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SCIENTIFIC INVESTIGATIONS

Utility of cyclic variation of heart rate score as a screening tool for sleep-disordered breathing in patients with heart failure

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Study Objectives: Patients with sleep-disordered breathing have cyclic variation of heart rate (CVHR) in response to respiratory events. However, limited data are available regarding the utility of CVHR as a screening tool for sleep-disordered breathing in patients with mixed heart failure (HF) and those without HF.

Methods: We enrolled consecutive patients with and without HF who underwent full polysomnographies with simultaneous Holter electrocardiogram monitoring. We determined the temporal position of the individual dips comprising the CVHR score using time-domain methods.

Results: The data of 101 patients, including 70 with and 31 without HF, were analyzed. The CVHR score was significantly correlated with the apnea-hypopnea index (r = .667, P < .001) and limits of agreement between the apnea-hypopnea index and CVHR score were −21.8 to 35.2. The receiver operating characteristic analysis demonstrated that the CVHR score (best cut-off of 23.5 events/h) identified severe sleep-disordered breathing with a sensitivity of 83.3%, specificity of 79.5%, and the area under the curve of 0.856. In addition, there was no interaction between the presence or absence of HF and the apnea-hypopnea index–CVHR score relationship (P = .323).

Conclusions: The CVHR score, determined by Holter electrocardiogram monitoring, is a useful tool for evaluating sleep-disordered breathing even in patients with mixed HF and patients without HF.

Keywords: cyclic variation of heart rate, Holter electrocardiogram, sleep-disordered breathing, heart failure, heart rate variability

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Holter electrocardiogram might be useful to assess sleep-disordered breathing (SDB) because patients with SDB showed cyclic variation of heart rate (CVHR). However, the ability to detect CVHR in patients with heart failure (HF) remained unknown; therefore, we aimed to evaluate whether CVHR was useful for detecting SDB in the population with HF.

Study Impact: The CVHR score was correlated with the apnea-hypopnea index assessed by full polysomnography in mixed patients with and without HF (r = .667, P < .001), and such correlations were consistent even when dividing the patients according to the presence of HF, taking β-blockers, and SDB patterns. Thus, our results showed Holter electrocardiogram might be useful for evaluating SDB in patients with HF.

INTRODUCTION

Sleep-disordered breathing (SDB) is a prevalent disorder that is known to be associated with poor cardiovascular outcomes in patients both with and without heart failure (HF).[1–3] Thus, it is important to identify SDB to determine the risk stratification for primary and secondary prevention of HF. However, many patients with SDB are undiagnosed because of the limited availability of polysomnography, which is the gold standard for SDB diagnosis.[4,5] Although some screening tools can be used to detect SDB, such as pulse oximetry and portable polygraphy,[5–7] these tools have not frequently been performed, particularly in patients with HF,[8] due to a lack of awareness of the importance of diagnosing SDB in patients with HF. It may be more possible for patients with HF and those at risk of HF (eg, stage A or B)[9,10] to undergo a Holter electrocardiogram rather than polysomnography or SDB screening. In addition, cardiac arrhythmia, particularly atrial fibrillation (AF) may play critical roles in the incidence and progression of HF[11] and SDB is known to be a risk factor for such cardiac arrhythmia in the primary and secondary prevention.[12] From these aspects, in the population of HF and not HF but having the risks of HF, it would be a great benefit to be able to evaluate SDB on Holter electrocardiogram.

Previous studies have suggested that with Holter electrocardiogram monitoring, patients with SDB showed cyclic variation of heart rate (CVHR) in response to each respiratory event, and that a Holter electrocardiogram might, therefore, be a useful screening tool for SDB.[13,14] However, the ability to detect CVHR in patients with HF has been considered limited because these patients are taking β-blockers and have complex SDB

patterns, including obstructive sleep apnea (OSA) and central sleep apnea (CSA). Nevertheless, for patients with HF, at least 2 studies have found a significant positive correlation between CVHR score and severity of SDB, assessed by home polygraphy, suggesting that the CVHR score can be used to assess SDB severity even in patients with HF.[15,16] However, it is still necessary to compare the CVHR score with SDB severity assessed by polysomnography, the gold standard of SDB assessment, in patients with HF and in mixed populations of patients both with and without HF to make the results more widely utilized and generalizable. However, to our knowledge, the CVHR score has never been validated by the apnea-hypopnea index (AHI) derived from polysomnography in populations including patients with HF, and limited data are available regarding the utility of CVHR as a screening tool for SDB in a mixed patient population of patients with HF and those without HF. In addition, whether the relationships between the CVHR score and severity of SDB on polysomnography differ between patients with and without HF remains unclear.

To explore the effectiveness of the Holter electrocardiogram in assessing SDB in a heterogeneous patient population including patients both with HF and without HF, we aimed to evaluate whether our CVHR assessment algorithm was useful for detecting SDB and if the CVHR score correlated with the severity of SDB assessed by polysomnography. Our specific hypothesis was that these correlations would remain significant even in a heterogeneous patient population of HF and non-HF and that there would be no interaction between the type of patients (with or without HF) that would affect the relationship between CVHR score and the severity of SDB.

