

Blunted cyclic variation of heart rate predicts mortality risk in post-myocardial infarction, end-stage renal disease, and chronic heart failure patients

Junichiro Hayano^{1*}, Fumihiko Yasuma², Eiichi Watanabe³, Robert M. Carney⁴, Phyllis K. Stein⁵, James A. Blumenthal⁶, Petros Arsenos⁷, Konstantinos A. Gatzoulis⁷, Hiroshi Takahashi⁸, Hideki Ishii⁹, Ken Kiyono¹⁰, Yoshiharu Yamamoto¹¹, Yutaka Yoshida¹, Emi Yuda¹, and Itsuo Kodama¹²

¹Department of Medical Education, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi Mizuho-cho Mizuho-ku, Nagoya 467-8601, Japan; ²Departments of Medicine, Suzuka National Hospital, Suzuka, Japan; ³Division of Cardiology, Department of Internal Medicine, Fujita Health University School of Medicine, Toyoake, Japan; ⁴Department of Psychiatry, Washington University School of Medicine, St Louis, MO 63108, USA; ⁵Departments of Medicine, Washington University School of Medicine, St Louis, MO 63108, USA; ⁶Department of Psychiatry, Duke University Medical Center, Durham, NC 27710, USA; ⁷First Cardiology Division, University of Athens Medical School, Hippokration Hospital, Athens, Greece; ⁸Division of Medical Statistics, Fujita Health University, Toyoake, Japan; ⁹Department of Cardiology, Nagoya University, Nagoya, Japan; ¹⁰School of Engineering Science, Osaka University, Suita, Japan; ¹¹Educational Physiology Laboratory, Graduate School of Education, University of Tokyo, Tokyo 113-0033, Japan; and ¹²Nagoya University, Nagoya, Japan

Received 8 February 2016; accepted after revision 27 June 2016; online publish-ahead-of-print 27 October 2016

Aims

Cyclic variation of heart rate (CVHR) associated with sleep-disordered breathing is thought to reflect cardiac autonomic responses to apnoeic/hypoxic stress. We examined whether blunted CVHR observed in ambulatory ECG could predict the mortality risk.

Methods and results

CVHR in night-time Holter ECG was detected by an automated algorithm, and the prognostic relationships of the frequency (F_{CV}) and amplitude (A_{CV}) of CVHR were examined in 717 patients after myocardial infarction (post-MI 1, 6% mortality, median follow-up 25 months). The predictive power was prospectively validated in three independent cohorts: a second group of 220 post-MI patients (post-MI 2, 25.5% mortality, follow-up 45 months); 299 patients with end-stage renal disease on chronic haemodialysis (ESRD, 28.1% mortality, follow-up 85 months); and 100 patients with chronic heart failure (CHF, 35% mortality, follow-up 38 months). Although CVHR was observed in $\geq 96\%$ of the patients in all cohorts, F_{CV} did not predict mortality in any cohort. In contrast, decreased A_{CV} was a powerful predictor of mortality in the post-MI 1 cohort (hazard ratio [95% CI] per 1 ln [ms] decrement, 2.9 [2.2–3.7], $P < 0.001$). This prognostic relationship was validated in the post-MI 2 (1.8 [1.4–2.2], $P < 0.001$), ESRD (1.5 [1.3–1.8], $P < 0.001$), and CHF (1.4 [1.1–1.8], $P = 0.02$) cohorts. The prognostic value of A_{CV} was independent of age, gender, diabetes, β -blocker therapy, left ventricular ejection fraction, sleep-time mean R-R interval, and F_{CV} .

Conclusion

Blunted CVHR detected by decreased A_{CV} in a night-time Holter ECG predicts increased mortality risk in post-MI, ESRD, and CHF patients.

Keywords

Ambulatory ECG • Holter ECG • Heart rate • Sleep apnoea • Mortality • Risk stratification

* Corresponding author. Tel: +81 52 853 8503; fax: +81 52 853 8761. E-mail address: hayano@med.nagoya-cu.ac.jp

© The Author 2016. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

What's new?

- Cyclic variation of heart rate (CVHR) is a characteristic pattern of heart rate associated with episodes of sleep-disordered breathing and is thought to represent a cardiac chronotropic response to spontaneously induced apnoeic/hypoxic stress. In this study, we examined the prognostic value of blunted CVHR observed in a night-time Holter ECG in post-myocardial infarction, end-stage renal disease, and chronic heart failure patients.
- CVHR was observed in $\geq 96\%$ of these patients. Although the frequency of CVHR did not predict mortality in any of cohort, decreased amplitude of CVHR predicted an increased risk for mortality in all cohorts independently of age, gender, diabetes, β -blocker therapy, left ventricular ejection fraction, night-time mean R-R interval, and CVHR frequency.
- This is the first study to report that blunted CVHR could be a new prognostic marker obtained from ambulatory ECG.

Introduction

Studies of heart rate variability (HRV) and those of heart rate dynamics indicate that cardiac autonomic dysfunction is an independent mortality risk in various clinical conditions including post-myocardial infarction (MI),^{1–3} end-stage renal disease (ESRD),⁴ and chronic heart failure (CHF).⁵ These studies suggest that more accurate and efficient assessment of cardiac autonomic function could provide better risk stratifications in these patients. Cyclic variation of heart rate (CVHR) is a characteristic heart rate pattern observed in night-time ECG monitoring in patients with sleep-disordered breathing (SDB).^{6,7} CVHR is thought to reflect cardiac autonomic responses to cardio-respiratory perturbation caused by apnoeic/hypoxic episodes. This fact suggests that cardiac autonomic dysfunction may result in blunted CVHR and thus leads to the hypothesis that blunted CVHR may predict increased mortality risk in certain clinical conditions.

