ORIGINAL

Electrocardiographic and Chronobiological Features of Paroxysmal AV Block Recorded by Ambulatory Electrocardiography

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Abstract : The goal of this study was to investigate the electrocardiographic and chronobiological features of paroxysmal atrioventricular (AV) block (PAVB) using data from ambulatory electrocardiography (AECG). The study population consisted of five men and six women aged from 47 to 82 years of age. Main presenting symptoms were pre-syncope in five patients (45.5%) and syncope in three patients (27.3%). Organic cardiovascular diseases were seen in eight patients (72.7%), and AV conduction disturbances were seen in six patients (54.5%), such as right bundle branch block, first to second degree AV block on standard 12-lead electrocardiography. Incidence of PAVB events were 1-329 (37.9 ± 98.0) episodes/patient/day, and the maximum pause during Holter recordings was 3.3-12.4 (6.39 ± 3.09) seconds. This maximum pause caused by intrinsic AV block was longer than that of vagally mediated AV block (8.4 ± 3.2 sec vs 4.7 ± 1.0 sec, p<0.05). In chronobiological analysis, episodes of PAVB exhibited a circadian rhythm characterized by a peak between 2 : 00 am and 4 : 00 am and a trough between 0 : 00 pm and 2 : 00 pm. AECG is a useful tool to detect the maximum pause occurring during sleep and provides critical data necessary to prevent the sudden cardiac death caused by PAVB. J. Med. Invest. 61 : 380-387, August, 2014

***Keywords* :** *Paroxysmal AV block, Ambulatory electrocardiography, Circadian rhythm, Syncope, Right bundle branch block*

INTRODUCTION

Paroxysmal atrioventricular (AV) block (PAVB) is a rare but life-threatening arrhythmia ; characterized by the sudden onset of repetitive block of

transmission of the atrial impulse to the ventricles accompanied by the prolonged ventricular asystole (1, 2). Although there is no definite diagnostic criteria and classification for this phenomenon (3), two types of PAVB have been demonstrated clinically : "vagally mediated AV block (4)" and "intrinsic AV block (5-10)." The latter contains tachycardia- and bradycardia- (pause-)dependent AV block and occurs in patients with underlying structural heart disease and/or abnormal findings on the standard 12-lead electocardiography (ECG) (3, 11), while the

former is not associated with these characteristics. Vagally mediated AV block is defined as a paroxysmal first, second, and third degree AV block, localized within the AV node, associated with slowing of the sinus rate (12).

Recently, an additional type of PAVB called "idiopathic paroxysmal AV block" was documented by Brignole *et al.* (13). The clinical features of this type of AV block includes long-term recurrent syncope, absence of structural heart disease, absence of ECG abnormalities, and absence of progression to persistent AV block.

Distinguishing between these three types of PAVB is important, because the efficacy of cardiac pacing differs according to the type of AV block (3). In this study, we present our experience with PAVB recorded by long-term ambulatory ECG monitoring and investigate the electrocardiographic and chronobiological features of PAVB.

SUBJECTS AND METHODS

In this study, we retrospectively collected ambulatory ECG data from the medical records of the patients with PAVB who underwent assessment at the ambulatory ECG Laboratory of the Sekishinkan Hospital from February 1, 1996 to May 1, 2011. Initially, the ambulatory ECG recorder used in this study was a two-channel (modified V_5-like and V_1-like lead) analog recorder (Model SM-28, Fukuda Denshi, Inc., Tokyo, Japan) ; later, a digital recorder (Models FM-100 and FM-180, Fukuda Denshi, Inc., Tokyo, Japan) was used.

We re-analyzed the 24-hour ambulatory ECG recordings using Fukuda Holter workstation (DMW-9000H, Fukuda Denshi, Inc.), and the following variables were measured for each record manually : maximum heart rate (HR), minimum HR, average HR, maximum R-R interval, and the total episodes of PAVB.

