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Original article

Assessment of a novel transdermal selective β1-blocker, the bisoprolol patch, for treating frequent premature ventricular contractions in patients without structural heart disease

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ABSTRACT

Background: The autonomic nervous system involves the genesis of premature ventricular contractions (PVCs). Previous studies demonstrated that heart rate (HR) dependency of idiopathic PVCs has different autonomic mechanisms. Recently, the bisoprolol patch, a novel transdermal β1-blocker formulation containing bisoprolol, became clinically available. We examined the efficacy of the bisoprolol patch for treating frequent PVCs in patients without structural heart disease (SHD) regarding the HR dependency of PVCs.

Methods: This prospective study included 44 consecutive patients without SHD (25 men, mean age, 63.6 ± 12.3 years) with PVC counts≥3000 beats as measured by 24-hour Holter electrocardiograms (ECGs). PVCs were divided into positive HR-dependent PVCs (P-PVCs) and non-positive HR-dependent PVCs (NP-PVCs) based on the relationship between the hourly PVC density and hourly mean HR. A bisoprolol patch was administered once daily at a dose of 4 mg. The 24-hour Holter ECGs were performed before and 1 month after the initiation of the therapy.

Results: In 44 patients, there were 24 P-PVCs and 20 NP-PVCs. The bisoprolol patch reduced the PVC count significantly (from 16,563 ± 10,056 to 7892 ± 8817 beats/24 hours, $p < 0.001$) in the P-PVC group, while the PVC count did not change significantly (from 16,409 ± 9571 to 13,476 ± 12,191beats/24 hours, $p = 0.34$) in the NP-PVC group. Moreover, in the P-PVC group, the patients with mean HRs ≥80 beats/minute had a significantly higher percent improvement in the PVC count than those with mean HRs <80 beats/minute ($p = 0.0080$). The bisoprolol patch resulted in a significant reduction in the PVC count from baseline during each time period for the changes within a 24-hour period in the P-PVC group.

Conclusions: The transdermal bisoprolol patch was effective for a PVC reduction in patients with P-PVCs, particularly in those with faster mean HRs. Furthermore, it demonstrated a stable PVC-reducing effect during the 24-hour period in the P-PVC group.

Introduction

Premature ventricular contractions (PVCs) are one of the most common arrhythmias in clinical practice. In general, patients with idiopathic PVCs have a good prognosis, but the symptoms such as palpitations may result in a quality of life (QOL) decline. Also, a high PVC burden can cause development of cardiomyopathy [1–3]. To treat idiopathic PVCs, medical therapy is carried out in some patients for a first-line therapy in terms of safety.

In arrhythmia management, β-blockers have been used widely to treat idiopathic PVCs because of their sympatholytic effect and safety profile compared to other antiarrhythmic drugs. However, several studies showed that β-blockers are not sufficient to suppress idiopathic PVCs [4–6].

In most cases, sympathetic activation could trigger the occurrence of idiopathic PVCs, but a few studies showed

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ventricular arrhythmias (VAs) develop when parasympathetic activation is increased in some patients [7]. He et al. suggested that the heart rate (HR) dependency of idiopathic PVCs revealed different autonomic mechanisms [8]. β-Blockers might have provided insufficient suppression of idiopathic PVCs due to the presence of PVCs not facilitated by sympathetic activation.

Among the β-blockers, bisoprolol has the most selective β1-blocking action. Recently, a novel transdermal β-blocker formulation containing bisoprolol became available clinically in Japan. The bisoprolol patch can be used for patients in a state unsuitable for oral administration, such as patients with dysphagia as well as ordinary patients [9,10].

In this study, we determined the efficacy of the transdermal bisoprolol patch for patients with frequent PVCs without structural heart disease (SHD) regarding the HR dependency and related autonomic mechanism.

Materials and methods

Study population

In this prospective study, a total of 44 consecutive patients (25 men, mean age, 63.6 ± 12.3 years) who visited Toho University Omori Hospital and Mitsui Memorial Hospital between October 2015 and August 2016 were enrolled. We studied patients with frequent PVCs without SHD ranging in age from 20 to 90 years.

The patients needed to have PVC counts ≥3000 beats as measured by 24-hour Holter electrocardiograms (ECGs), regardless of subjective symptoms. A right ventricular outflow tract (RVOT) PVC origin was defined as a QRS morphology with an inferior axis and left bundle-branch block documented by the 12-lead ECG. SHD was excluded by a history, physical examination, and echocardiography. The left ventricular ejection fraction needed to be 50% without any evidence of wall motion abnormalities or left ventricle dilatation. Patients with the following were excluded: kidney disease (serum creatinine ≥3.0 mg/dl), liver dysfunction, marked hypotension (systolic BP <80 mmHg), marked bradycardia (HR <45 beats/minute), or second or third-degree atrioventricular block, asthma, obstructive pulmonary disease, or refusal to participate in this study.

