT and VO_2 during exercise at 19 min after exercise initiation. The graphs on the right show the Bland–Altman plots, which indicate the respective differences between the VO_2 at VT and VO_2 during exercise at each time point (y-axis) against the mean of the VO_2 at VT and VO_2 during exercise at 19 min after exercise initiation. The thinner horizontal lines in Bland–Altman plot represent a ± 1.96 SD; SD: standard deviation; VO_2: oxygen uptake; VT: ventilatory threshold.

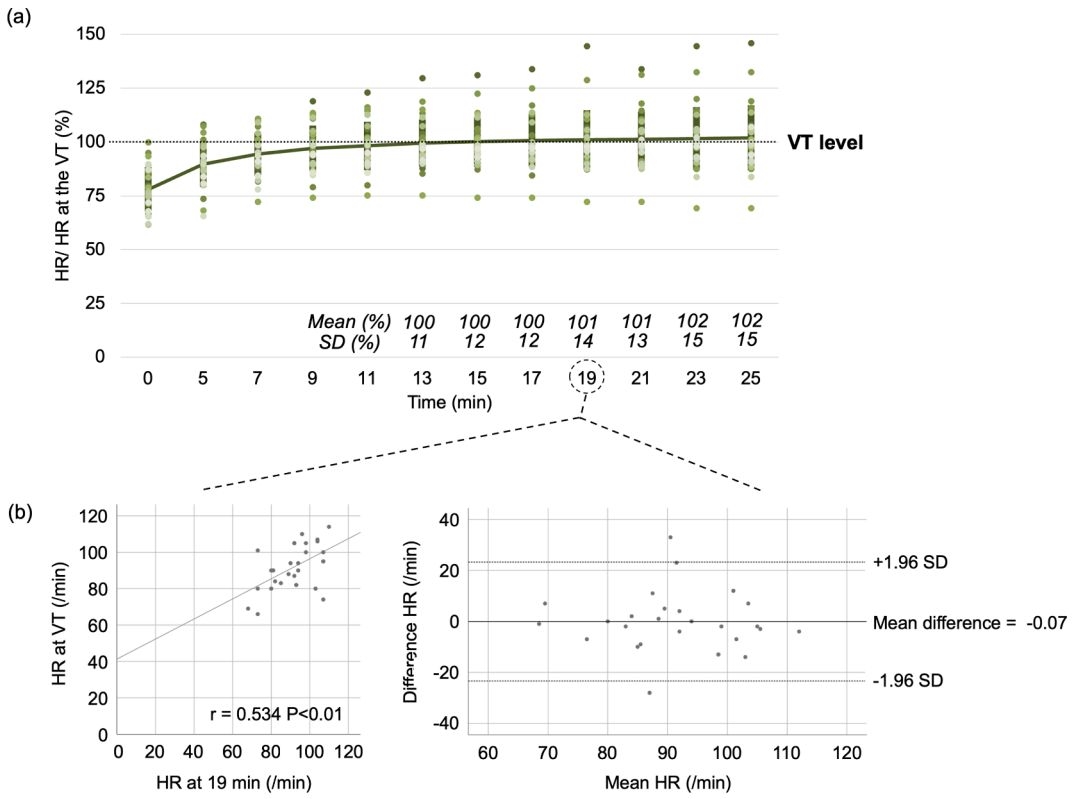

Fig. 4. HR during exercise based on HR variability. (a) Individual patient data regarding the mean percentage of the HR during the exercise in relation to the HR at VT. The mean ± SD values for each time point are shown at the bottom. "100%" on the vertical axis indicates HR at VT. (b) The graphs on the left show the relationship between the HR at VT and HR during exercise at 19 min after exercise initiation. The graphs on the right show the Bland–Altman plots, which indicate the respective differences between the HR at VT and HR during exercise at each time point (y-axis) against the mean of the HR at VT and HR during exercise at 19 min after exercise initiation (x-axis). The thinner horizontal lines in each Bland–Altman plot represent a ± 1.96 SD. HR: heart rate; SD: standard deviation; VT: ventilatory threshold.

percentage of HR during the exercise to HR are shown in Fig. 4a. HR was maintained at 100%–102% of VT-HR at 13–25 min after exercise initiation. The relationship between HR during exercise and VT-HR showed a good correlation coefficient in the range of 0.5–0.6 (Fig. 4b, Supplementary Fig. 2, Supplementary Table S2). The Bland–Altman plot revealed that there were very small mean differences ranging from −0.04 to −1.46 /min and no bias between the mean values, which indicated strong agreements (Fig. 4b, Supplementary Figure S2, Supplementary Table S2).