PAVB was defined as a block of more than two consecutive P waves, with a pause defined as "ventricular asystole" (i.e., the time interval between the last conducted beat before the block to the first conducted beat after the PAVB or escape beat) (14, 15). Classification of PAVB was performed synthetically according to underlying etiology, associated vagally mediated symptoms, and specific electrocardiographic findings. ECG parameters used to classify the PAVB included a variation ratio of the PP interval (ΔPP) and a PR interval (ΔPR) immediately

before the onset of AV block as well as a HR changing ratio (ΔHR) just before and after the PAVB. We also measured the coupling interval of atrial premature beat to evaluate the electrophysiological mechanism of PAVB.

Physical examination, standard 12-lead ECG, chest X-ray and other cardiovascular examinations, such as two dimensional Doppler echocardiography and exercise electrocardiography, were performed for accurate diagnosis of heart disease. Informed consent was waived for this study because the study involved only the review of existing 12-lead and ambulatory ECG records.

In addition to the present study, heart rate variability (HRV) was analyzed from ambulatory ECG recordings previously performed in young healthy students. HRV was calculated using the maximum entropy method (MemCalc/CHIRAM ; GMS Co., Tokyo, Japan). The very low (VLF power, 0.003-0.04 Hz), low (LF power, 0.04-0.15 Hz) and high (HF power, 0.15-0.40 Hz) frequency power as well as the LF/HF ratio were calculated by consecutively processing 5-minute RR intervals. Spectral components of HRV were expressed as absolute units. Sleep periods were determined from each subject's diary, and spectral power was compared between sleep (night) and wake (day) periods. Analysis of circadian rhythm of HRV indices was performed according to the cosinor method (16) (MemCalc/Ver.2 ; GMS Co.).

STATISTICS

Statistical analysis was performed with MedCalc 12.3.0.0 (MedCalc Software, Ostend, Belgium). All continuous variables are presented as mean $\pm$ standard deviation. The Student's t-test was used to compare two groups, and an analysis of variance (ANOVA) was used to multiple groups. For categorical variables, which are presented as number of patients or percentages, comparisons were performed using χ^2 analysis or Fisher's exact test. For all statistical analysis, p value < 0.05 was considered to indicate statistical significance.

RESULTS

Patient profile (Table 1)

Table 1 shows the demographic and clinical features of patients with PAVB. Over a period of 5 years

Table 1 : Clinical and demographic features in patients with paroxysmal AV block.

Number	Age	Sex	Symptoms	Clinical Diagnosis	ECG Findings
1	74	F	Syncope	Hypertension	CRBBB
2	71	F	Presyncope	Hypothyroidism	WNL
3	51	M	Palpitation	Arrhythmia susp.	WNL
4	82	F	Presyncope	Angina Pectoris	WNL
5	53	M	(-)	Angina Pectoris	WNL
6	56	F	Presyncope, Palpitation	CAD, 2nd degree AV block	2nd degree AV block IRBBB+LAFB
7	66	M	(-)	AV block (1st)	AV block (1st)
8	82	M	Syncope	HHD	LVH
9	82	M	Syncope	AR (mild)	CRBBB
10	56	F	Presyncope	HT, 2nd degree AVB	WNL
11	47	F	Presyncope	TOF(p/o), 1st degree AV block	CRBBB

Abbreviations : CRBBB : complete right bundle branch block, WNL : within normal limit, CAD : Coronary Artery Disease, IRBBB : incomplete right bundle branch block, LAFB : left anterior fascicular block, AV : atrioventricular, HHD : hypertensive heart disease, LVH : left ventricular hypertrophy, AR : aortic regurgitation, HT : hypertension, TOF : tetralogy of Fallot, p/o : post operation

and 2 months, 11 patients had spontaneous PAVB. The mean patient age was 65.4 ± 13.4 years (range, 47 to 82 years). Five patients (45.5%) were male, and six patients (54.5%) were female. The presenting symptoms were pre-syncope in five patients (45.5%), syncope in three patients (27.3%), palpitations in two patients (18.2%), and the remaining two patients did not have outstanding symptoms (one patient had both pre-syncope and palpitations).