Ethical consideration

The bisoprolol patch has not yet been approved for the treatment of PVCs (it is currently only for hypertension). Therefore, the study was approved by each local ethics committee (number 27-157 and 22), and informed consent was obtained from all patients before participation.

Study procedures

The bisoprolol patch was administered once daily at a dose of 4 mg. The patients applied the bisoprolol patch to their chest, back, or upper arm between the time from waking up in the morning until 12 pm. The systolic blood pressure (sBP), diastolic blood pressure (dBP), and HR were measured, subjective symptoms such as palpitations relating to PVCs were evaluated, and 24-hour Holter ECGs were recorded before and 1 month after the initiation of the bisoprolol patch therapy.

24-hour Holter ECGs

A 2-channel ECG recording was performed in each patient for a 24-hour period during their normal daily activities using a Model SCM-8000 (Fukuda Denshi, Tokyo, Japan). VAs detected by 24-hour Holter ECGs were analyzed for the PVC count, PVC density, bigeminy and trigeminy, and ventricular tachycardia [(VT), more than 3 consecutive PVCs]. The PVC density was defined as the percentage the PVC count was of the total HR. When analyzing the mean 24 hours, the PVC count was performed the entire 24 hours, during day-time (7 am to 8 pm) and night-time (8 pm to 7 am). According to the day-to-day variability of the PVCs [11,12], the response to the bisoprolol patch with a PVC number reduction of 70% was regarded as a "responder."

Evaluation of subjective symptoms

To evaluate the subjective symptom improvement, we checked the symptom logbook recorded by the patient 1 month after the initiation of therapy. The frequency of symptoms was monitored, and when the frequency decreased, the condition was considered an "improvement."

Relationship between the PVC density and HR

PVCs were divided into two types based on their HR dependency, which was evaluated by the relationships between the hourly PVC density and hourly mean HR measured by 24-hour Holter ECGs. The methods were fundamentally the same as those reported by He *et al.* [8]. Then their relationship was analyzed by a Pearson's correlation. If the *p*-value was less than 0.05, this correlation was considered significant.

The relationships between the hourly PVC density and hourly mean HR are shown in Fig. 1. PVCs with their density positively related to the HR were defined as positive HR-dependent PVCs (P-PVCs). When no evident positive relationship between the PVC density and HR was found, those PVCs were defined as non-positive HR-dependent PVCs (NP-PVCs). NP-PVCs consisted of PVCs with their density negatively and not related to the HR. Representative cases classified by the HR dependency of PVCs are described in Fig. 1. Cases (a) (positive HR-dependent PVCs) and (b) (negative HR-dependent PVCs) were regarded as cases with the strongest positive and negative correlations between the PVC density and HR, respectively.

Adverse events

The safety was evaluated based on the incidence of adverse events that were considered treatment-related.

Statistical analysis

Data analyses were performed using EZR on R-commander version 1.24 software (Saitama Medical Center, Jichi Medical University, Saitama, Japan). All continuous variables were tested for normality of the distribution using the Kolmogorov-Smirnov test. Continuous variables with a normal distribution were described as the mean ± standard deviation (SD), continuous variables with a skewed distribution were described as the median (quartile: 25%-75%), and categorical variables were described as frequencies and percentages. The relationship between the hourly PVCs and hourly mean HR density was analyzed by a Pearson's correlation. A paired *t*-test and Wilcoxon signed-rank test were used for the comparison of the baseline data and data after medical therapy when the efficacy of the bisoprolol patch was considered. Comparisons between groups were analyzed using a univariate logistic regression analysis (Fisher's exact test, Unpaired *t*-test, or Mann–Whitney test) and multivariate logistic regression analysis using a Cox proportional hazard model. The predictive power of the resulting model was determined by calculating the area under the receiver operating characteristic (ROC) curve. In all tests, the criterion for statistical significance was a *p*-value <0.05.