To test this hypothesis, we examined if blunted CVHR detected by night-time Holter ECG monitoring predicts increased mortality risk in patients after MI, those with ESRD, and those with CHF. We selected these patients, because the predictive value of cardiac autonomic dysfunction has been established^{1–5} and SDB is common, among these patients.⁸ We used a previously validated algorithm^{9,10} for measuring the hourly frequency of CVHR (F_{CV}). Also, we developed an algorithm for quantifying the amplitude of CVHR (A_{CV}) by a signal averaging method. We defined blunted CVHR as a reduction in A_{CV} .

Methods

Derivation and validation cohorts

We derived our hypothesis from a cohort of patients with a recent MI (post-MI 1). They were post-MI patients recruited as the control group of Enhancing Recovery in Coronary Heart Disease (ENRICH) ancillary study on HRV between October 1997 and January 2000.¹¹ Later, we blindly validated the models obtained from the derivation cohort against

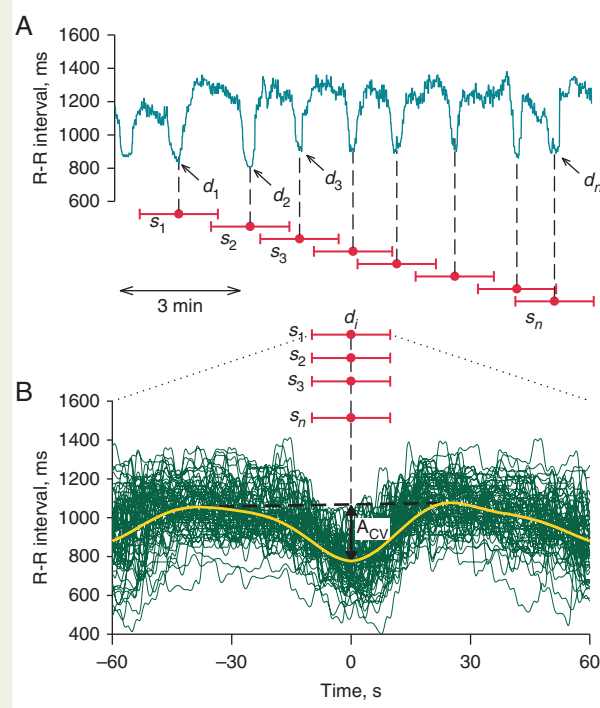


Figure 1 Assessment of the amplitude of CVHR (A_{CV}) by a signal averaging method. CVHR appears as characteristic cyclic dips in R-R intervals of night-time ECG recordings (A). To calculate the A_{CV} , all dips attributable to CVHR are detected, and temporal positions of the nadir point of dips ($d_1, d_2, d_3, \dots, d_n$) are determined using automated algorithms, such as ACAT.^{9,10} Second, segments of interval data (length, 120 s) around the nadir points ($s_1, s_2, s_3, \dots, s_n$), where segments that surround adjacent nadir points can overlap, are collected. Third, all segments are aligned at the nadir points and averaged (B). A_{CV} is then measured as the dip depth of the signal-averaged interval curve, i.e. the vertical distance from the nadir of central dip to the line connecting the local maxima on both sides of the dip.

three independent cohorts. The first validation cohort comprised post-MI patients (post-MI 2) who were referred for sudden cardiac death risk stratification at the Electrophysiology Lab of Hippokraton Hospital in Athens, Greece, between January 2005 and December 2013.^{12,13} The second comprised patients with ESRD who were receiving regular chronic haemodialysis therapy (three times per week) at the Hemodialysis Center of Nagoya Kyoritsu Hospital and were recruited between January 2002 and May 2004.⁴ The third comprised patients with CHF consecutively referred to Fujita Health University Hospital and admitted to the hospital between January 2000 and December 2001.⁴

Inclusion criteria were patients aged ≥ 20 years whose index Holter ECG recording showed a sinus rhythm during $\geq 90\%$ of sleep time. The sleep time was determined individually from patient diary in post-MI 1 and ESRD cohorts, while it was defined uniformly as 23:00–06:00 in post-MI 2 and CHF cohorts in which patient diary data were unavailable. Patients were excluded if they had persistent atrial fibrillation, a permanent or temporary cardiac pacemaker, or a malignancy. The collection and analysis of Holter ECG recordings were approved by the ethics committees of the corresponding clinical sites. All participants provided written informed consent to participate in the studies.

Table 1 Study and patient characteristics and treatment by cohort

Cohort	Post-MI 1 (n = 717)	Post-MI 2 (n = 220)	ESRD (n = 299)	CHF (n = 100)
Study characteristics				
Follow-up, months	25 (19–32)	45 (20–53)	85 (69–90)	38 (18–45)
Death	43 (6.0%)	56 (25.5%)	84 (28.1%)	35 (35.0%)
Patient characteristics				
Age, years	59 (51–68)	67 (57–75)	64 (56–70)	65 (56–76)
Women	284 (39.6%)	37 (16.8%)	133 (44.5%)	47 (47.0%)
Diabetes mellitus	197 (27.5%)	72 (32.7%)	140 (46.8%)	–
History of MI	147 (20.5%)	–	–	–
LVEF, %	46 (38–55)	30 (25–40)	66 (58–72)	40 (27–50)
LVEF ≤ 30%	61 (8.5%)	114 (51.8%)	4 (1.3%)	38 (38.0%)
Treatment				
β-Blockers	589 (82.1%)	145 (65.9%)	52 (17.4%)	31 (31.0%)
Angiotensin-converting enzyme inhibitors	335 (46.7%)	142 (64.5%)	130 (43.5%)	47 (47.0%)
Aspirin	617 (86.1%)	135 (61.4)	163 (54.5%)	–
Thrombolysis	216 (30.1%)	12 (5.5%)	–	–
Percutaneous coronary intervention	437 (60.9%)	62 (28.2%)	–	–

Data are median (IQR) or number (%).

Post-MI 1, the Enhancing Recovery in Coronary Heart Disease (ENRICHD) cohort;¹¹ Post-MI 2, patients after a myocardial infarction;^{12,13} ESRD, patients with end-stage renal disease on chronic haemodialysis therapy;⁴ CHF, patients with chronic heart failure;⁵ LVEF, left ventricular ejection fraction.