Organic cardiovascular diseases included ischemic heart disease in three patients (27.3%), essential hypertension in two patients (18.2%), hypertensive heart disease, and valvular heart disease and postoperative state of tetralogy of Fallot in one patient (9.1%). The other three patients (27.3%) had no organic cardiovascular disease, but one patient (9.1%) had hypothyroidism.

On the rest standard 12-lead ECG, four patients (36.4%) had right bundle branch block (RBBB), two patients (18.2%) had first or second degree AV block, and one patient (9.1%) had left anterior fascicular block (LAFB).

Ambulatory ECG findings of paroxysmal AV block

In this study, 431 episodes of PAVB (defined as a block of more than two consecutive P waves) were found in a total of 267 hours of ambulatory ECG recordings from 11 patients. Figure 1 is a bar diagram of the distribution of ventricular asystole in patients with PAVB. The number of episodes of PAVB was the most frequent at the length of < 4

seconds, with 78.9% of the ventricular asystoles existing in this range. The incidence of PAVB also decreased as length of the pause increased. Ventricular asystole of 5 seconds or more (an absolute indication for pacemaker implantation at that time) was seen in about 11.1% of all pauses (48/431 episodes).

The total numbers of the episodes of PAVB per patient over 24 hours ranged from 1 to 329 (mean, 37.9 ± 98.0), and there was no statistically significant correlation between the length of the ventricular asystole, the incidence of PAVB, and 24-hr averaged HR from ambulatory ECG recordings. The P : QRS ratio in PAVB was 4 : 1 to 12 : 1, and the maximum R-R interval in 24-hr ECG recordings was 3.3 to 12.4 seconds (Table 2).
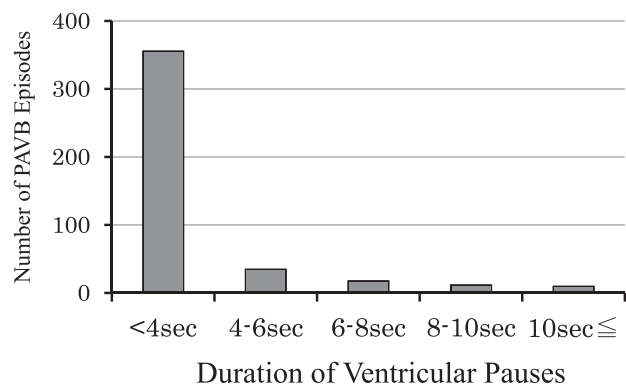
Figure 1 : Number of episodes of paroxysmal atrioventricular block (PAVB) (n=431).

Table 2 : Ambulatory ECG findings in patients with paroxysmal AV block.

Number	Age	Sex	Max.R-R (Time)	Average HR of 24hrs	Incidence of Pause (/day)	P : QRS ratio in paroxysmal AVB
1	74	F	12.4 sec(23 : 05)	55.2	59	10 : 1
2	71	F	5.4 sec(23 : 31)	55.5	1	5 : 1
3	51	M	4.2 sec(23 : 32)	68.9	2	4 : 1
4	82	F	4.6 sec(10 : 24)	62	329	5 : 1
5	53	M	3.3 sec(08 : 11)	76.3	1	4 : 1
6	56	F	5.4 sec(03 : 28)	58.3	1	6 : 1
7	66	M	6.0 sec(01 : 20)	57.6	6	7 : 1
8	82	M	12.0 sec(06 : 02)	59.9	1	5 : 1
9	82	M	8.8 sec(04 : 10)	44.5	4	12 : 1
10	56	F	6.1 sec(11 : 08)	58.2	12	9 : 1
11	47	F	5.4 sec(05 : 20)	78	3	6 : 1

Major forms of paroxysmal AV block

PAVB is due to intrinsic AV conduction distur-bance or heightened vagal tone (12, 17). Criteria that are useful to help distinguish between the two forms of AV block have been described by several groups of investigators (3, 12). Electrocardiographic main findings highly suggestive of vagally mediated AV block are (1)significant PR interval prolongation before initiation of AV block, (2)prolonging P-P in-terval during ventricular asystole, and (3)resumption of AV conduction on sinus acceleration (shortening P-P interval). On the other hand, evidence support-ing intrinsic type of PAVB includes the following ob-servations : (1)intrinsic AV block usually initiated by atrial, *His, or ventricular premature beat, (2)tachy-cardia can initiate PAVB, (3)shortening P-P interval during ventricular asystole, and (4)resumption of AV conduction generally occurs after appropriately timed escape beat or premature beats (3).