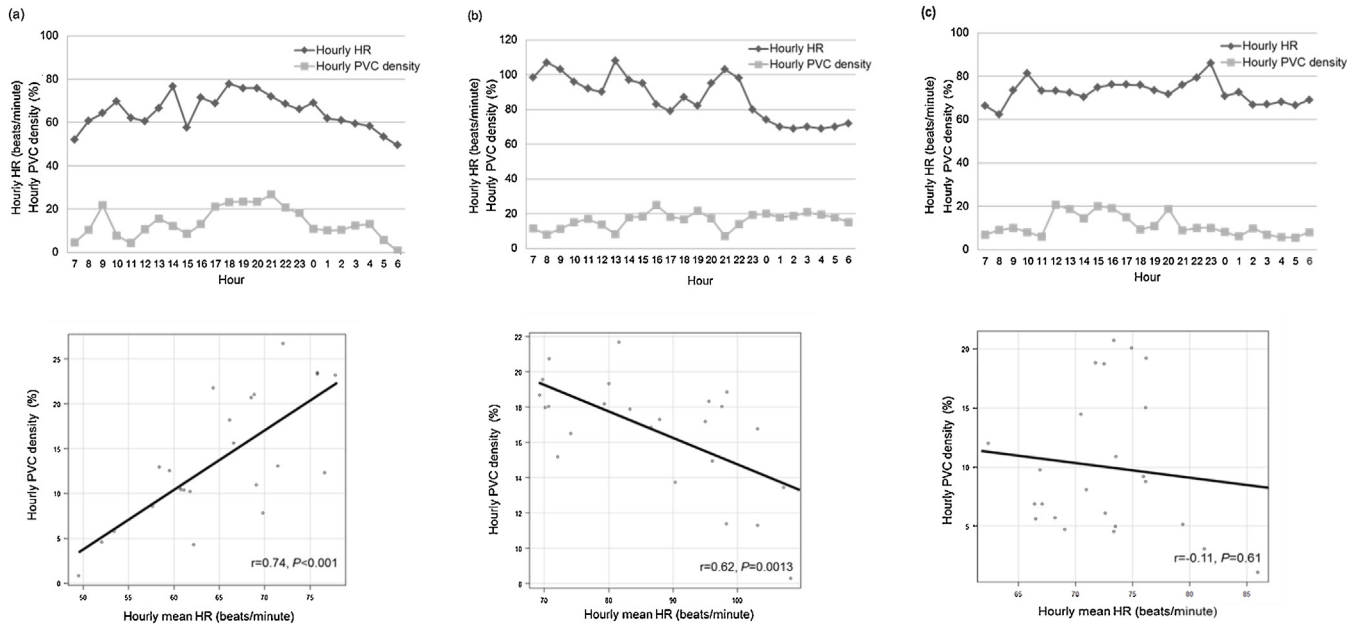

Fig. 1. Relationships between the hourly PVC density and hourly mean HR. The fluctuation pattern of the hourly PVC density and hourly mean HR are shown in the upper panel, and the relationships analyzed by the Pearson's correlation are shown in the lower panel. The correlations between the PVC density and HR were positive (a), negative (b), and not evident (c). HR, heart rate; PVC, premature ventricular contraction.

Results

Patient characteristics

Table 1 shows the baseline characteristics. The 24-hour Holter ECGs exhibited a mean HR of 79.8 ± 9.3 beats/minute, and the total PVC count was 16,493 ± 9725 beats/24 hours, PVC count during the day-time was 9974 ± 5919 beats/13 hours, and PVC count during the night-time was 6374 ± 4362 beats/11 hours.

According to the relationship between the hourly PVC density and hourly mean HR, 44 patients were divided into 24 P-PVC and 20 NP-PVC patients. The NP-PVC group had either PVCs with their density negatively (5 patients) or not (15 patients) related to the HR. There were no differences in the patient characteristics between the two groups. As shown in Fig. 1, the mean HR of cases (a), (b), and (c) were 67.2 beats/minute, 90.0 beats/minute, and 74.1 beats/minute, respectively, and the PVC count in each case was 13,437 beats/24 hours, 20,596 beats/24 hours, and 10,442 beats/24 hours, respectively.

Efficacy of bisoprolol patch

All patients

The efficacy of the bisoprolol patch in all patients is shown inthe upper panel of Table 2. The total PVC count decreased significantly after the bisoprolol patch therapy ($p = 0.0015$). Considering the bisoprolol patch effect on the PVCs during the day-time and night-time, the results revealed that the bisoprolol patch decreased the PVCs during both the day-time ($p = 0.0064$) and night-time ($p = 0.0023$). The responder rate for treatment was 34.1% (15/44 patients), and the improvement rate of subjective symptoms was 68.2% (15/22 patients).

Comparison between the P-PVC and NP-PVC groups

The bisoprolol patch significantly decreased the mean HR during each time period in the P-PVC and NP-PVC groups.

Table 1
Baseline characteristics.