Procedures

Holter ECG recordings were obtained within 28 days (median [IQR], 13 [2–28]) after the index MI for the post-MI 1 cohort; within the hospitalization period (1–5 days after the MI) during the risk stratification process for the post-MI 2 cohort; within 1 month after study entry and between haemodialysis sessions for the ESRD cohort; and prior to hospital discharge for the CHF cohort. The ECG recordings were analysed with Holter scanners (SXP Laser scanner, Marquette Electronics for the post-MI 1 cohort; SyneScope 3.10, Sorin Group for the post-MI 2 cohort; DSC-3300, Nihon Koden for the ESRD cohort; and Cardy Analyzer II, Suzuken for the CHF cohort), and all R waves were detected and automatically labelled. The results of the automatic analysis were reviewed, and any errors in R wave detection and QRS labelling were manually edited.

We used an automated CVHR detection algorithm called autocorrelated wave detection with adaptive threshold (ACAT) to detect CVHR and determine its temporal position. Details of the algorithm have been reported elsewhere.^{9,10} Briefly, ACAT identifies CVHR as cyclic and autocorrelated dips in R-R intervals. First, R-R interval time series during sleep time were extracted. They were interpolated with a horizontal-step function using only normal-to-normal (N-N) intervals, resampled at 2 Hz, and smoothed by second-order polynomial fitting. Second, CVHR was detected as a dip in the interbeat interval that meets the following criteria: (1) width from 10 to 120 s; (2) depth-to-width ratio > 0.7 ms/s; (3) depth > 40% of the 90% CI of local interbeat interval variations; (4) cycle length (interdip interval) from 25 to 120 s; (5) similar waveforms among four consecutive dips (morphological correlation coefficients > 0.4); and (6) three equivalent consecutive cycle lengths with a tolerance of 22% against the mean cycle length. Finally, F_{CV} was calculated as the number of CVHR cycles per hour.

We used a signal averaging method to quantify A_{CV} (Figure 1). For all dips attributed to CVHR, N-N interval segments around the nadir point of the dips, where segments that surround adjacent nadir points could overlap, were collected (Figure 1A). All segments were aligned at the nadir points and averaged (Figure 1B). Then, A_{CV} was measured as the dip

depth of the signal-averaged interval curve, i.e. the vertical distance from the nadir to the line connecting the local maxima on both sides of the dip (Figure 1B). In this study, the signal averaging of the segments was performed only when ≥ 4 cycles of CVHR per night were detected.

Statistical analyses

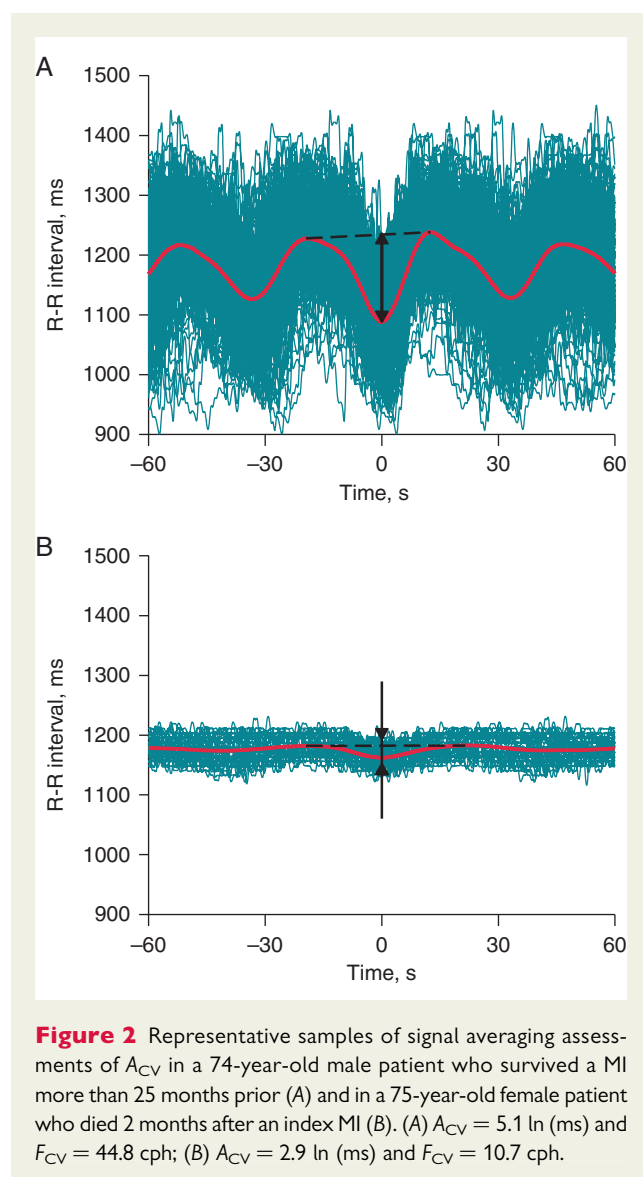
We used SAS 9.4 software (SAS Institute, Cary, NC) for the statistical analysis. To normalize the distributions, we transformed A_{CV} in the natural logarithmic values. We used Wilcoxon rank sum tests and χ^2 statistics to compare survivors and non-survivors on the basis of demographic and medical variables. We evaluated the predictive powers of F_{CV} and A_{CV} by the Cox proportional hazards regression model. To determine whether A_{CV} has predictive power even in subclinical SDB, analyses were also performed in subgroups of patients with $F_{CV} < 5$ cycles per hour (cph).