METHODS

Study participants

We enrolled consecutive patients from our cardiologist-run sleep clinic who had undergone a full polysomnography to assess SDB from November 2016 to June 2018. The patients with HF met the following criteria: (1) men and women aged ≥ 20 years, (2) previous history of hospitalization for HF, (3) symptomatic patients with New York Heart Association Functional classification of II or III, (4) taking optimal medical therapy of HF, and (5) stable clinical status evidenced by the absence of acute exacerbations of dyspnea. For the control group, we enrolled patients without HF who were admitted for polysomnography to evaluate for SDB and met the following inclusion criteria: (1) men and women aged ≥ 20 years, (2) without a history of HF but with a risk of developing HF (stage A to B), (3) left ventricular ejection fraction > 50% confirmed by recent echocardiogram, and (4) plasma brain natriuretic peptide < 100 pg/mL. Thus, in patients without HF, we enrolled only patients whose brain natriuretic peptide and echocardiographic data were available within the previous 1 month. Patients with permanent/persistent AF, implanted pacemakers, frequent supraventricular/ventricular premature beats, known SDB on positive airway pressure therapy, and severe cognitive dysfunction were excluded because CVHR assessment would have been difficult. We also excluded patients who could not perform Holter electrocardiogram simultaneously with polysomnography in association with availability of the device and refusal to participate in the study or whose eligible data of polysomnography or Holter electrocardiogram were less than 180 minutes because of noisy signals, unexpected frequent premature beats, AF during the night of the study, or premature Holter removal because of difficulty sleeping.

Study protocol

This study was a prospective, single-center, observational study at the Sleep and Sleep-Disordered Breathing Center and the Department of Cardiovascular Medicine of Juntendo University Hospital in Tokyo, Japan. All the participants simultaneously underwent overnight polysomnography and Holter electrocardiogram during a 1-night hospital stay. Polysomnographic data and Holter electrocardiogram data were synchronized by aligning the Holter electrocardiogram recording time with the corresponding polysomnography recording time. The polysomnographic scoring and synchronization of time for heart rate analysis were performed by 2 independent investigators, each one blinded to the results of the other.

The study protocol was approved by the Institutional Review Board of our hospital and the study complied with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Overnight polysomnography

Overnight polysomnography was performed according to standard protocol and criteria using a digital polygraph system (Alice; Philips Respironics Inc., Murrysville, PA).[17] Polysomnographic data were manually scored by a sleep technician who was blinded to the CVHR score. Thoracoabdominal motion was monitored via respiratory inductance plethysmography, and airflow was measured by an oronasal thermal airflow sensor and nasal pressure cannula. Oxyhemoglobin saturation (SaO_2) was monitored by oximetry. Definitions and scoring methods were based on the American Academy of Sleep Medicine manual version 2.2.[17] Apnea and hypopnea events were quantified, and SDB severity was assessed using the frequency of apnea and hypopnea events per hour of sleep (AI [apnea index]; HI [hypopnea index]). Obstructive and central AHI scores were computed separately,[17] and participants were divided into an OSA-dominant group (≥ 50% of events obstructive) and a CSA-dominant group (> 50% of events central).

Holter electrocardiogram and CVHR measurement

Holter electrocardiogram recorders (FM-180S; Fukuda Denshi, Tokyo, Japan) were utilized simultaneously with polysomnography for CVHR data acquisition. The sampling frequency for the Holter electrocardiogram recordings was 128 Hz. In addition, the SCM-8000 Holter electrocardiogram analysis program (Fukuda Denshi Co, Ltd, Tokyo, Japan) was used for the CVHR analysis, and CVHR scores were automatically scored by the program. In the present study, the CVHR score was calculated by determining the number of CVHR events from sleep onset to arousal, which was determined using the period of sleep indicated on polysomnography. If supraventricular/ventricular premature beats were detected at more than 500 beats/h, we excluded these terms from the analysis.

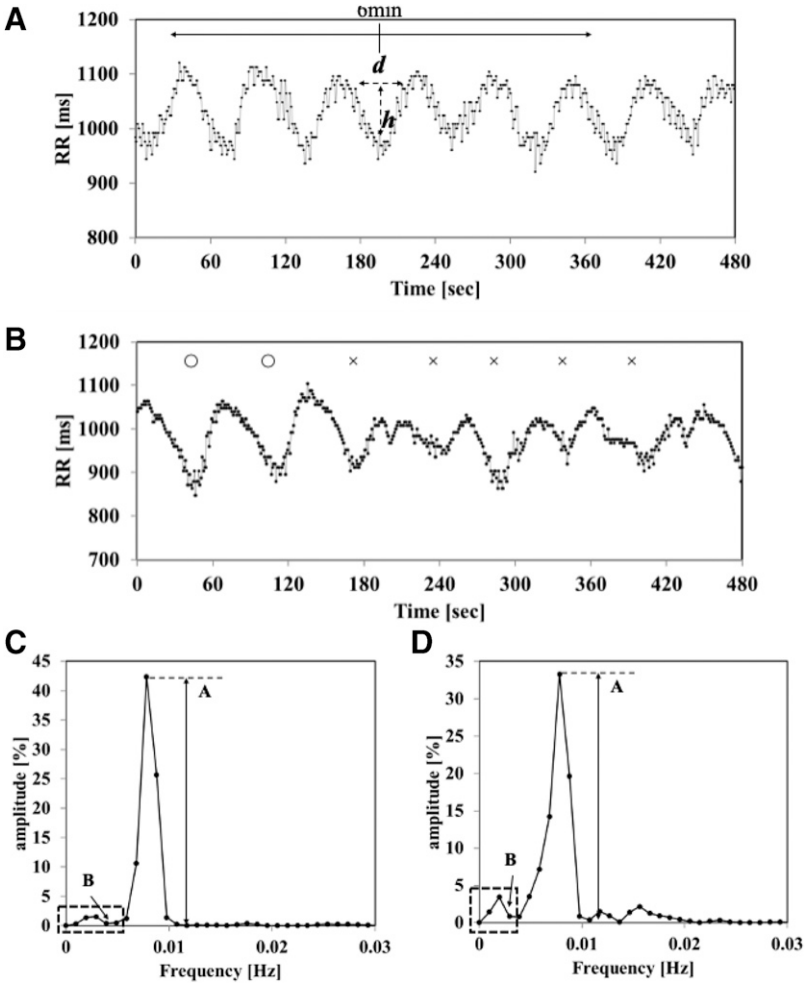
The outline of the algorithm (**Figure 1A**) is as follows: (1) CVHR is defined as a respiratory rate (RR) interval trend pattern with a depth *h* and a width *d* as 1 cycle; (2) the parameter *h* is updated using the RR interval data's statistics in the window and the current threshold.[16]