All patients ($n = 44$)	
Male, number (%)	25 (56.8%)
Age (years)	63.6 ± 12.3
BMI (kg/m^2)	23.1 ± 3.4
Hypertension, number (%)	21 (47.7%)
Diabetes melitus, number (%)	10 (22.7%)
Hyperlipidemia, number (%)	15 (34.1%)
Smoking, number (%)	17 (38.6%)
Alchohole, number (%)	12 (27.9%)
Systolic blood pressure (mmHg)	132.9 ± 16.3
Diastolic blood pressure (mmHg)	76.2 ± 13.4
HR (beats/minute)	79.2 ± 13.7
Laboratory data	
Creatinine (mg/dl)	0.82 ± 0.43
eGFR (ml/min/1.73 m^2)	73.4 ± 19.5
BNP (pg/ml)	29.9 (19.2–64.6)
Echocardiography	
LVEF (%)	67.4 ± 8.1
LVDd (mm)	50.2 ± 4.9
Symptom relating to PVCs, number (%)	22 (50%)
P-PVC, number (%)	24 (52.3%)
RVOT origin, number (%)	18 (40.9%)
24-hour Holter ECGs	
Mean HR (beats/minute)	79.8 ± 9.3
Mean day-time HR (beats/minute)	82.1 ± 9.3
Mean night-time HR (beats/minute)	73.4 ± 10.2
Total PVC count (per 24 hours)	16,493 ± 9725
PVC burden (%)	14.7 ± 8.3
Day-time PVC count (per 13 hours)	9974 ± 5919
Night-time PVC count (per 11 hours)	6374 ± 4362
Bigeminy/trigeminy count (per 24 hours)	3635 (1275–10,087)
VT count (per 24 hours)	0 (0–10.0)

BMI indicates body mass index; HR, heart rate; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptid; LVEF, left ventricular ejection fraction; LVDd, left ventricular end-diastolic diameter; PVCs, premature ventricular contractions; P-PVC, positive HR-dependent PVC; ECGs, electrocardiograms; RVOT, right ventricular outflow tract and VT, ventricular tachycardia. Data are expressed as the mean ± SD, median (25%-75%), or number (%).

Table 2
Efficacy of the bisoprolol patch.

	Pre	Post	*P* value
All patients (n = 44)			
Systolic blood pressure (mmHg)	132.9 ± 16.2	126.6 ± 15.2	0.0060*
Diastolic blood pressure (mmHg)	76.2 ± 13.4	72.6 ± 9.6	0.018*
HR (beats/minute)	79.2 ± 13.7	67.9 ± 13.9	<0.001*
24-hour Holter ECGs			
Mean HR (beats/minute)	79.8 ± 9.3	69.8 ± 9.1	<0.001*
Mean day-time HR (beats/minute)	82.1 ± 9.3	71.0 ± 9.3	<0.001*
Mean night-time HR (beats/minute)	73.4 ± 10.2	63.7 ± 9.5	<0.001*
Total PVC count (per 24 hours)	16,493 ± 9725	10,430 ± 10,732	0.0015*
PVC density (%)	14.7 ± 8.3	10.5 ± 10.6	0.011*
Day-time PVC count (per 13 hours)	9974 ± 5919	6419 ± 6864	0.0064*
Night-time PVC count (per 11 hours)	6374 ± 4362	3911 ± 4203	0.0023*
Bigeminy/trigeminy count (per 24 hours)	3635 (1275–10,087)	956.0 (31.0–5944)	0.0051**
VT count (per 24 hours)	0 (0–10.0)	0 (0–0)	0.042**
P-PVC (n = 24)			
Systolic blood pressure (mmHg)	136.0 ± 18.1	129.8 ± 17.0	0.076*
Diastolic blood pressure (mmHg)	75.3 ± 14.7	73.1 ± 11.1	0.35*
HR (beats/minute)	77.2 ± 14.8	66.2 ± 15.1	<0.001*
24-hour Holter ECGs			
Mean HR (beats/minute)	80.6 ± 10.8	68.2 ± 10.3	<0.001*
Mean day-time HR (beats/minute)	82.7± 9.7	69.8 ± 10.7	<0.001*
Mean night-time HR (beats/minute)	73.1 ± 11.5	61.6 ± 10.7	<0.001*
Total PVC count (per 24 hours)	16,563 ± 10,056	7892 ± 8817	<0.001*
PVC density (%)	14.8 ± 8.6	8.2 ± 8.7	<0.001*
Day-time PVC count (per 13 hours)	10,919 ± 6187	4822 ± 5399	<0.001*
Night-time PVC count (per 11 hours)	5609 ± 4392	2820 ± 3595	0.0071*
Bigeminy/trigeminy count (per 24 hours)	2242 (588.3–10,450)	273.0 (0–3182)	0.014**
VT count (per 24 hours)	1.0 (0–12.8)	0 (0–4.5)	0.11**
NP-PVC (n = 20)			
Systolic blood pressure (mmHg)	129.4 ± 13.4	122.5 ± 11.9	0.031*
Diastolic blood pressure (mmHg)	77.2 ± 12.0	71.9 ± 7.4	0.0015*
HR (beats/minute)	81.5 ± 12.3	69.8 ± 12.6	0.0078*
24-hour Holter ECGs			
Mean HR (beats/minute)	78.7 ± 7.4	71.8 ± 7.3	<0.001*
Mean day-time HR (beats/minute)	81.3 ± 8.9	72.4 ± 7.5	<0.001*
Mean night-time HR (beats/minute)	72.1 ± 8.5	66.2 ± 7.7	<0.001*
Total PVC count (per 24 hours)	16,409 ± 9571	13,476 ± 12,191	0.34*
PVC density (%)	14.8 ± 8.2	13.2 ± 12.4	0.62*
Day-time PVC count (per 13 hours)	8839 ± 5521	8255 ± 7983	0.76*
Night-time PVC count (per 11 hours)	7290 ± 4252	5219 ± 4586	0.12*
Bigeminy/trigeminy count (per 24 hours)	5112 (2316–9370)	3255 (75.0–7128)	0.13**
VT count (per 24 hours)	0 (0–4.0)	0 (0–0)	0.27**

