



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

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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,  $\beta$ -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

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## 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,  $\beta$ -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

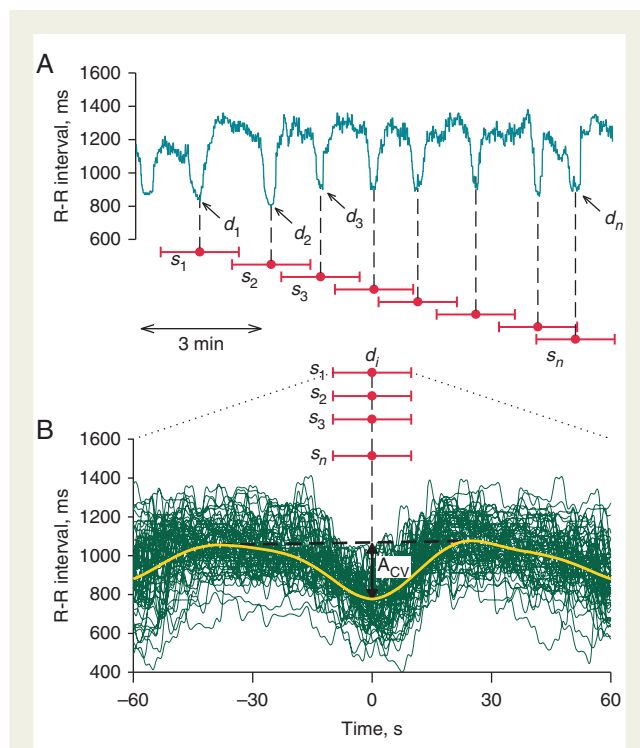
Studies of heart rate variability (HRV) and those of heart rate dynamics indicate that cardiac autonomic dysfunction is an independent mortality risk in various clinical conditions including post-myocardial infarction (MI),<sup>1–3</sup> end-stage renal disease (ESRD),<sup>4</sup> and chronic heart failure (CHF).<sup>5</sup> 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).<sup>6,7</sup> 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<sup>1–5</sup> and SDB is common, among these patients.<sup>8</sup> We used a previously validated algorithm<sup>9,10</sup> 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.<sup>11</sup> 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.<sup>9,10</sup> 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.<sup>12,13</sup> 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.<sup>4</sup> The third comprised patients with CHF consecutively referred to Fujita Health University Hospital and admitted to the hospital between January 2000 and December 2001.<sup>4</sup>

Inclusion criteria were patients aged  $\geq 20$  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 (ENRICH) cohort;<sup>11</sup> Post-MI 2, patients after a myocardial infarction;<sup>12,13</sup> ESRD, patients with end-stage renal disease on chronic haemodialysis therapy;<sup>4</sup> CHF, patients with chronic heart failure;<sup>5</sup> 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; SynScope 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.<sup>9,10</sup> 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  $\geq 4$  cycles of CVHR per night were detected.