However, using this simple time-domain method, it was difficult to detect if the amplitude of the dip was low or if there was a large difference in the amplitude of each dip (cross mark in **Figure 1B**). To manage these problems, in the present study, the algorithm was updated by adding the ratio A/B of the spectrum amplitude "A" of the fundamental frequency to the average spectrum amplitude "B" lower than the fundamental frequency in the RR interval as the periodicity reliability parameter. **Figure 1C** shows a typical spectrum pattern of CVHR (**Figure 1A**). If the parameter "B" increased when a slow cycle overlapped with the RR trend data or when multiple cycles other than the fundamental frequency were mixed, the reliability parameter A/B would be reduced and it would be difficult to detect a CVHR. However, if the reliability parameter A/B was still high as shown in **Figure 1D**, which was the spectrum pattern of the cross mark of **Figure 1B**, the RR trend fluctuated at a constant cycle, and it was highly likely that a CVHR event had occurred. Therefore, the updated algorithm detected the CVHR events when the reliability parameter of A/B was 6 or more and improved the quality of the CVHR detection.[18] The CVHR score (events/h) is an index of the frequency of CVHR.

Other data collection

On the same day of polysomnography, height and body weight were obtained, and body mass index was calculated as weight in kilograms divided by height in meters squared. The presence or absence of AF was determined according to recent

Figure 1—The outline of the CVHR algorithm.



(A) An example of typical pattern of CVHR and the measuring window; *h* is the depth and *d* the width of the CVHR event. **(B)** An example of a difficult pattern for detecting the CVHR score. Although the cross marks in this figure seemed to have cyclic variations in RR interval, they could not be detected by the previous algorithm. **(C, D)** A spectral pattern comparison between stable **(C)** and the nonstable **(D)** CVHR patterns. **(C** and **D)** Spectral pattern of A and B, respectively. The amplitudes A and B were normalized to the integrated value of the full frequencies. The stable CVHR pattern **(C)** had a low amplitude B and a high A/B compared with those of the nonstable CVHR pattern **(D)**. However, the A/B ratio of **(D)** was still high, and the updated algorithm could detect these unstable CVHR pattern and improve the ability of detecting CVHR. CVHR = cyclic variation of heart rate, RR = respiratory rate.

electrocardiogram or Holter electrocardiogram data. Blood pressure and heart rate were obtained early in the morning after the overnight polysomnography. Plasma brain natriuretic peptide levels and a 2-dimensional echocardiography were obtained within the previous 1 month. The left ventricular ejection fraction was calculated according to the modified Simpson method.

Statistical analysis

Data are presented as the mean ± standard deviation or medians (interquartile range) for continuous variables and as ratio (%) for categorical variables. Characteristics between the 2 groups were compared using the independent Student's *t* test and the Mann-Whitney *U* test for continuous variables and the χ^2 test for categorical variables. Correlations between the AHI and CVHR score were assessed using the Spearman rank correlation coefficient, while Bland-Altman plots were used to visually represent mean bias and the limit of agreement between the AHI and CVHR score values. To assess the power of the CVHR score to detect severe SDB (ie, AHI ≥ 30 events/h), we computed the area under the receiver operating characteristic curve. The best cut-off CVHR score for predicting severe SDB was identified as the value that minimized the expression (sensitivity – [1 – specificity]). To compare correlation slopes, the interaction of the AHI-CVHR score with the groups (patients with HF or without HF, those taking or not taking β-blockers, those taking or not taking amiodarone, and those with central-dominant or obstructive-dominant SDB) was analyzed using the analysis of covariance. Correlations between separate AI, HI, and central/obstructive AHI and CVHR score were assessed using the Spearman rank correlation coefficient. A *P* value of < .05 was considered statistically significant. These analyses were performed using JMP 12.0.1 MDSU statistical software (SAS Institute, Cary, NC).