HR, heart rate; ECGs, electrocardiograms; PVCs, premature ventricular contractions and VT, ventricular tachycardia. Data are expressed as the mean ± SD, median (25%-75%). P values were determined by a *paired *t*-test or **Wilcoxon signed-rank test.

However, a significant reduction was observed with respect to the change in the mean night-time HR from baseline in the P-PVC group compared with the NP-PVC group ($p = 0.049$) (Table 2, mid and lower panels).

We found that 12 patients (50.0%) in the P-PVC group were responders, compared to 3 (15.0%) in the NP-PVC group ($p = 0.025$). A subjective symptom improvement was observed in 6 patients (60.0%) in the P-PVC group as compared to 9 (75.0%) in the NP-PVC group ($p = 0.65$). The bisoprolol patch reduced the total PVC count significantly ($p < 0.001$), PVC count during the day-time ($p < 0.001$), and PVC count during the night-time ($p = 0.0071$) in the P-PVC group (Table 2, mid-panel).

On the other hand, the total PVC count ($p = 0.34$), PVC count during the day-time ($p = 0.76$), and PVC count during the night-time ($p = 0.12$) did not change significantly in the NP-PVC group (Table 2, lower panel). The changes within a 24-hour period in the P-PVC group are shown in Fig. 2. Significant reductions were observed during each time period for the changes in the PVC count from baseline.

Responders in the P-PVC patients

We divided the 24 P-PVC patients into two groups: the responder group (R-group) and non-responder group (NR-group),

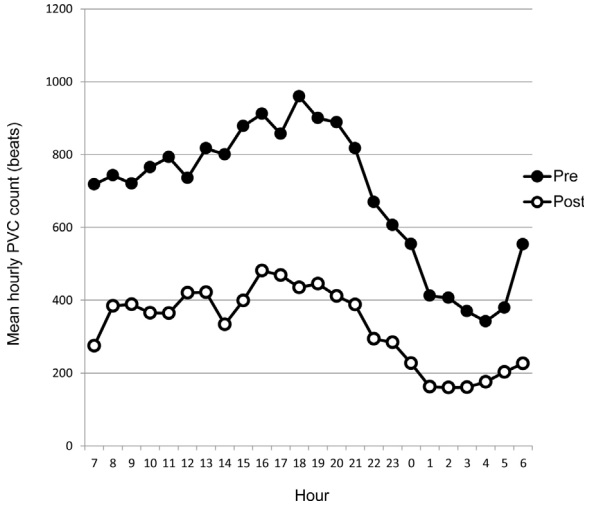

Fig. 2. Mean hourly PVC count at baseline (solid circle) and at one month (open circle) with the bisoprolol patch in the P-PVC patients. Significant reductions in the changes in the PVC count from baseline were observed during each time period. PVC, premature ventricular contraction; P-PVC, positive heart rate-dependent premature ventricular contraction.

Table 3
Comparison of patient characteristics between responder and non-responder in the P-PVC group.