On the basis of earlier studies,^{9,10} the patients were classified into three categories by F_{CV} : no-to-mild SDB as category 0 ($F_{CV} < 15$ cph), moderate SDB as category 1 ($15 \text{ cph} \leq F_{CV} < 30$ cph), and severe SDB as category 2 ($F_{CV} \geq 30$ cph). The patients were also classified into three categories by the level of A_{CV} as low-, intermediate-, and high-risk groups. The cut-off A_{CV} values were identified by the maximum log-rank statistic in the post-MI 1 cohort. These risk-stratification categories were then evaluated in the post-MI 2, ESRD, and CHF cohorts. We also estimated survival curves for the categories using the Kaplan–Meier method and compared them with log-rank statistics. We used $\alpha < 0.05$ to guard against type 1 statistical error.

Results

Patient characteristics

Demographic and clinical characteristics for the four cohorts are summarized in Table 1. None of the patients reported to have SDB or its prior history at the entry.



Correlates of A_{CV}

In the post-MI 1, post-MI 2, ESRD, and CHF cohorts, CVHR of ≥ 4 cycles per night was detected in 96, 98, 96, and 98% of patients, respectively, among whom A_{CV} and F_{CV} were obtained. A_{CV} showed no significant correlation with F_{CV} in any of the cohorts ($r = 0.04, 0.006, 0.04$, and 0.1 for post-MI 1, post-MI 2, ESRD, and CHF cohorts, respectively). While A_{CV} was correlated positively with sleep-time mean N-N interval ($r = 0.5, 0.3, 0.5$, and 0.4 , respectively), F_{CV} showed no such correlations ($r = 0.1, 0.2, 0.1$, and -0.09 , respectively).

Associations with mortality in the derivation cohort

Figure 2 shows representative samples of A_{CV} in surviving (A) and non-surviving (B) post-MI patients. In the post-MI 1 cohort, ≥ 4 cycles of CVHR per night were detected in 688 (96%) of 717 patients, and A_{CV} was lower in non-survivors than in survivors ($P < 0.001$;

Table 2). In contrast, F_{CV} did not differ significantly between non-survivors and survivors ($P = 0.6$).

In the post-MI 1 cohort, a survival time analysis for A_{CV} showed two distinct maxima in the log-rank statistics that corresponded to cut-off values of 4.0 and 3.0. Therefore, we adopted a categorical risk-stratification scheme for A_{CV} . We classified low-risk patients as category 0 ($A_{CV} > 4.0$), intermediate-risk patients as category 1 ($3.0 < A_{CV} \leq 4.0$), and high-risk patients as category 2 ($A_{CV} \leq 3.0$).

Associations with mortality in validation cohorts

We tested the hypothesis in three validation cohorts. In each cohort, A_{CV} was lower in non-survivors than in survivors, and decreases in A_{CV} and A_{CV} categories were associated with an increased mortality rate and risk in all cohorts (Tables 2, 3, and 4). In addition, multivariate models showed that the predictive power of A_{CV} and its categories were independent of age, gender, diabetes, β -blocker therapy, LVEF, sleep-time mean N-N interval, and F_{CV} (Table 4). In contrast, neither F_{CV} nor its categories showed a significant association with mortality or predictive power in any of the cohorts except F_{CV} category 1, which showed modest associations with mortality risk.

Figure 3 shows the Kaplan–Meier survival curves for the A_{CV} categories in each cohort. The mortality probability increased as the A_{CV} category increased in the post-MI 1 ($P < 0.001$), post-MI 2 ($P < 0.001$), ESRD ($P < 0.001$), and CHF ($P = 0.007$) cohorts.

Predictive power in subclinical SDB

The predictive power of decreased A_{CV} was observed even in patients estimated to have subclinical SDB. Even among patients with $F_{CV} < 5$ cph, decreased A_{CV} predicted mortality in the post-MI 1 (HR [95% CI], 3.0 [1.7–5.3], $P < 0.001$, $N = 172$, 10 deaths); post-MI 2 (1.6 [1.1–2.3], $P = 0.02$, $N = 48$, 16 deaths); and CHF (1.7 [1.1–2.5], $P = 0.009$, $N = 39$, 16 deaths) cohorts, although it had no significant predictive power in the ESRD cohort (1.1 [0.8–1.5], $P = 0.4$, $N = 84$, 27 deaths).

Effects of β -blockers on risk variables

To determine whether CVHR parameters are associated with β -blocker therapy, sleep-time mean N-N interval, A_{CV} , and F_{CV} were compared in patients who were and were not taking a β -blocker at the time of the Holter monitoring in each cohort (Table 5). Patients taking a β -blocker showed a longer sleep-time mean N-N interval in the post-MI 1 and ESRD cohorts. A_{CV} was greater in patients taking β -blocker in the post-MI 1 cohort, whereas there was no significant difference in the other cohorts. No significant difference with β -blocker was observed in F_{CV} .

Discussion

To our knowledge, this is the first study to report the prognostic association of blunted CVHR with mortality risk. We found that blunted CVHR detected by decreased A_{CV} in night-time Holter ECG monitoring predicts increased mortality risk in post-MI, ESRD, and CHF patients. Also, we developed the categorical risk-stratification scheme for A_{CV} that was optimized for the post-MI 1

