Blunted cardiac response to sleep apnea
A Marker of Depression after Acute Myocardial Infarction

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***Abstract*—While depression is often overlooked in patients after acute myocardial infarction (AMI), it is an important risk of death among these patients. We examined if heart rate variability (HRV) particularly those related to sleep apnea can be a maker of depression after AMI. According to the prognosis of depression, 707 post-AMI patients were divided into 349 never, 138 remitting, 25 newly onset, and 195 persistent depression. Regardless of future prognosis, currently depressed patients had higher heart rate, lower HRV, and blunted cyclic variation of heart rate to sleep apnea during the night.**

I. INTRODUCTION

Depression is an increased risk of death after acute myocardial infarction. Earlier studies have reported 2 to 5 times higher risk of death in depressed post-AMI patients compared with non-depressed patients [1, 2]. In the very busy clinical sites of AMI care, depression is often overlooked or recognized as inevitable psychological reaction to acute disaster and consequently, left untreated. To improve this situation, objective makers that can be automatically obtained from bio-signals available in these clinical sites are desirable.

In this study, we examined if heart rate variability derived from nocturnal electrocardiogram (ECG) can be makers of depression and of its prognosis among post-AMI patients. We particularly focused on cyclic variation of heart rate (CVHR), because we previously observed that blunted CVHR is a strong and useful predictor of death that can be automatically obtained from nighttime ECG in these patients [3, 4].

II. METHODS

Patient cohort

We studied 758 post-AMI patients; 357 (47%) of them were depressed, meeting the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for either major or minor depression, and participated in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) clinical trial [5]; 401 (53%) were otherwise eligible for ENRICHD but had no prior episodes of major depression or current depression symptoms (Beck Depression Inventory (BDI) score <10) [6]. This study was approved by the Institutional Review Board of the Washington University School of Medicine (number, 96-0849).

Patients were excluded if they: 1) had other life-threatening illnesses, cognitive impairment, or other major psychiatric disorders; 2) showed sinus rhythm <80% of nighttime during the Holter ECG recording; 3) had atrial fibrillation, atrial flutter, or an implanted pacemaker; or 4) were currently taking tricyclic or monoamine oxidase inhibitor antidepressants. None of the patients was receiving treatment for sleep apnea.

The depressive state of patients was evaluated repeatedly after 6 months, by which they were divided into 4 groups: never depressed, remitting depression, newly onset, and persistent depression (TABLE I).

Measurements

At baseline, demographic and clinical information was recorded, and the Beck Depression Inventory (BDI) [7] was administered. Holter ECG was recorded for 24 hours within 28 (median, 13; range 2-28) days after the index AMI but data only during nighttime were used for this study.

Data analysis

The Holter ECG data were scanned on an SXP Laser scanner (Marquette Electronics). The labeled R-R interval files were exported to a computer on which CVHR was detected by an automated algorithm of autocorrelated wave detection with adaptive threshold (ACAT) [8]. Briefly, R-R interval time series during nighttime were interpolated with a horizontal-step function using only normal-to-normal (N-N) intervals consisting of consecutive sinus beats and resampled at 2 Hz. The resampled R-R interval time series were smoothed by second-order polynomial fitting and submitted to the ACAT algorithm. The ACAT algorithm detects transient tachycardia (dips in R-R interval trend) as CVHR when they meet 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 R-R interval variations, 4) cycle length (interdip

TABLE I
PATIENTS GROUPED BY CURRENT AND AFTER- 6-MONTH DEPRESSIVE STATES

Group	Depression		N	Female (%)	Age (yr)	CVHR+ (%)
	Base -line	6 mo				
Never	-	-	376	118 (31.4)	61 ± 10	349 (92.8)
Remitting	+	-	142	52 (36.6)	59 ± 12	138 (97.2)
New onset	-	+	25	11 (44)	58 ± 11	25 (100)
Persistent	+	+	215	118 (54.6)	55 ± 12	195 (90.7)

CVHR+ = number of patients who showed cyclic variation of heart rate.