	Responder ($n = 12$)	Non-responder ($n = 12$)	P value
Male, number (%)	7 (58.3%)	4 (33.3%)	0.41**
Age (years)	66.9 ± 13.0	59.9 ± 7.8	0.12*
BMI (kg/m^2)	24.2 ± 4.0	22.7 ± 4.0	0.40*
Systolic blood pressure (mmHg)	136.3 ± 20.1	135.8 ± 16.7	0.96*
Diastolic blood pressure (mmHg)	76.3 ± 17.0	74.2 ± 12.4	0.74*
HR (beats/minute)	82.4 ± 15.9	72.1 ± 12.2	0.11*
Hypertension, number (%)	7 (58.3%)	5 (41.7%)	0.68**
Diabetes mellitus, number (%)	5 (41.7%)	2 (16.7%)	0.37**
Hyperlipidemia, number (%)	5 (41.7%)	6 (50.0%)	1.0**
Smoking, number (%)	3 (25.0%)	2 (16.7%)	1.0**
Alchohole, number (%)	3 (25.0%)	2 (16.7%)	1.0**
Laboratory data			
Creatinine (mg/dl)	0.82 ± 0.14	0.74 ± 0.19	0.31*
eGFR (ml/min/1.73m^2)	65.4 ± 15.9	74.5 ± 11.9	0.14*
BNP (pg/ml)	27.5 (15.3–71.1)	30.7 (24.3–60.1)	0.72***
Echocardiography			
LVEF (%)	69.1 ± 8.0	63.3 ± 6.4	0.07*
LVDd (mm)	48.2 ± 5.2	51.3 ± 5.2	0.17*
Symptom relating to PVCs, number (%)	4 (33.3%)	6 (50.0%)	0.68**
RVOT origin, number (%)	2 (16.7%)	5 (41.7%)	0.37**
24-hour Holter ECGs			
Mean HR (beats/minute)	85.2 ± 10.8	76.1 ± 8.9	0.036*
Mean day-time HR (beats/minute)	85.6 ± 10.0	79.8 ± 8.9	0.14*
Mean night-time HR (beats/minute)	78.8 ± 10.2	67.4 ± 10.3	0.013*
Total PVC count (per 24 hours)	15,105 ± 10,897	18,022 ± 9835	0.49*
Day-time PVC count (per 13 hours)	9486 ± 6408	121,352 ± 5873	0.27*
Night-time PVC count (per 11 hours)	5576 ± 4735	5643 ± 4234	0.97*

BMI indicates body mass index; HR, heart rate; BNP, brain natriuretic peptid; eGFR, estimated glomerular filtration rate; PVCs, premature ventricular contractions; RVOT, right ventricular outflow tract and ECGs, electrocardiograms. Data are expressed as the mean ± SD, median (25%-75%) and number (%). P values were determined by a *unpaired t-test, **Fisher's exact test, or ***Mann–Whitney test.

and the patient characteristics were compared between the two groups. When comparing the two groups, the mean HR ($p = 0.036$), and mean night-time HR ($p = 0.013$) as measured by 24-hour Holter ECGs was significantly faster in the R-group than NR-group (Table 3). Among the patient characteristics, only a mean HR ≥80 beats/minute measured by 24-hour Holter ECGs was a significant factor for detecting responders of the bisoprolol patch therapy in the P-PVC patients by a multivariate logistic regression analysis ($p = 0.014$).

Since the average mean HR in the P-PVC group was 80.6 ± 10.8 beats/minute, we decided the mean HR cut-off point should be 80.0 beats/minute. The ROC curve comparing the mean HR and responders showed that the mean HR cut-off value was 80.0 beats/minute (sensitivity, 83.3%; specificity, 66.7%; AUC, 0.76; 95% confidence interval, 0.55–0.96) (Fig. 3).

We divided the 24 P-PVC patients into two groups: a mean HR ≥80 beats/minute group (Fast-HR) and mean HR <80 beats/minute group (Slow-HR). The bisoprolol patch significantly reduced the total PVC count (from 18,899 ± 10,947 to 5843 ± 7750 beats/24 hours, $p < 0.001$), PVC count during the day-time (from 12,042 ± 6838 to 4027 ± 5057 beats/13 hours, $p < 0.001$), and PVC count during the night-time (from 6798 ± 4625 to 1921 ± 2771 beats/11 hours, $p = 0.0012$) in the Fast-HR group. However, the total PVC count (from 13,294 ± 8062 to 10,760 ± 9812 beats/24 hours, $p = 0.26$), PVC count during the day-time (from 9347 ± 5058 to 6062 ± 5983 beats/13 hours, $p = 0.16$), and PVC count during the night-time (from 3947 ± 3624 to 4077 ± 4350 beats/11 hours, $p = 0.90$) did not change significantly in the Slow-HR group.

Fig. 4 shows the comparison of the percent improvement in the total PVC count, mean day-time PVC count, and mean night-time PVC count between the Fast-HR and Slow-HR groups. All of them differed significantly. At a 70% PVC reduction level, the bisoprolol patch was effective in 10 out of 14 patients (71.9%) in the Fast-HR group, but only in 2 out of 10 patients (20.0%) in the Slow-HR group ($p = 0.036$).

Adverse events

Adverse events that were considered treatment-related were observed in 4 patients (1 patient, application site pruritus; 2 patients, application site dermatitis; 1 patient, bradycardia with light headedness).