Using these criteria, vagally mediated AV block was found in five patients (Cases 2, 3, 4, 5, 7), and intrinsic (pause-dependent) AV block was found in six patients (Cases 1, 6, 8, 9, 10, 11). Among the ECG parameters used to classify the PAVB, the vari-ation ratio of the PR interval (ΔPR) increased only in patients with vagally mediated AV block in this study. On the other hand, a consistent response was not found in the variation ratio of PP interval (ΔPP) or the HR changing ratio (ΔHR) before and after the PAVB (Table 3).

Although there was no statistically significant difference in age (66.2 ± 15.1 vs 64.6 ± 12.9 years : not significant (NS)), gender (Male/Female : 2/4 vs 3/2 : NS), 24-hour averaged HR (59.1 ± 10.8 vs 64.1 ± 10.8 bpm : NS) or the number of episodes of AV block (13.3 ± 22.7 vs 61.8 ± 146.0/day : NS) in the two forms of PAVB (intrinsic and vagally medi-ated AV block), maximum pause derived from ven-tricular asystole was statistically longer in patients
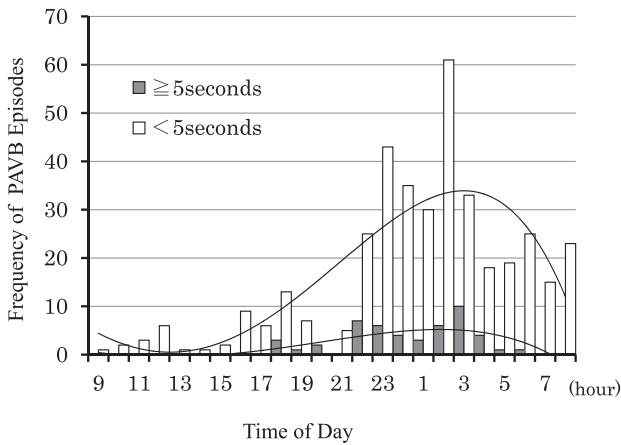
Table 3 : ECG parameters immediately before paroxysmal AV block.

Number	Age	pre.HR	post.HR	ΔHR(%)	ΔPP(%)	ΔPR(%)	Trigger
1	74	50	68	36	30	0	Bradycardia
2	71	48	66	37.5	0	0	Urination
3	51	43	54	25.6	0	80	(-)
4	82	72	103	44.8	51	11	(-)
5	53	58	109	87.9	6	8	(-)
6	56	56	60	7.1	22	0	(-)
7	66	69	60	-13.1	15	14	(-)
8	82	55	46	-16.4	0	0	(-)
9	82	66	66	0	0	0	(-)
10	56	55	57	3.6	0	0	(-)
11	47	56	57	1.8	0	0	(-)

with intrinsic AV block (8.4 ± 3.2 seconds [n=6]) than in those with vagally mediated AV block (4.7 ± 1.0 seconds [n=5]) (p< 0.05).