RESULTS

Group characteristics

A flowchart of this study is shown in **Figure 2**. During the study period, 159 patients with HF and 381 patients without HF underwent polysomnography under the cardiologists' orders. Among them, 82 with HF and 34 without HF met inclusion and exclusion criteria and were enrolled. In addition, those patients who had noisy signals on Holter electrocardiogram, unexpected frequent premature beats, AF during the night of the study, and those who took the Holter electrocardiogram off prematurely because of difficulty sleeping were also excluded from the study. In the end, data from 70 patients with and 31 without HF were analyzed. The baseline characteristics of the patients are shown in **Table 1**. In the entire group, the participants had a mean age of 61.3 years, were predominantly male (83.2%), and tended to be over weight (body mass index of 25.9). All patients without HF had risk factors for HF, such as hypertension, diabetes, and coronary artery disease. None of the patients took other antiarrhythmic medicines, such as verapamil or I-c antiarrhythmic medicine. Left ventricular ejection fraction was significantly lower, but heart rate, brain natriuretic peptide, central AHI, and use of β-blockers and amiodarone were significantly higher in patients with HF compared with those without HF.

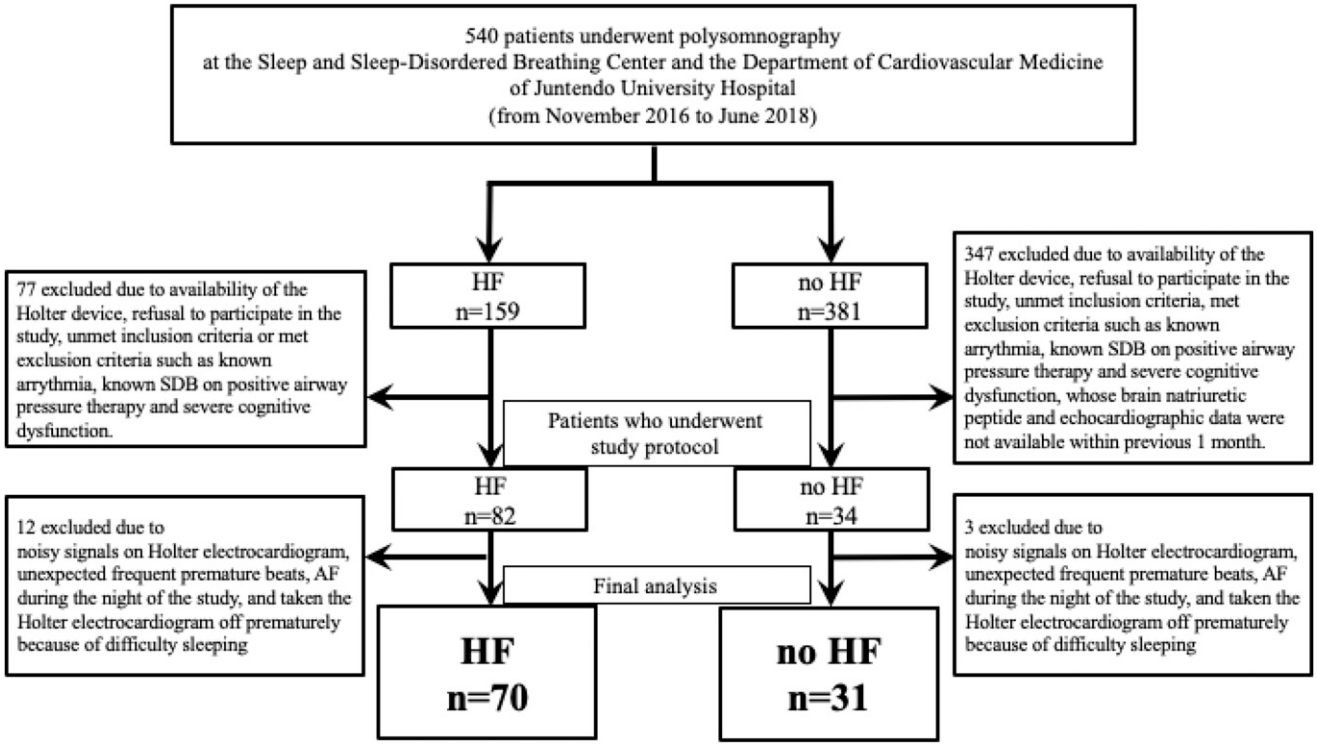
Correlation between AHI and CVHRs

Figure 3A shows the correlation between the AHI and CVHR score assessed in the entire study population (n = 101), demonstrating a significant positive correlation between the 2 scores (r = .667, P < .001). A Brand-Altman plot, in which the mean bias and limits of agreement were 6.67 and −21.8 to 35.2, respectively, is shown in **Figure 3B**. **Figure 4** shows the receiver operating characteristics analysis, demonstrating that the area under the curve was 0.856. In addition, the best CVHR score cut-off value for identifying severe SDB (AHI ≥ 30 events/h) was 23.5 events/h, with a sensitivity, specificity, and positive and negative predict value of 83.3%, 79.7%, 74.4%, and 87.0%, respectively. The interaction between HF and non-HF patients and the AHI-CVHR score relationship is shown in **Figure 5**. There was no significant relationship between the presence or absence of HF and the AHI-CVHR score (*P* for interaction = .323). However, there were significant positive correlations between the AHI and CVHR score for patients with HF (r = .644, P < .001) and for those without HF (r = .716, P < .001). In addition, no significant interaction was detected between the presence or absence of β-blocker use and the relationship between AHI and CVHR score (*P* for interaction = .972), but there were significant positive correlations between AHI and CVHR score for patients taking β-blockers (r = .680, P < .001) and for those not taking β-blockers (r = .659, P < .001) (**Figure 6A**). Although a significant positive correlation was detected between the groups with and without amiodarone intake (r = .746, P = .008 and r = .653, P < .001, respectively), there were no significant interactions between the 2 groups (*P* for interaction = .581). There were no significant interactions between CSA-dominant and OSA-dominant patients (*P* for interaction = 0.353) and the AHI-CVHR relationship, but there were significant positive correlations between AHI and CVHR score in CSA-dominant patients (r = .753, P < .001) and OSA-dominant patients (r = .660, P < .001) (**Figure 6B**). The correlations between separated central/obstructive AHI, AI, or HI and CVHR score are shown in **Figure 7**. There were significant positive correlations between each index and CVHR score (r = .289, P = .003; r = .551, P < .001; r = .536, P < .001; and r = .345, P < .001, respectively).