Table 2 Association of risk variables with mortality by cohort

	Post-MI 1 (n = 717)	Post-MI 2 (n = 220)	ESRD (n = 299)	CHF (n = 100)
Patients with CVHR, n (%) ^a	688 (96%)	215 (98%)	287 (96%)	98 (98%)
A_{CV} , ln (ms)				
All patients	4.9 (4.0–5.6)	4.5 (3.7–5.2)	4.0 (3.3–4.9)	3.9 (2.9–4.8)
Survivors	5.0 (4.2–5.7)	4.7 (3.9–5.3)	4.2 (3.5–4.9)	4.1 (3.4–4.8)
Non-survivors	3.4 (2.7–3.9)	3.8 (2.8–4.8)	3.6 (2.6–4.4)	3.2 (2.6–4.6)
p^{\dagger}	<0.001	<0.001	<0.001	0.02
A_{CV} category 0/1/2, %				
All patients	76/17/7	64/26/10	52/30/18	47/25/28
Survivors	80/15/5	71/26/4	59/29/12	54/29/17
Non-survivors	18/42/40	44/27/29	35/31/34	34/20/46
p^{\ddagger}	<0.001	<0.001	<0.001	0.01
F_{CV} , cph				
All patients	8.8 (4.5–15.4)	11.0 (5.8–21.0)	8.6 (3.9–14.7)	4.5 (0.9–11.9)
Survivors	8.7 (4.6–15.0)	10.6 (6.1–19.8)	8.8 (4.0–14.6)	4.8 (1.3–15.6)
Non-survivors	10.5 (3.7–22.5)	14.3 (3.5–24.7)	8.0 (3.7–15.5)	4.0 (0.5–5.9)
p^{\dagger}	0.6	0.7	0.7	0.1
F_{CV} category 0/1/2, %				
All patients	73/17/10	63/23/13	74/20/6	79/14/7
Survivors	75/16/9	67/19/14	75/21/4	75/16/10
Non-survivors	58/29/13	51/36/13	73/18/9	86/11/3
p^{\ddagger}	0.07	0.03	0.4	0.4

Data are medians (IQR) or percentages of patients among categories.

A_{CV} category 0: >4.0 ln (ms), 1: $3.0 - \leq 4.0$ ln (ms), and 2: ≤ 3.0 ln (ms).

F_{CV} category 0: $0 - <15$ cph, 1: $15 - <30$ cph, and 2: ≥ 30 cph.

A_{CV} , amplitude of cyclic variation of heart rate; cph, cycle per hour; CVHR, cyclic variation of heart rate; F_{CV} , frequency of cyclic variation of heart rate.

^aNumber (%) in total of patients with ≥ 4 cycles of CVHR per night.

[†]Significance of difference between survivors and non-survivors (Wilcoxon rank sum test).

[‡]Significance of difference between survivors and non-survivors (χ^2 test).

Table 3 Mortality rate per 100 person-years by cohort

	Post-MI 1 Rate (95% CI)	Post-MI 2 Rate (95% CI)	ESRD Rate (95% CI)	CHF Rate (95% CI)
A_{CV} category 0	0.6 (0.3–1.3)	4.9 (3.1–7.2)	2.9 (2.0–4.3)	8.4 (4.4–14.7)
A_{CV} category 1	6.3 (3.6–10.3)	8.3 (4.7–13.8)	5.0 (3.2–7.4)	10.4 (4.2–21.3)
A_{CV} category 2	18.3 (10.3–30.2)	31.9 (18.2–51.8)	11.0 (7.3–15.9)	27.6 (15.7–44.7)
F_{CV} category 0	2.1 (1.3–3.1)	6.0 (4.0–8.6)	4.7 (3.5–6.0)	14.7 (9.9–20.9)
F_{CV} category 1	4.6 (2.3–8.3)	12.2 (7.6–19.1)	4.2 (2.4–7.0)	10.4 (2.9–26.7)
F_{CV} category 2	3.7 (1.2–8.6)	7.6 (3.0–15.6)	8.0 (3.2–16.5)	4.0 (0.1–22.2)

cohort and examined its validity in the three independent cohorts of post-MI 2, ESRD, and CHF. We observed that the A_{CV} categorical scheme is useful for predicting mortality risk in all of the three validation cohorts. Because CVHR is thought to reflect cardiac autonomic responses to cardio-respiratory perturbation caused by apnoeic/hypoxic episodes, blunted CVHR may be a marker of cardiac autonomic dysfunction. Our findings seem consistent with the hypothesis that blunted CVHR predicts mortality risk that is most likely mediated by cardiac autonomic dysfunction.

In this study, we used an automated CVHR detection algorithm called ACAT to detect CVHR and to measure the frequency and amplitude of CVHR as F_{CV} and A_{CV} , respectively. In our previous study of 862 patients referred for diagnostic polysomnography⁹ and 165 healthy male truck drivers,¹⁰ we observed that F_{CV} obtained from this algorithm is closely correlated with apnoea-hypopnoea index (AHI) with $r = 0.84$ and 0.86 , respectively, and that using a cut-off threshold of $F_{CV} \geq 15$ cph, patients with AHI ≥ 15 can be detected at 83 and 88% sensitivity and 88 and 97% specificity,

Table 4 Proportional hazards risk (HR) for mortality by cohort

	Post-MI 1			Post-MI 2			ESRD			CHF		
	HR (95% CI)	P		HR (95% CI)	P		HR (95% CI)	P		HR (95% CI)	P	
Univariate												
Acv per decrement of 1 ln (ms)	2.9 (2.2–3.7)	<0.001		1.8 (1.4–2.2)	<0.001		1.5 (1.3–1.8)	<0.001		1.4 (1.1–1.8)	<0.001	
Acv category 0	Reference			Reference			Reference			Reference		
Acv category 1	9.7 (4.0–24)	<0.001		1.8 (0.9–3.3)	0.09		1.7 (1.0–2.9)	0.05		1.2 (0.4–3.1)	0.05	
Acv category 2	29 (12–71)	<0.001		6.0 (3.2–11)	<0.001		4.0 (2.3–6.4)	<0.001		2.9 (1.4–6.2)	<0.001	
Fcv per increment of 1 cph	1.0 (0.9–1.0)	0.06		1.0 (0.9–1.0)	0.8		1.0 (0.9–1.0)	0.7		1.0 (0.9–1.0)	0.7	
Fcv category 0	Reference			Reference			Reference			Reference		
Fcv category 1	2.2 (1.1–4.5)	0.03		1.9 (1.1–3.5)	0.02		0.9 (0.5–1.6)	0.7		0.7 (0.2–1.9)	0.7	
Fcv category 2	1.8 (0.7–4.7)	0.2		1.3 (0.6–2.9)	0.6		1.7 (0.8–3.8)	0.1		0.3 (0.04–2.1)	0.1	
Multivariate												
Acv per decrement of 1 ln (ms) ^a	1.8 (1.3–2.4)	<0.001		1.5 (1.1–1.9)	0.009		1.3 (1.1–1.7)	0.006		1.5 (1.1–2.0)	0.006	
Acv category 0	Reference			Reference			Reference			Reference		
Acv category 1	3.0 (0.9–9.7)	0.06		1.1 (0.5–2.3)	0.9		1.5 (0.9–2.8)	0.2		1.3 (0.5–3.4)	0.2	
Acv category 2	9.5 (2.6–34)	<0.001		4.2 (1.9–9.3)	<0.001		2.4 (1.3–4.5)	0.007		4.4 (1.9–10)	0.007	
Fcv per increment of 1 cph [†]	1.0 (0.9–1.0)	0.3		1.0 (0.9–1.0)	0.9		1.0 (0.9–1.0)	0.4		1.0 (0.9–1.0)	0.4	
Fcv category 0	Reference			Reference			Reference			Reference		
Fcv category 1	1.5 (0.6–3.8)	0.3		2.2 (1.1–4.3)	0.02		0.9 (0.5–1.6)	0.8		0.5 (0.1–1.8)	0.8	
Fcv category 2	2.0 (0.6–6.4)	0.3		1.0 (0.4–2.6)	1.0		2.0 (0.9–4.5)	0.09		0.3 (0.04–2.7)	0.09	