Diurnal variation of paroxysmal AV block

Figure 2 shows the circadian variation of ventricular asystole (< 5 seconds and ≥ 5 seconds) derived from the PAVB in all patients. The incidence of AV block formed a biphasic curve with a peak between 2 : 00 am and 4 : 00 am and a trough between 0 : 00 pm and 2 : 00 pm, suggesting a distinctive circadian rhythm of the episodes of PAVB. Episodes during sleep comprised 76.8% of all the episodes (331/431 episodes), and this tendency did not vary according
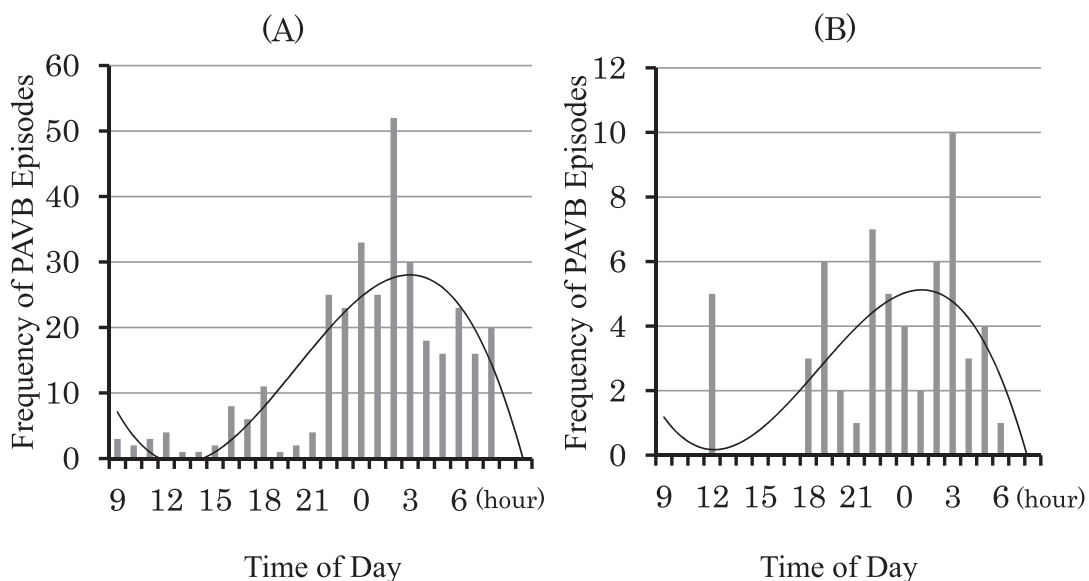
to the length of ventricular asystole or the specific form of PAVB (Figure 3).

A patient with pause-dependent AV block induced by an atrial premature beat (Case 1)

In the present study, a typical case of pause-dependent AV block (Case 1) triggered by non-conducted atrial premature beats was observed (Figure 4). The patient had hypertension and a history of syncope. There were no obvious structural heart diseases, and she had complete RBBB on 12-lead ECG. The 24-hour ambulatory ECG showed the reduction of heart rate (maximum HR=93 bpm, minimum HR=40 bpm, average HR=55 bpm) and sporadic episodes of PAVB, with ventricular asystole lasting up to 12.4 seconds (at 11 : 05 pm).

Figure 5 shows the coupling interval ratio of atrial premature beats to the basic cycle length that triggered (A) and did not trigger (B) AV block. The coupling interval ratio of atrial premature beats followed by PAVB (A) (0.86 ± 0.17 basic cycle length ratio [n=55]) was significantly prolonged when compared with atrial premature beats not followed by PAVB (B) (0.73 ± 0.05 basic cycle length ratio [n= 8]) statistically (p< 0.0001). In this case, AV block usually occurred after the pauses following atrial premature beats, including non-conducted type, and involvement of phase 4 block was suggested as a mechanism of PAVB.

Figure 2 : Circadian variation of ventricular asystole (< 5 seconds and ≥ 5 seconds) due to paroxysmal atrioventricular block (PAVB).

Figure 3 : Circadian variation of episodes in one patient with vagally mediated AV block (A : Case 4), and another patient with intrinsic AV block (B : Case 1). There are no differences in diurnal variation of the episodes of paroxysmal atrioventricular block (PAVB) in patients with two types of AV block.