3.4. Relationship between WR during exercise and WR at VT

Finally, we compared the WR during the second half of exercise with the VT-WR determined by the CPX (Supplementary Table S1). The mean percentage of the WR during exercise in VT-WR is shown in Fig. 5a. WR was 76%– 80% of VT-WR and significantly lower than VT-WR. The correlation between the WR during the exercise and VT-WR was poor, with a coefficient in the range of 0.2–0.4 from 23 to 25 min after exercise initiation (Fig. 5b, Supplementary Figure S3, Supplementary Table S2). The Bland–Altman plots revealed that there were mean differences ranging from −10.0 to −12.5 W, and a distribution biased in a negative direction of the x-axis. In addition, the Bland–Altman plots showed the presence of proportional error 23–25 min after exercise initiation (Fig. 5b, Supplementary Figure S3, Supplementary Table S2). Therefore, these findings demonstrated that there was bias between the mean values.

3.5. Surveillance of exercise therapy for heart diseases at seven major CR centers in Japan

We surveyed 40 health care providers about their concerns during exercise therapy and approximately 90% of them were concerned about providing exercise therapy to patients with CVD. More than three-quarters of the health care providers used HR, blood pressure, Borg scale, and exercise workload as guides for exercise therapy (Fig. S4a). Of these, HR was the most trusted indicator (Fig. S4b). In addition, concerns regarding the current system of exercise therapy were as follows: (1) anxiety about how much load should be applied, (2) fear of worsening heart failure, and (3) difficulty gauging patient condition (Fig. S4c).

4. Discussion

The most striking result to emerge from this study is that VO_2 during exercise adjusted with an HF value of 5–10 was strongly correlated with VO_2 at the VT determined by CPX. To the best of our knowledge, this is the first study to reveal that real-time HRV assessment during exercise facilitates determination of the exercise intensity at VT in patients with CVD.

CR supported by multidisciplinary professionals plays an important role in disease management for patients with CVD [17,18], leading to improved exercise tolerance and quality of life as well as reduced hospitalization. Many benefits of CR are derived from exercise training, which has been found to reduce all-cause mortality and hospitalization [19,20], and to improve quality of life in patients with both heart failure and coronary artery disease. Currently, CPX using the RAMP protocol is the most effective tool used to prescribe exercise intensity for CR. Unlike

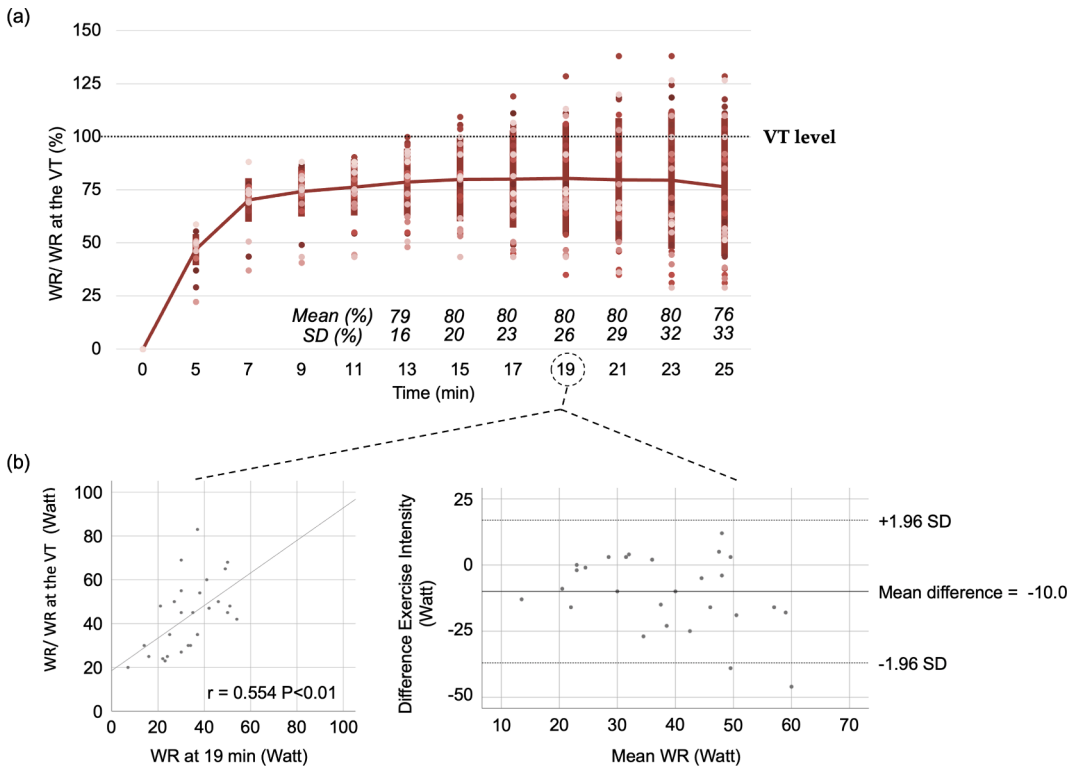

Fig. 5. WR during exercise based on HR variability. (a) Individual patient data regarding the mean percentage of the WR during the exercise to the WR at VT. The mean ± SD values for each time point are shown at the bottom. "100%" on the vertical axis indicates WR at VT. (b) The graphs on the left show the relationship between the WR at VT and WR during exercise at 19 min after exercise initiation. The graphs on the right show the Bland–Altman plot, which indicate the respective differences between the WR at VT and WR during exercise at each time point (y-axis) against the mean of the WR at VT and WR during exercise at 19 min after exercise initiation (x-axis). The thinner horizontal lines in each Bland–Altman plot represent a ± 1.96 SD. SD: standard deviation; VT: ventilatory threshold; WR: work rate.