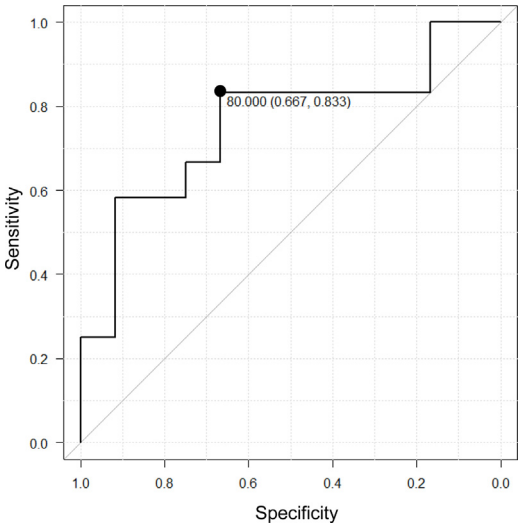

Fig. 3. Receiver operating characteristic (ROC) curve between the mean heart rate (HR) over 24 hours and responders in the positive heart rate-dependent premature ventricular contraction (P-PVC) patients. The ROC curve between the mean HR over 24 hours and P-PVC group responders reveals that the mean HR cut-off value was 80.0 beats/minute (area under the curve 0.76; 95% confidence interval: 0.55–0.96).

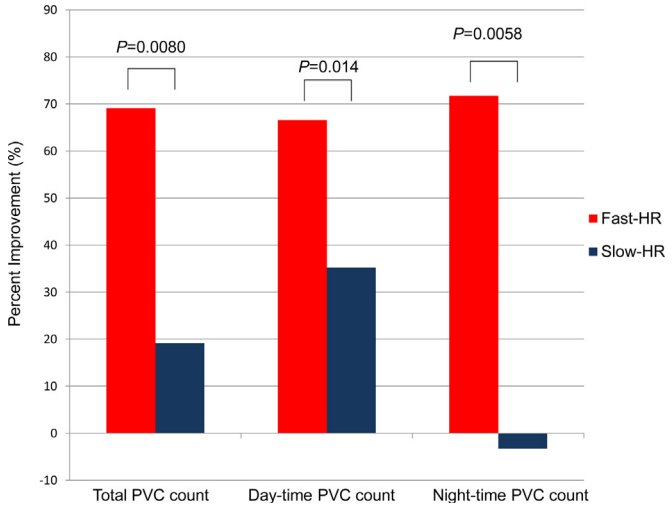

Fig. 4. Comparison of the percent improvement in the total PVC count, day-time PVC count, and night-time PVC count between the Fast-HR and Slow-HR groups. The percent improvement in the total PVC count, day-time PVC count, and night-time PVC count differed significantly between the two groups. HR, heart rate; PVC, premature ventricular contraction.

Discussion

Main findings

The main findings of the present study were as follows. First, the bisoprolol patch decreased the PVC count and improved the subjective symptoms. Second, it was effective for reducing the PVCs in the P-PVC patients, particularly in those with faster mean HRs. Third, the bisoprolol patch demonstrated a stable PVC-reduction effect during a 24-hour period in the P-PVC patients.

HR dependency of PVCs

The autonomic nervous system has a close relationship to the genesis of PVCs. Sympathetic activation can induce increased intracellular cyclic AMP-mediated delayed after depolarizations and enhance the development of triggered activity, which might explain its effect on producing idiopathic PVCs [13]. However, early after depolarizations (EADs) in normal cardiac tissue are also considered as a form of triggered activity. EADs are implicated as the primary mechanism of promoting VAs. Classically, EADs emerge during bradycardia. Weiss et al. also showed that EADs occur at slower HRs, and are completely suppressed at faster HRs [14]. Thus, it is possible that EAD-mediated PVCs could be facilitated by an increased parasympathetic activation accompanied by a slow HR. However, the detailed mechanism by which the autonomic nervous system influences idiopathic PVCs remains unknown.

He et al. demonstrated that there are different relationships between the PVC density and HR in idiopathic PVCs, and that PVCs with their density positively related to the HR might be facilitated by sympathetic activation, PVCs with their density negatively related to the HR might be facilitated by the parasympathetic activation, and when no evident relationship between the PVC density and HR exists, those PVCs might have an independent autonomic mechanism [8]. We analyzed the relationship between the hourly PVC density and hourly mean HR to estimate the HR dependency of PVCs following this method, and investigated the efficacy of the bisoprolol patch on decreasing the frequency of PVCs in patients without SHD by considering the HR dependency and related autonomic mechanism.

Representative cases classified by HR dependency of PVCs

As described in Fig. 1, the mean HR among the three representative cases classified by the HR dependency of PVCs differed. Case (b) (negative HR-dependent PVCs) had a greater PVC count compared with the other cases. The total HR count contains the PVC count, so case (b) might have had an increased mean HR compared with the other cases. In addition, during the 24-hour Holter ECG recordings the patients were instructed to go about their normal daily work activities in this study. So it was possible that the activity intensities, one of the factors that influences the HR among cases, differed greatly. There were no significant differences in the mean HR and PVC count among the three types of PVC groups classified by the HR dependency. So, we consider the differences in the mean HR among the three cases as being within the limits of the differences among individuals.