[ECG Strip of Paroxysmal AV block]
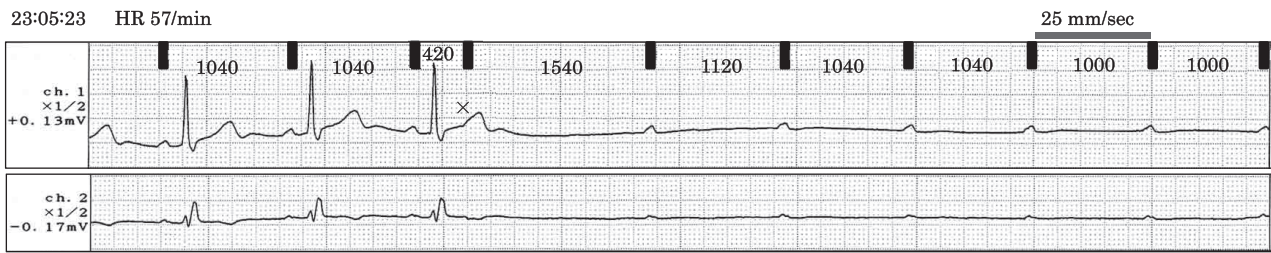
Figure 4 : Clinical case of pause-dependent paroxysmal atrioventricular block (PAVB) in a 74-years-old women with syncope and complete right bundle branch block on 12-lead ECG. PAVB is initiated by a long atrial cycle that followed the non-conducted atrial premature beat, marked X. Sinus acceleration during asystole does not affect the block until appropriately timed escape abolishes asystole.
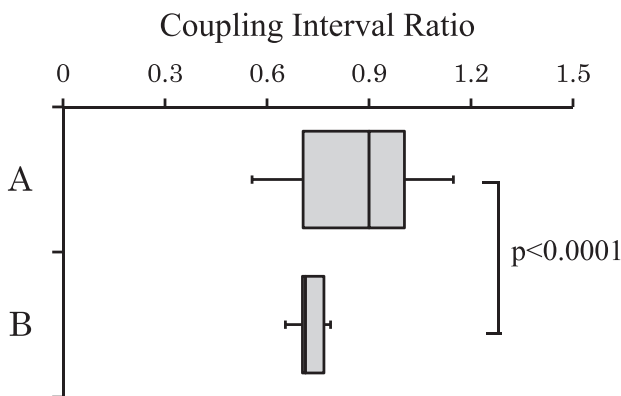

Figure 5 : Coupling interval ratio of atrial premature beats that trigger (A) and that do not trigger the paroxysmal AV block (B) in a patient with pause-dependent AV block.

DISCUSSION

The present study demonstrated the electrocardiographic and chronobiological features of PAVB. As previously reported in the literature (1-3, 18), this arrhythmia was more frequent in the elderly with peripheral AV conduction disturbances. In our study, the majority of patients (54.5%) was patients over the age of 65 years (6, 18), and the incidence of RBBB was higher (36.4%) than that in the general population. Lee *et al.* reported that 45% of patients with PAVB had RBBB (3). In most cases, patients with PAVB (particularly intrinsic AV block) had organic cardiovascular disease, such as ischemic heart disease or hypertension. This might account for why RBBB is seen at a high rate in patients with PAVB.

On the other hand, the prevalence of RBBB in the general population has been reported to be between 0.2% and 2.3% (19-21), and it increases with age. Erikson *et al.* demonstrated that the prevalence of RBBB increased from 0.8% at age 50 years to 4.9% at age 67 years (cumulative incidence, 5.7%) in the epidemiological study from the general male population (19). In the present study, the majority of patients were older than 65 years, which might be another reason for the increased incidence of RBBB in patients with PAVB. Therefore, when considering the cause of syncope in the elderly, if the patient has an AV conduction disturbance, such as RBBB, the clinician should be aware of the risk of PAVB.

This study also investigated the circadian rhythm of the PAVB, as there is little literature dealing with circadian rhythm of PAVB. Owing to its poor recognition, it is probably underestimated in the literature. Castellanos *et al.* (22) reported that 75% of episodes of PAVB occurred during the night and 25% during the day. However, there are no reports regarding the pattern and extent of diurnal variations in ventricular asystole.