the constant-load test, HR and VO_2 are associated with a delayed physiological response in the incremental-load exercise [21]. As a result, exercise at the intensity at the VT determined using the exercise test with the RAMP protocol is considered to be at a stronger intensity than that at VT. Therefore, in clinical practice, starting exercise therapy at an intensity of 1 min before VT has been recommended [22,23]. In our study, WR measured by real-time HF assessment was significantly lower than R at 1 min before VT. This suggested that exercise intensity at even 1 min before VT is stronger than that at VT. These findings suggest that the conventional approach using intermittent CPX cannot fully support the appropriate exercise intensity in daily practice.

In addition, surveillance of exercise therapy for CVD at major CR centers in Japan revealed that approximately 90% of health care providers had anxiety about how much load should be applied, feared worsening heart failure, and were concerned about difficulty gauging patient condition (Figure S4). Alternative methods of detecting the aerobic exercise threshold in real time is needed to resolve these concerns. This will decrease physicians' and co-medicals' anxiety about exercise training for patients with CAD and prevent worsening of heart failure.

HRV is widely used to noninvasively evaluate the cardiac autonomic nervous activity and is associated with mortality and morbidity in patients with myocardial infarction and left ventricular dysfunction [8–10]. We previously demonstrated that real-time evaluation of HRV with single-lead ECG during CPX could be helpful for detecting the aerobic exercise threshold [14]. In particular, VT was predicted using a cut-off HF value of 5. In the present study, maintaining an HF value of 5–10 during exercise was shown to provide the anaerobic metabolic threshold oxygen uptake. HF was re-evaluated every 2 min, and sufficient time was given for HF to stabilize due to the changes in WR. In the future, methods for real-time adjustment of WR should be developed to assign WR at VT. Moreover, surveillance of exercise therapy revealed that HR could be used as a reliable indicator of exercise therapy (Figure S4). In this study, HR during exercise coincided with that at the anaerobic metabolic threshold. However, a combination of HR with HRV for aerobic exercise could be more reliable because HR tends to be unreliable due to a chronotropic effect and use of beta-blockers in patients with CVDs.

Despite recommendations for CR for patients with CVD, the application of CR is extremely low, especially in the outpatient setting [24–28]. Physician recommendation for participation is the most powerful predictor of entry into CR, according to a multivariate analysis [29]. The need for expensive analyzers and expertise for the assessment of CPX could be reasons for physicians lacking a more aggressive attitude toward CR. If our method is used in exercise therapy, an appropriate aerobic exercise level could be attained safely in patients with CVDs without CPX. To date, exercise therapy has focused on quantity (frequency and duration of exercise) rather than quality (exercise intensity). Our method is of significance for future developments in CR and exercise therapy. In the future, if the algorithm of this study is incorporated in wearable devices that can record ECGs, CR centers can be relocated from hospitals to other institutions, such as commercial fitness clubs or even patients' homes. Moreover, this innovative system can improve the use of CR programs in outpatients.

4.1. Limitations

The findings of our study should be interpreted in light of the following limitations. First, with respect to patient selection, we targeted patients who had sinus rhythm but not arrhythmia, such as atrial fibrillation, because HRV analysis is not applicable in patients with irregular RR intervals on ECG. Hence, we excluded patients with

frequent ectopic beats and atrial fibrillation. Second, we also excluded patients with low HF value at rest (HF < 10). Previous studies have reported that such patients are at high risk of adverse events. Factors that may explain low HF such as comorbidities (including hypertension or diabetes mellitus), use and/or dose of beta-blockers, and LVEF could be present in these patients. Further research is warranted to develop a method to assess VT in such patients. Lastly, the number of subjects was small and the majority of patients were men. A further randomized study with a large sample size and long-term follow-up is required to address these limitations.

5. Conclusions

The results of this study showed that continuous monitoring of the HF values obtained from HRV using a wireless cardiac data transfer system during exercise can provide continuous aerobic exercise intensity measurements in patients with CVDs. This finding supports the concept that an exercise program with real-time HRV analysis of electrocardiographic data could help prescribe aerobic exercise without the need for a respiratory gas analyzer in patients with cardiovascular disease. Our method could assist health care providers in administering exercise therapy to patients with CVD.

6. Registration number

The study protocol was approved by the Institutional Review Board of Keio University School of Medicine (permission numbers: 20140023).

Funding

This work was supported by a grant from JST Grant Number JPMJPF210, Takeda Japan Medical Affairs Funded Research Grant 2018, the Nakatomi Foundation, and Meiji Yasuda Health Development Foundation. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

This work was supported by a grant from Takeda Japan Medical Affairs Funded Research Grant 2018, the Nakatomi Foundation, and Meiji Yasuda Health Development Foundation. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2022.101147.

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