DISCUSSION

This is the first study to examine the ability of a Holter electrocardiogram–based CVHR score to estimate SDB using polysomnography in patients with HF and those without HF, and it was found to be effective in both groups. Our study provided several novel insights into the use of the CVHR score clinically to detect SDB in a heterogeneous patient population, which included patients with HF and those at risk of HF. First, this study showed that the CVHR score, using an updated algorithm, had significant positive correlations with the AHI. Second, these positive correlations were analyzed by full polysomnography, the gold-standard diagnostic tool for SDB. Third, the CVHR score could be used to identify severe SDB with a cut-off value of 23.5 events/h in a mixture of patients with and without HF. Fourth, correlation slopes between the CVHR score and AHI did not

Figure 2—Flow chart of this study.



A total of 540 patients consecutively underwent polysomnography at the Sleep and Sleep-Disordered Breathing Center and the Department of Cardiovascular Medicine of Juntendo University Hospital from November 2016 to June 2018. Among the 159 with and 381 without HF, 77 with HF and 347 without HF were excluded due to availability of the Holter device, refusal to participate in the study, unmet inclusion criteria, or for meeting the exclusion criteria. In addition, 12 with HF and 3 without HF who underwent this study protocol were excluded due to noisy signals on Holter electrocardiography, unexpected frequent premature beats, AF during the night of the study, or premature removal of the Holter monitor because of difficulty sleeping. Finally, 70 with and 31 without HF were analyzed. AF = atrial fibrillation, HF = heart failure, SDB = sleep-disordered breathing.

differ between patients with and without HF. Fifth, neither the presence or absence of β-blocker use nor the SDB pattern (CSA-dominant or OSA-dominant) altered the correlation between the CVHR score and AHI. These findings suggest that the CVHR score, based on Holter electrocardiogram recordings, could be a useful tool for assessing SDB. However, it is clinically important that a validation study be performed to confirm the ability of CVHR to detect SDB among a mixture of patients with and without HF.

SDB has been identified as a risk factor and comorbidity of HF and is prevalent, affecting approximately 50–75% of patients with HF.[19–21] Previous studies have suggested that SDB is not only a factor associated with HF progression, but also an independent predictor of worse clinical outcomes in patients who are at high risk of developing HF.[22] However, because of physicians' limited awareness and the low availability of polysomnography, SDB is not adequately diagnosed.[4] Although several screening tools are available for SDB, such as pulse oximetry and polygraphy,[5–7] these modalities have not been used globally to detect SDB, and therefore, most cases remain undiagnosed. One recent report suggested that SDB was tested for in only 2% of patients with HF.[8] Holter electrocardiography has been used more frequently in patients with HF to detect complicated atrial and ventricular arrythmias. In Japan, although approximately 1.3 million Holter electrocardiograms are performed annually, only 10,000 polysomnographies, 30,000 pulse oximetries, and 230,000 polygraphies have been performed based on the Fourth National Data Base Open Data Japan.[23] Thus, if the CVHR score could be used to detect SDB, those with a potential for SDB will more likely be detected than if only Holter electrocardiographies are performed.

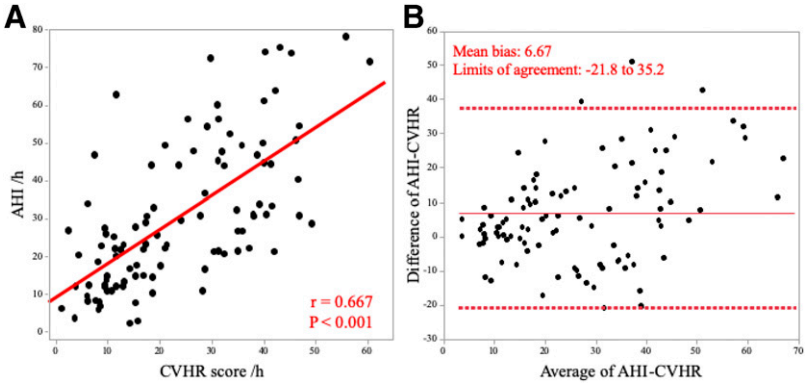
Several reports have suggested that there are significant correlations between CVHR and SDB.[14,24] Hayano et al[14] reported that CVHR was significantly correlated with the AHI (r = .84) in a large-scale study (n = 862). However, these studies did not focus on patients with HF. Two previous studies also showed a significant correlation between CVHR and SDB in patients with HF. One study reported a correlation between the CVHR score and the severity of SDB, which was determined using a nonrestrictive, sheet-like monitor, with which a small number of hospitalized patients were assessed due to worsening HF (n = 49).[15] Another study reported there was a modest positive correlation between the CVHR score and severity of SDB assessed using a type 3 polygraphy in 110 patients with symptomatic HF (New York Heart Association class ≥ II).[16] However, there were several differences between these previous 2 studies and ours. First, the

Table 1—Baseline characteristics.