In this study, the number of the episodes of ventricular asystole due to PAVB showed circadian

variation with the greatest night values and a peak of hourly episodes of AV block between 2 : 00 am and 4 : 00 am. Similar circadian variation has been reported for the HF power spectrum of HRV, which is an index of the cardiac parasympathetic function (22-24). Figure 6 shows data regarding the diurnal variation of the HF power spectrum in a re-analysis of ambulatory ECG monitoring data from the young healthy students (mean age, 20.1 ± 0.8 years ; 16 men and 16 women). The power spectral density of HF component also showed a biphasic circadian rhythm with the greatest values at night. The acrophase of the HF power spectrum was at 3 : 00 am, and a close relationship between the occurrence of PAVB and HF power (cardiac parasympathetic activity) was osberved. These data support the presence of a circadian rhythm in the episodes of PAVB, with autonomic dysfunction and a significantly higher risk of life-threatening pauses derived from PAVB occuring at night.
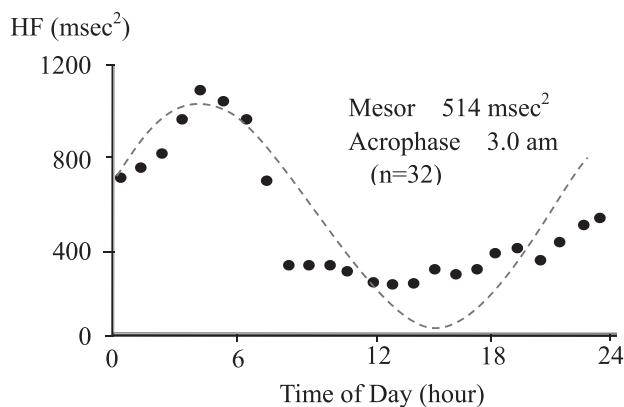
Figure 6 : Circadian variation of spectral power of HF component of heart rate variability calculated by ambulatory ECG recordings from young healthy subjects (n=32 ; mean age, 20.1 ± 0.8 years ; 16 males, 16 females).

Data regarding the circadian rhythms of PAVB is important to understand its pathogenesis as well as to facilitate accurate diagnosis and proper treatment of this arrhythmia. Because long pauses due to ventricular asystole frequently occur at night, long-term ECG recording that includes nighttime monitoring is necessary to capture the maximum ventricular pause and to prevent sudden cardiac death. In fact, a case of sudden cardiac death due to PAVB has already reported (25), and ambulatory 24-hr ECG monitoring is recommended for the accurate diagnosis of this arrhythmia.

Ambulatory ECG monitoring is also useful to investigate the mechanism of occurrence of PAVB.

In this study, a typical case of phase 4 block was observed after a long pause induced by atrial premature beats. Because there are almost no reports that have investigated the coupling interval ratio of atrial premature beats as a trigger for PAVB using the ambulatory ECG monitoring, this report is valuable.

CONCLUSIONS

We analyzed 11 cases of PAVB and investigated the electrocardiographic and chronobiological features by re-analyzing data from ambulatory ECG recordings. This phenomenon was rare, and because awareness of PAVB is low, PAVB is often overlooked. However, it is a life-threatening bradyarrhythmias leading to sudden cardiac death or syncope. Because the episodes of ventricular asystole shows a definitive circadian rhythm characterized by a peak at midnight, long-term ambulatory ECG monitoring is useful for the accurate diagnosis and the evaluation of severity of this arrhythmia, and these data are vital when deciding the indications for pacemaker implantation.

In addition, PAVB is at least composed of three groups with different pathogenesis : intrinsic AV block, vagally mediated AV block, and idiopathic AV block. Because there is still controversy regarding implantable pacemakers for patients with vagally mediated AV block, distinguishing between these three types of paroxysmal AV block is also necessary. Ambulatory ECG monitoring is a useful tool to classify the form of PAVB and provides vital information necessary to prevent sudden cardiac death due to PAVB.

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