^aAdjusted for age, gender, diabetes, β -blocker therapy, left ventricular ejection fraction, sleep-time mean N-N interval, and F_{CV} for the post-MI 1, post-MI 2, and ESRD cohorts and for age, gender, β -blocker therapy, left ventricular ejection fraction, sleep-time mean N-N interval, and F_{CV} for the CHF cohort.

[†]Adjusted for age, gender, diabetes, β -blocker therapy, left ventricular ejection fraction, and sleep-time mean N-N interval for the post-MI 1, post-MI 2, and ESRD cohorts and for age, gender, β -blocker therapy, left ventricular ejection fraction, and sleep-time mean N-N interval for the CHF cohort.

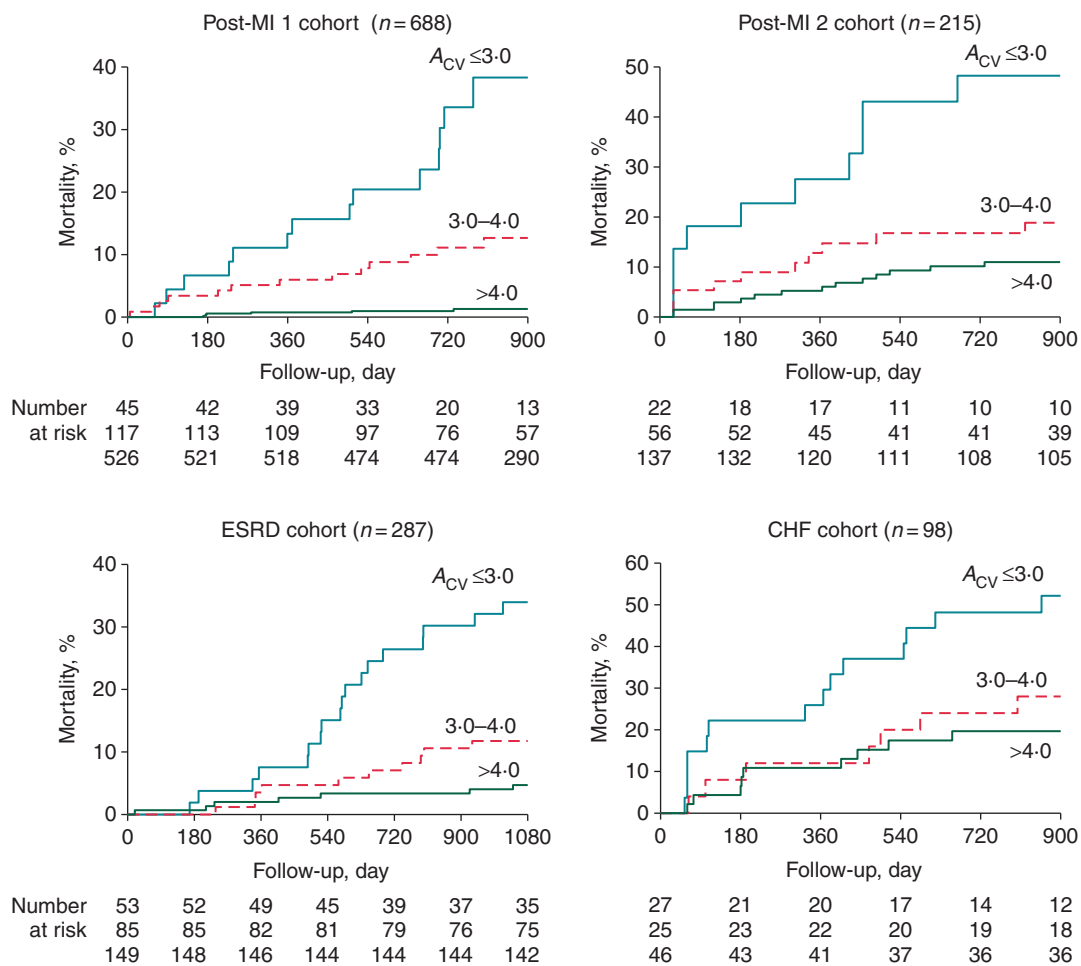


Figure 3 Kaplan–Meier curves of mortality for patients in four cohorts stratified by A_{CV} . Mortality probabilities in four cohorts of patients stratified by the same criteria of A_{CV} cut-off values (4.0 and 3.0) that were optimized for the post-MI 1 cohort: low-risk patients ($A_{CV} > 4.0$), intermediate-risk patients (3.0–4.0), and high-risk patients (≤ 3.0). The mortality probabilities differed significantly among the post-MI 1 (log-rank $\chi^2 = 105.8$, $P < 0.001$); post-MI 2 (38.9, $P < 0.001$); ESRD (28.7, $P < 0.001$); and CHF (9.9, $P = 0.007$) cohorts.

respectively. In this study, we observed no substantial predictive power of F_{CV} for mortality risk in any of the cohorts, whereas decreased A_{CV} predicted mortality risk in all of the cohorts. Also, we observed no significant correlation between F_{CV} and A_{CV} in any of the cohorts and that the prognostic association of A_{CV} with mortality was independent of F_{CV} in all of the cohorts. These indicate that A_{CV} and F_{CV} reflect different pathophysiologic properties and that the prognostic association of A_{CV} is independent of the frequency of SDB.