## Statistical analyses

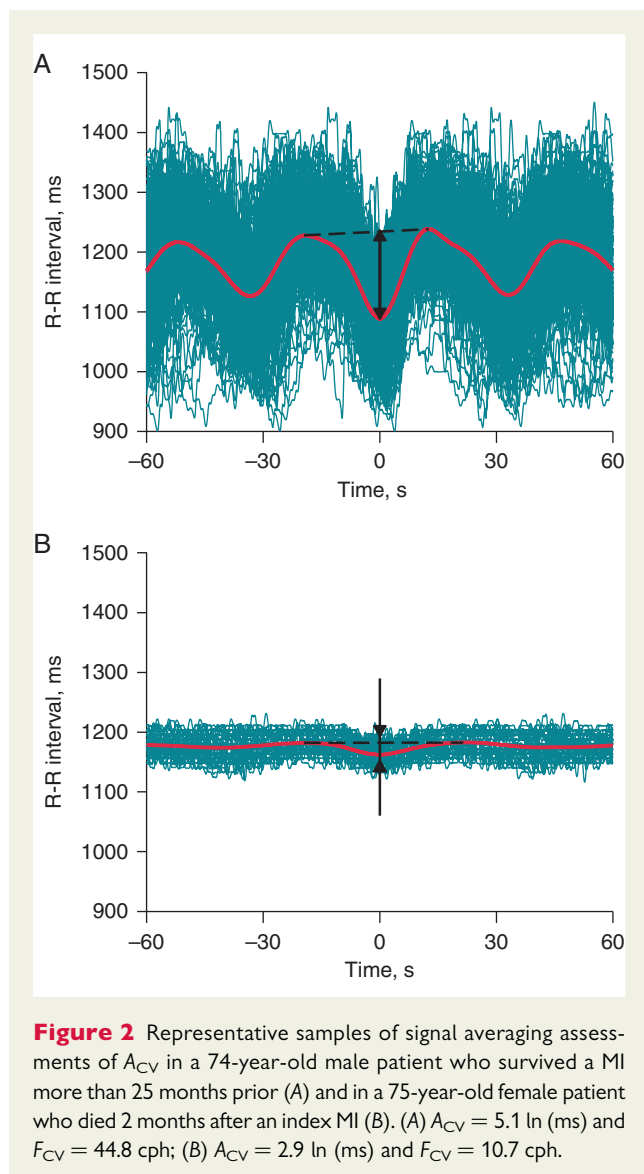
We used SAS 9.4 software (SAS Institute, Cary, NC) for the statistical analysis. To normalize the distributions, we transformed  $A_{CV}$  in the natural logarithmic values. We used Wilcoxon rank sum tests and  $\chi^2$  statistics to compare survivors and non-survivors on the basis of demographic and 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,<sup>9,10</sup> 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  $\geq 4$  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,  $\geq 4$  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,  $\beta$ -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 $\beta$ -blockers on risk variables

To determine whether CVHR parameters are associated with  $\beta$ -blocker therapy, sleep-time mean N-N interval,  $A_{CV}$ , and  $F_{CV}$  were compared in patients who were and were not taking a  $\beta$ -blocker at the time of the Holter monitoring in each cohort (Table 5). Patients taking a  $\beta$ -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  $\beta$ -blocker in the post-MI 1 cohort, whereas there was no significant difference in the other cohorts. No significant difference with  $\beta$ -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 (%) <sup>a</sup>	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–≤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.

<sup>a</sup>Number (% in total) of patients with ≥4 cycles of CVHR per night.

<sup>†</sup>Significance of difference between survivors and non-survivors (Wilcoxon rank sum test).

<sup>‡</sup>Significance of difference between survivors and non-survivors ( $\chi^2$  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.