	Overall (n = 101)	Non-HF (n = 31)	HF (n = 70)	*P*
Age, y	61.3 ± 14.1	60.8 ± 13.7	61.6 ± 14.3	.820
Male, n (%)	84 (83.2)	25 (80.6)	59 (84.3)	.655
BMI, kg/m^2	25.9 ± 5.9	27.1 ± 8.2	25.3 ± 4.5	.152
Hypertension, n (%)	43 (42.6)	20 (64.5)	38 (54.3)	.335
Diabetes, n (%)	35 (34.7)	8 (25.8)	27 (38.6)	.207
Coronary artery disease, n (%)	22 (21.8)	12 (38.7)	10 (14.3)	.006
Systolic BP, mm Hg	123.0 (26.0)	118.0 (20.0)	127.0 (23.0)	.065
Diastolic BP, mm Hg	64.0 (18.0)	62.0 (12.0)	65.5 (28.3)	.398
Respiratory rate, /min	14.7 (3.9)	14.8 (4.2)	14.5 (4.1)	.632
Heart rate, /min	71.0 (26.0)	70.0 (15.0)	73.5 (28.5)	.035
Ejection fraction, %	54.5 (30.0)	67.5 (10.0)	43.0 (25.0)	<.001
Ejection fraction < 50%, n (%)	41 (40.6)	0 (0)	41 (58.6)	<.001
Brain natriuretic peptide, pg/mL	66.0 (166.7)	25.6 (27.5)	117.4 (211.2)	.003
β-Blocker, n (%)	63 (63.0)	11 (35.5)	52 (75.4)	<.001
Amiodarone, n (%)	10 (9.9)	0 (0)	10 (14.3)	.027
Total sleep time, min	371.4 ± 84.0	404.6 ± 84.7	356.7 ± 79.9	.008
AHI, events/h	25.9 (29.8)	26.7 (34.6)	25.8 (31.5)	.566
AHI categories				.006
Mild	24 (23.8)	2 (6.5)	21 (30.0)	
Moderate	32 (31.7)	16 (51.6)	17 (24.3)	
Severe	42 (41.6)	11 (35.5)	31 (44.3)	
Central-dominant, n (%)	16 (15.8)	2 (6.45)	14 (20.0)	.066
Central AHI, events/h	2.4 (7.9)	0.7 (2.0)	4.1 (10.38)	<.001
CVHR score, events/h	20.1 (24.2)	21.3 (21.1)	19.8 (26.8)	.962

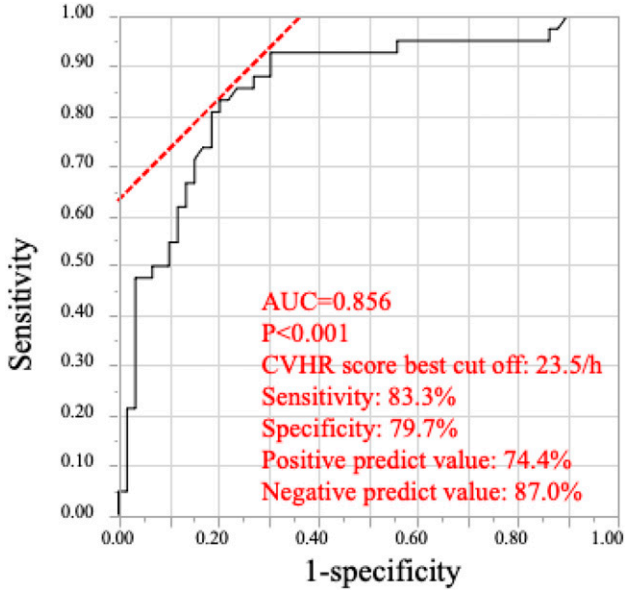
Values are means (standard deviation). AHI = apnea-hypopnea index, BMI = body mass index, BP = blood pressure, CVHR = cyclic variation of heart rate, HF = heart failure.

Figure 3—The correlation between the AHI and CVHR score in the entire population.