A variety of autonomic indices of HRV and heart rate dynamics obtained from Holter ECG recordings have been reported as useful markers for risk stratification in various clinical groups including post-MI, ESRD, and CHF patients. Among patients after MI, decreased deceleration capacity³ and abnormal heart rate turbulence,² which are thought to reflect mainly cardiac vagal dysfunctions of phasic and reflex heart rate modulations, respectively, are known as the most powerful predictors of mortality. Decreased scaling exponent α_1 , which may reflect, at least partly, increased sympathetic

activity,¹⁴ has been reported as mortality predictor in patients after MI¹⁵ and those with ESRD.⁴ While most indices of HRV has no substantial predictive power in patients with CHF, an increase in non-Gaussianity index of λ , which is thought to reflect sympathetic over activations, has been reported to predict mortality in these patients.⁵ Because this study has not been designed to compare predictive power between A_{CV} and these conventional indices, we cannot discuss quantitatively the advantage or disadvantage of A_{CV} . However, the fact that A_{CV} requires only ECG data during sleep may be a possible merit in its applicability to other monitoring devices, while the fact that it can be used only in patients with CVHR of ≥ 4 cycles per night is an apparent demerit. Also, while earlier studies proposed different autonomic indices with respect to each disease, our results suggest that A_{CV} may be used for at least three different diseases (post-MI, ESRD, and CHF). This may represent a potential advantage of A_{CV} over the other autonomic indices.

Although cardiac autonomic dysfunction is the most likely mechanism that mediates the association of decreased A_{CV} with increased

Table 5 Association of risk variables with β -blocker therapy by cohort

	Post-MI 1	Post-MI 2	ESRD	CHF
Mean N-N interval ^a , ms				
β -Blocker (–)	864 (736–990)	903 (819–977)	846 (759–962)	866 (715–994)
β -Blocker (+)	973 (857–1076)	919 (827–1012)	924 (828–999)	801 (752–890)
p^{\dagger}	<0.001	0.3	0.01	0.4
A_{CV} , ln (ms)				
β -Blocker (–)	4.4 (3.5–5.5)	4.4 (3.5–5.2)	4.0 (3.3–4.9)	4.0 (2.6–4.8)
β -Blocker (+)	5.1 (4.2–5.7)	4.7 (3.8–5.2)	4.3 (3.1–5.3)	3.7 (3.2–4.1)
p^{\dagger}	<0.001	0.5	0.2	0.8
F_{CV} , cph				
β -Blocker (–)	8.4 (4.2–17.8)	13.0 (3.8–26.3)	8.8 (4.3–15.5)	4.7 (2.2–11.8)
β -Blocker (+)	9.5 (5.2–15.4)	10.73 (6.8–21.5)	8.8 (3.3–14.7)	9.7 (4.0–23.7)
p^{\dagger}	0.3	0.9	0.5	0.1

Data are medians (IQR).

N-N interval, normal-to-normal R-R interval.

^aMean N-N interval during sleep time.[†]Significance of difference between patients who were and were not taking a β -blocker during Holter monitoring by the Wilcoxon rank sum test.

mortality risk, there may be other intervenient factors affecting the associations. First, we observed modest positive correlation of A_{CV} with sleep-time mean N-N interval in all cohorts. Because A_{CV} is thought to reflect the increase in heart rate caused primarily by vagal withdrawal at the termination of each apnoea/hypopnoea episode,^{6,7} A_{CV} would be decreased in patients with a higher baseline heart rate during sleep due to reduced heart rate reserve. In fact, we also observed a greater A_{CV} and a longer sleep-time mean N-N interval in patients taking β -blocker than in those not taking β -blocker in the post-MI 1 cohort. In multivariate analyses, however, A_{CV} was a significant and powerful predictor of mortality risk even after adjusting for the effect of sleep-time mean N-N interval, indicating that the association between decreased A_{CV} and mortality risk is explained by increased night-time heart rate only partially. Second, although CVHR is caused by SDB, similar cyclic heart rate variations are observed in patients with genuine periodic leg movements in sleep (PLMS), which are also detected by the ACAT algorithm as CVHR particularly when the cycle length of PLMS is longer than 25 s.⁹ PLMS has been known to be accompanied by activations of the sympathetic nervous system.¹⁶ Prognostic association of heart rate responses accompanying PLMS seems to deserve future studies. Finally, although A_{CV} assumes the presence of SDB, A_{CV} was able to be measured in 96–98% of post-MI, ESRD, and CHF patients who had not reported to have SDB. Also, the predictive power of A_{CV} was independent of F_{CV} that reflects the quantitative severity of SDB and the significant prognostic association of A_{CV} was observed even in patients with $F_{CV} < 5$ in all but ESRD cohorts. These indicate that for the purpose of risk stratification, A_{CV} may be used practically in most of these patients and that if CVHR occurs, then A_{CV} can predict mortality, irrespective of whether clinical SDB is present or not.