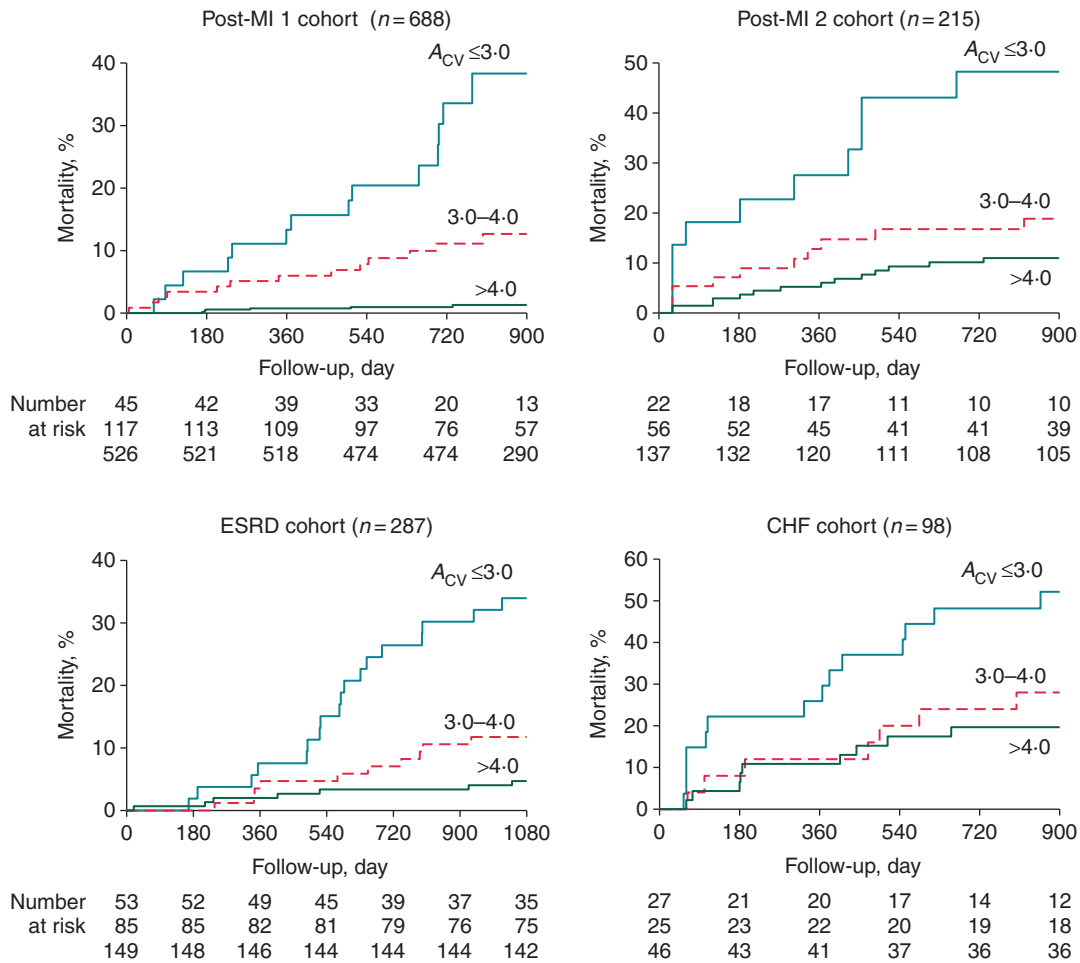
In this study, we used an automated CVHR detection algorithm called ACAT to detect CVHR and to measure the frequency and amplitude of CVHR as  $F_{CV}$  and  $A_{CV}$ , respectively. In our previous study of 862 patients referred for diagnostic polysomnography<sup>9</sup> and 165 healthy male truck drivers,<sup>10</sup> 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  $\geq 15$  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
<b>Univariate</b>								
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)	0.02
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)	0.7
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)	0.005
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)	0.09
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)	0.5
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)	0.2
<b>Multivariate</b>								
Acv per decrement of 1 ln (ms) <sup>a</sup>	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)	0.005
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)	0.6
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)	<0.001
Fcv per increment of 1 cph <sup>†</sup>	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)	0.2
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)	0.3
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)	0.3

<sup>a</sup>Adjusted for age, gender, diabetes, β-blocker therapy, left ventricular ejection fraction, sleep-time mean N-N interval, and F<sub>CV</sub> 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<sub>CV</sub> for the CHF cohort.

<sup>†</sup>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 ( $\leq 3.0$ ). 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 capacity<sup>3</sup> and abnormal heart rate turbulence,<sup>2</sup> 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  $\alpha_1$ , which may reflect, at least partly, increased sympathetic

activity,<sup>14</sup> has been reported as mortality predictor in patients after MI<sup>15</sup> and those with ESRD.<sup>4</sup> While most indices of HRV has no substantial predictive power in patients with CHF, an increase in non-Gaussianity index of  $\lambda$ , which is thought to reflect sympathetic over activations, has been reported to predict mortality in these patients.<sup>5</sup> 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  $\geq 4$  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  $\beta$ -blocker therapy by cohort**

	Post-MI 1	Post-MI 2	ESRD	CHF
Mean N-N interval <sup>a</sup> , ms				
$\beta$ -Blocker (–)	864 (736–990)	903 (819–977)	846 (759–962)	866 (715–994)
$\beta$ -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)				
$\beta$ -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)
$\beta$ -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				
$\beta$ -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)
$\beta$ -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.

<sup>a</sup>Mean N-N interval during sleep time.

<sup>†</sup>Significance of difference between patients who were and were not taking a  $\beta$ -blocker during Holter monitoring by the Wilcoxon rank sum test.

mortality risk, there may be other intercurrent 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,<sup>6,7</sup>  $A_{CV}$  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  $\beta$ -blocker than in those not taking  $\beta$ -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.<sup>9</sup> PLMS has been known to be accompanied by activations of the sympathetic nervous system.<sup>16</sup> 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.)].

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