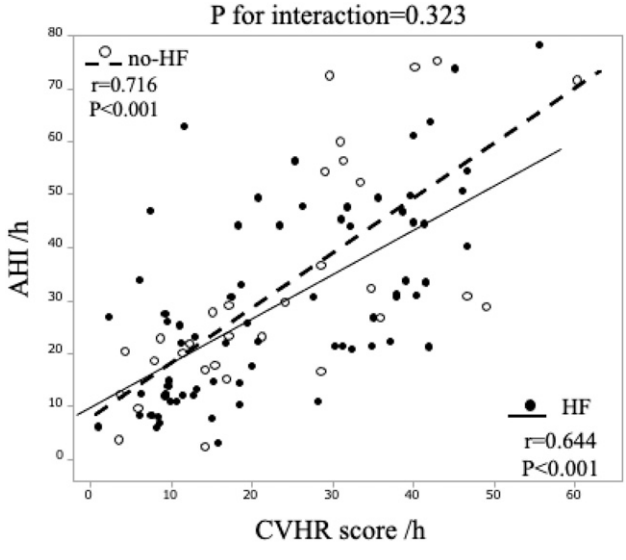
(A) Scatterplot and Bland-Altman plot assessing the AHI and CVHR score in the entire population, which consisted of a mixture of patients with and without HF. There was a significant positive correlation between the AHI and CVHR score (r = .667, P < .001). **(B)** Mean bias and limits of agreement were 6.67 and −21.8 to 35.2, respectively. AHI = apnea-hypopnea index, CVHR = cyclic variation in heart rate, HF = heart failure.

Figure 4—Receiver operating characteristics curve of identifying severe SDB (AHI > 30 events/h).



Receiver operating characteristics curve used to identify severe SDB cases (AHI > 30 events/h) in the entire patient population, which consisted of patients with HF and without HF. The AUC was 0.856. The best cutoff for the CVHR score to identify severe SDB was 23.5 events/h, with sensitivity, specificity, and positive and negative predictive values of 83.3%, 79.7%, 74.4%, and 87.0%, respectively. AHI = apnea-hypopnea index, AUC = area under the curve, CVHR = cyclic variation in heart rate, HF = heart failure, predict = predictive, SDB = sleep-disordered breathing.

Figure 5—The correlation between the AHI and CVHR score in patients with and without HF.



Scatterplots of the AHI and CVHR score in patients with and without HF. There was a significant positive correlation for patients with HF (r = .644, P < .001) and for those without HF (r = .716, P < .001). There were no significant interactions between the 2 groups (P = .323). AHI = apnea-hypopnea index, CVHR = cyclic variation in heart rate, HF = heart failure.

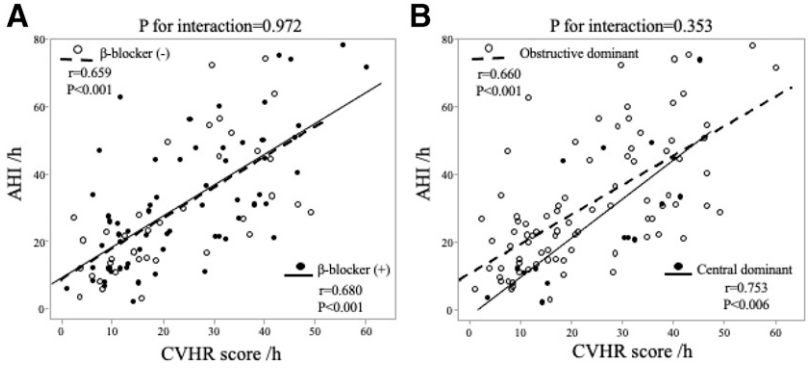
participants of those studies were diagnosed with HF and there was no comparison to patients without HF. In addition, although a full polysomnography has been recommended for assessing SDB in patients with HF,[25] SDB in those studies were evaluated using type 3 or 4 SDB testing. From these features, our study was the first to provide validation data for the use CVHR score-to-AHI ratio assessed by full polysomnography in a heterogeneous patient population including patients both with HF and without HF and found that the relationships between the CVHR score and AHI were similar regardless of the presence or absence of HF.

Abnormality in heart rate variability has been reported in patients with SDB.[26] SDB is associated with an altered sympathovagal balance determined by nocturnal cyclic breathing alternating between bradycardia during apnea and abrupt tachycardia with postapneic hyperventilation.[26] β-Blockers, which are recommended for patients with HF with left ventricular dysfunction, change the autonomic nerve balance and reduce the heart rate.[27] In addition, recent studies suggested that β-blockers did not affect SDB related bradyarrhythmias and protected apnea-induced heart rate acceleration.[28,29] Though these mechanisms suggest that taking β-blockers might affect the CVHR score, our results showed no significant difference between the CVHR score and AHI in terms of the presence or absence of β-blockers.

Even though the autonomic modulation of heart rate during CSA and OSA in patients with SDB has been shown to be different,[30] in the present study, the correlation between the CVHR score and the AHI was not significantly different between patients with predominant CSA and OSA. Although OSA and CSA may have different patterns of heart rate variability and CVHR as indicated in a previous report,[31] there have been no reports that heart rate variability or CVHR pattern could be used to differentiate between OSA and CSA. Such discrepancies may be explained by the differences between event-by-event analyses and patient-based analyses. Further analyses regarding CVHR events in relation to respiratory events are required. However, to our knowledge, there is no report assessing differences in the CVHR score according to the presence or absence of β-blockers or SDB type and thus, this is the first report to show that no significant difference was found in the AHI-CVHR score relationship between patients with and without β-blockers, or between CSA-dominant and OSA-dominant patients.