From a clinical standpoint, our findings may offer a novel and practical approach to risk management in post-MI, ESRD, and CHF patients. According to the Survey of Medical Care Activities in Public

Health Insurance conducted by the Japanese Ministry of Health, Labor and Welfare in 2014, at least 1 420 000 Holter ECG examinations are performed each year in Japan alone. Cardiovascular patients, who are the most likely to undergo a Holter ECG examination, are also the highest-risk population for SDB. In this study, A_{CV} could be analyzed in $\geq 96\%$ of these patients, and the predictive power of A_{CV} was preserved even among patients with only a few CVHR events ($F_{CV} < 5$ cph). The analysis of A_{CV} by Holter ECG monitoring seems to be a low-cost method that can provide useful information for identifying high-risk patients who require prompt evaluation and treatment.

Limitations

This study has several limitations. First, the study cohorts were post-MI, ESRD, and CHF patients. Our findings may not apply to the other clinical groups or populations. Second, although we observed significant predictive power of A_{CV} , the A_{CV} may reflect not only the amplitude of CVHR accompanying SDB but also the magnitude of cyclic heart rate variations caused by PLMS and other factors, such as involuntary breath-holding accompanying roll-over during sleep. To clarify this point, future polysomnographic studies are needed in these patients. Third, we analyzed ECG data during sleep time that was determined using patient's diary in post-MI 1 and ESRD cohorts, while it was defined uniformly as 23:00–06:00 in post-MI 2 and CHF cohorts. Thus, there is the possibility that patients were not sleeping or in bed during the analyzed periods, although this would have worked for weakening the prognostic power of A_{CV} .

Conclusions

In this study, we found that blunted CVHR detected by decreased A_{CV} in night-time Holter ECG monitoring predicts increased mortality risk in post-MI, ESRD, and CHF patients. Our findings support

the hypothesis that blunted CVHR predicts mortality risk that is most likely mediated by cardiac autonomic dysfunction in these patients.

Conflict of interest

The autocorrelated wave detection with adaptive threshold (ACAT) algorithm is installed in a Holter ECG scanner (Cardy Analyzer; Suzuken Company Limited, Nagoya, Japan). Dr Hayano is a consultant for Suzuken Company Limited. Dr Kodama is an advisor for Suzuken Company Limited. Other authors have reported that no potential conflicts of interest exist with any companies or organizations whose products or services may be discussed in this article.

Funding

This work was supported by the Japan Society for the Promotion of Science, Japan [Grant-in-Aid for Scientific Research (C) 20590832, 23591055 (to J.H.)].

References

1. Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ, the Multicenter Post-Infarction Research G. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987;**59**:256–62.
2. Schmidt G, Malik M, Barthel P, Schneider R, Ulm K, Rolnitzky L et al. Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. *Lancet* 1999;**353**:1390–6.
3. Bauer A, Kantelhardt JW, Barthel P, Schneider R, Makikallio T, Ulm K et al. Deceleration capacity of heart rate as a predictor of mortality after myocardial infarction: cohort study. *Lancet* 2006;**367**:1674–81.
4. Suzuki M, Hiroshi T, Aoyama T, Tanaka M, Ishii H, Kishihara M et al. Nonlinear measures of heart rate variability and mortality risk in hemodialysis patients. *Clin J Am Soc Nephrol* 2012;**7**:1454–60.
5. Kiyono K, Hayano J, Watanabe E, Struzik ZR, Yamamoto Y. Non-Gaussian heart rate as an independent predictor of mortality in patients with chronic heart failure. *Heart Rhythm* 2008;**5**:261–8.
6. Guilleminault C, Connolly S, Winkle R, Melvin K, Tilkian A. Cyclical variation of the heart rate in sleep apnoea syndrome. Mechanisms and usefulness of 24 h electrocardiography as a screening technique. *Lancet* 1984;**1**:126–31.
7. Zwillich C, Devlin T, White D, Douglas N, Weil J, Martin R. Bradycardia during sleep apnea. Characteristics and mechanism. *J Clin Invest* 1982;**69**:1286–92.
8. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council On Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). *Circulation* 2008;**118**:1080–111.
9. Hayano J, Watanabe E, Saito Y, Sasaki F, Fujimoto K, Nomiyama T et al. Screening for obstructive sleep apnea by cyclic variation of heart rate. *Circ Arrhythm Electrophysiol* 2011;**4**:64–72.
10. Hayano J, Tsukahara T, Watanabe E, Sasaki F, Kawai K, Sakakibara H et al. Accuracy of ECG-based screening for sleep-disordered breathing: a survey of all male workers in a transport company. *Sleep Breath* 2013;**17**:243–51.
11. Carney RM, Blumenthal JA, Stein PK, Watkins L, Catellier D, Berkman LF et al. Depression, heart rate variability, and acute myocardial infarction. *Circulation* 2001;**104**:2024–8.
12. Arsenos P, Gatzoulis K, Manis G, Gialernios T, Dilaveris P, Tsiachris D et al. Decreased scale-specific heart rate variability after multiresolution wavelet analysis predicts sudden cardiac death in heart failure patients. *Int J Cardiol* 2012;**154**:358–60.
13. Gatzoulis KA, Tsiachris D, Arsenos P, Archontakis S, Dilaveris P, Voulgiotis A et al. Prognostic value of programmed ventricular stimulation for sudden death in selected high risk patients with structural heart disease and preserved systolic function. *Int J Cardiol* 2014;**176**:1449–51.
14. Huikuri HV, Perkiomaki JS, Maestri R, Pinna GD. Clinical impact of evaluation of cardiovascular control by novel methods of heart rate dynamics. *Philos Trans A Math Phys Eng Sci* 2009;**367**:1223–38.
15. Huikuri HV, Mäkilä TH, Peng CK, Goldberger AL, Hintze U, Moller M et al. Fractal correlation properties of R-R interval dynamics and mortality in patients with depressed left ventricular function after an acute myocardial infarction. *Circulation* 2000;**101**:47–53.
16. Guggisberg AG, Hess CW, Mathis J. The significance of the sympathetic nervous system in the pathophysiology of periodic leg movements in sleep. *Sleep* 2007;**30**:755–66.