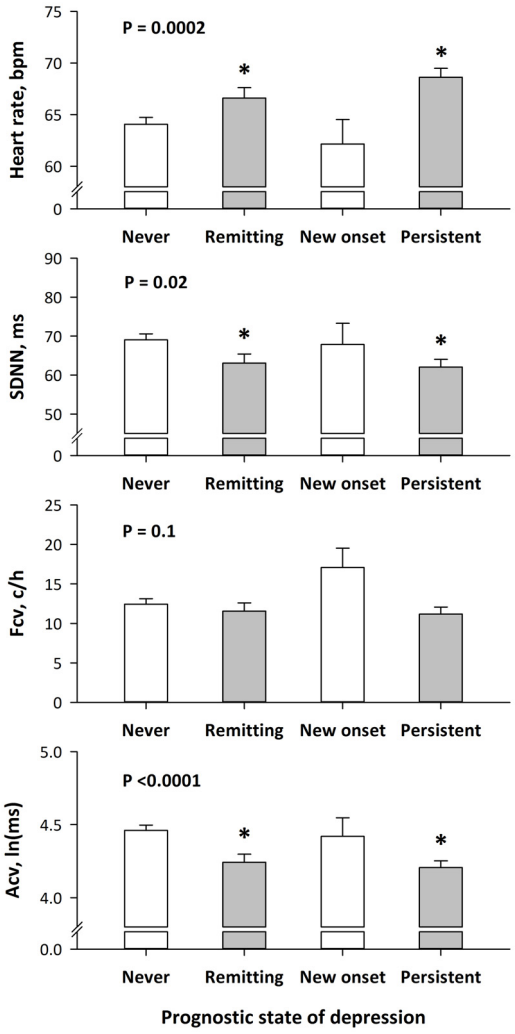

Fig. 1. Heart rate and heart rate variability during nighttime in patients grouped by the prognostic stateof depression.
*Significantly different from the value in never depressed patients with post-hoc multiple comparisons.
SDNN = standard deviation of normal-to-normal R-R interval, Fcv = frequency of cyclic variation of heart rate, Acv = signal averaged amplitude of cyclic variation of heart rate.

interval) from 25 to 120 s, 5) similar waveforms among 5 consecutive dips (morphological correlation coefficients >0.4) and 6) three equivalent consecutive cycle lengths with a tolerance of 22% against the mean cycle length.

We calculated the frequency of CVHR (Fcv) as the number of cycles per hour. We also measured the amplitude of CVHR (Acv) by signal averaging of all CVHR detected during night [4]. Additionally, average heart rate and standard deviation (SDNN) were calculated only using N-N intervals.

III. RESULTS

As shown in Fig 1, heart rate was higher (P = 0.0002) and SDNN was lower (P = 0.02) in patients with remitting and persistent depression than in never-depressed patients. CVHR was observed >90% of patients in all groups (TABLE I). In these patients, no significant difference in Fcv was observed with prognostic state of depression. In contrast, Acv was lower in patients with remitting and persistent depression than in never-depressed patients (P <0.0001).

IV. DISCUSSION

We observed increased heart rate and reduced heart rate variability among patients with remitting and persistent depression. Because these changes were not observed in patients who showed newly onset of depression after 6 months, they may be associated with current depression regardless of the prognosis.

Among indices measured, Acv showed the most significant association with depression. Acv is thought to reflect the magnitude of reflex autonomic function, i.e., vagal withdrawal occurring at the cessation of each episode of sleep apnea [9]. We previously reported, reduction in Acv is one of the most powerful predictor of all-cause mortality after AMI [4]. The present observations not only indicate that reduced Acv may be used as a maker of depression after AMI but also suggest that reduction in Acv may be improved by the treatment of depression in those patients. Given our limited means for the treatment for autonomic dysfunction detected by heart rate variability, this finding seems important suggesting the treatment of depression as one of such approaches.

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