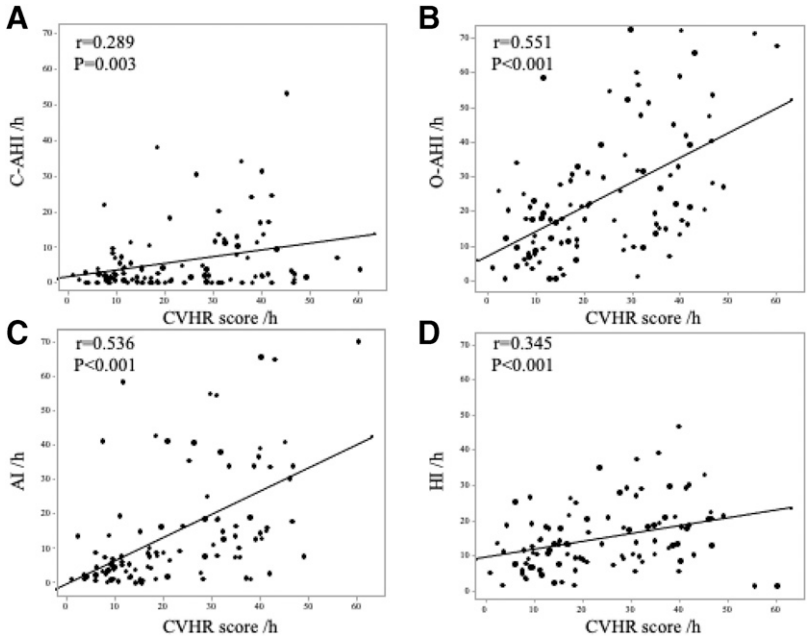
We also assessed the correlations between central/obstructive AHI, AI, or HI and CVHR score. Despite significant correlations between obstructive AHI or AI and CVHR score, weaker correlations were observed between central AHI or HI and CVHR score. Since it is not possible at this time to separately classify central and obstructive events or separately classify apnea and hypopnea events using the CVHR technology, we could only analyze the correlations between "total CVHR score" and each separate index (**Figure 7**). Thus, these findings should be interpreted with caution. It is important to differentiate OSA and CSA from hypopnea using the CVHR technology, but further investigations are needed. It was necessary to first establish the utility of CVHR score as a screening tool for SDB in a mixed patient population of those with HF and those without HF as shown in the present study.

Figure 6—The correlation between the AHI and CVHR score in patients taking or not taking β-blockers and whose SDB patterns were central-dominant or obstructive-dominant.



(A) Scatterplots of the AHI and CVHR score in patients taking or not taking β-blockers. There was a significant positive correlation for patients taking β-blockers (r = .680, P < .001) and in those not taking β-blockers (r = .659, P < .001). There were no significant interactions between the 2 groups (P = .972). **(B)** Scatterplots of the AHI and CVHR score in patients whose SDB patterns were central-dominant or obstructive-dominant. There was a significant positive correlation for central-dominant patients (r = .753, P < .001) and obstructive-dominant patients (r = .660, P < .001). There was no significant interaction between the 2 groups (P = .353). AHI = apnea-hypopnea index, CVHR = cyclic variation in heart rate, SDB = sleep-disordered breathing.

Figure 7—Correlations between central/obstructive AHI, AI, and HI and CVHR score.



Scatterplots of central AHI and CVHR score (r = .289, P = .003) **(A)**, obstructive AHI and CVHR score (r = .551, P < .001) **(B)**, AI and CVHR score (r = .536, P < .001) **(C)**, and HI and CVHR score (r = .345, P < .001) **(D)**. AI = apnea index, AHI = apnea-hypopnea index, C = central, CVHR = cyclic variation in heart rate, HI = hypopnea index, O = obstructive.

Study limitations

This study has several limitations. First, our sample size was modest, especially in terms of patients without HF. Although further large-scale studies may be necessary to confirm these results, it is valuable that we found a strong correlation between the CVHR score and the AHI in such a small sample. Second, because the time spent awake could not be detected on the Holter monitor, CVHR data might have been included when the patient was awake. Although we synchronized the times of the polysomnography and the Holter electrocardiogram, this may have caused a bias in the CVHR score and the AHI. Third, although we found a correlation between the frequency of CVHR and AHI, we did

not assess the relationship between CVHR and duration of SDB, sleep stage, or body position. Fourth, we excluded several patients with HF due to arrhythmia, a major comorbidity of HF because no algorithms are as yet available for detecting CVHR during irregular beats. However, a previous report suggested that heart rate variability analysis was a useful tool even in patients with arrhythmia, such as atrial fibrillation.[32] Therefore, more studies are needed to establish the utility of detecting CVHR in these populations in the future. Finally, CVHR is assessed using only electrocardiogram analyses and cannot discriminate the type of SDB, such as central/obstructive vs apnea/hypopnea. From these perspectives, further studies that enable event-by-event analysis should be undertaken.

The CVHR score was correlated with the AHI, assessed using full polysomnography, in a heterogeneous sample of patients with and without HF. Such correlations between the CVHR score and AHI were consistent even when accounting for the presence or absence of β-blocker use and the predominant type of SDB (CSA-predominant or OSA-predominant). The use of the CVHR score, determined by Holter electrocardiogram, may enable increased screening of patients for SDB in the clinical setting.

ABBREVIATIONS

AF, atrial fibrillation
AHI, apnea-hypopnea index
AI, apnea index
CVHR, cyclic variation of heart rate
CSA, central sleep apnea
HF, heart failure
HI, hypopnea index
OSA, obstructive sleep apnea
RR, respiratory rate
SDB, sleep-disordered breathing

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