Treatment of PVCs in patients without SHD

Frequent idiopathic PVCs are known to be associated with a reversible form of cardiomyopathy [1–3]. Baman et al. showed that the presence of a PVC density of more than 24% allows the suppression of PVCs by medical therapy or catheter ablation (CA) in order to avoid the development of cardiomyopathy even if patients have no subjective symptoms [15]. Symptoms related to PVCs might induce anxiety and the QOL would decline in some patients and this should also be factored into the treatment decisions. CA of frequent PVCs has been demonstrated to be effective in PVC suppression [16,17], even when patients have SHD [18], but a better understanding of the procedural risk is important for performing CA in patients with PVCs. In a multicenter study of 1185 patients with idiopathic PVCs undergoing CA, the major complication rate was 2.4% [19]. Mujović et al. described idiopathic VA ablation as one of the risk factors for major complications of CA such as cardiac tamponade [20]. Some patients who have success with medical therapy can avoid the risk of CA. Patients failing or intolerant to medical therapy can be referred for CA [21,22].

β-Blockers are recommended as the first choice of antiarrhythmic drug for PVC reduction because of their sympatholytic effect and safety profile. Other antiarrhythmic agents might occasionally be used, but the significant risk of side effects needs to be considered [6].

There is little evidence about the dose-response relationship of β-blockers in patients with PVCs. Sugimoto *et al.* showed that the antiarrhythmic effects of oral bisoprolol can be assessed starting at a mid-range dose in order to determine its optimal effective dose [23]. In clinical practice, high-dose β-blockers occasionally induces side effects such as light headedness, bradycardia, and hypotension. So a mid-range β-blocker dose is often administered to treat PVCs. Therefore, we assessed to what extent the bisoprolol patch at 4 mg was effective in treating idiopathic frequent PVCs.

Efficacy of the bisoprolol patch on frequent PVCs in patients without SHD

The bisoprolol patch significantly decreased the PVC count during the 24-hour period in the P-PVC patients, but induced no significant reduction in the NP-PVC patients. This result seems to be reasonable because the bisoprolol patch reduces the sympathetic active tone. The difference in the degree of night-time PVC suppression between the P-PVC and NP-PVC groups may have contributed to a significant mean night-time HR reduction in the P-PVC group compared to the NP-PVC group. There was no significant difference observed in the change in the mean day-time HR ($p = 0.28$) from baseline, however, a trend was observed in that the degree of the change in the mean day-time HR was larger in the

P-PVC group than NP-PVC group. The insufficient suppression of night-time PVCs in the NP-PVC group may have resulted in a relatively high mean night-time HR after the bisoprolol patch therapy.

β-Blockers, including the bisoprolol patch, might rather increase negative HR-dependent PVCs. He et al. demonstrated that the fluctuation pattern of the hourly PVC density over 24 hours was similar to that of the HR variability (HRV) indices [high frequency component expressed as a normalized unit (HFnu) used as the parasympathetic activity index], and had an inverse relationship to that of the HRV indices [low-frequency component to high-frequency component ratio (LF/HF) used as the sympathetic activity index] in patients with negative HR-dependent PVCs [8]. In this study, the bisoprolol patch did not change the PVC count significantly ($p = 0.080$) in patients with negative HR-dependent PVCs. However, those patients were too few (5 patients) to assess its validity. For treating negative HR-dependent PVCs, antiarrhythmic agents with parasympathetic blocking effects might be effective. This suggests that when considering the HR dependency of PVCs it is useful to treat idiopathic PVCs with antiarrhythmic agents. Similarly He et al. showed that β-blockers (oral bisoprolol or metoprolol) decreased the PVC density in patients with positive HR-dependent PVCs [8]. However, the patients prescribed with β-blockers were too few to allow for reliable results, and they did not primarily focus on the β-blocker effect.

There was a higher responder rate in the P-PVC patients than NP-PVC patients, and this difference reached a statistically significant level ($p = 0.025$). Furthermore, we could show that the rate of responders and percent improvement in the total PVC count in the P-PVC patients with mean HRs ≧80 beats/minute were achieved in 71.9% and 69.1%, respectively.

According to He et al., a similar fluctuation pattern of the circadian rhythm over 24 hours between the hourly PVC density and sympathetic indices (LF/HF), and an inverse fluctuation pattern between the hourly PVC density and parasympathetic indices (HFnu), were found in patients with positive HR-dependent PVCs [8]. Therefore, an increase in the sympathetic activity meant a decrease in the parasympathetic activity when the P-PVCs were generated. However, the detailed information on the effects of β-blockers considering the cardiac autonomic balance in patients with positive HR-dependent PVCs was unknown. In the present study, the mean HR and percent improvement in the total PVC count over 24 hours was found to have a positive relationship in the P-PVC patients ($r = 0.45$, $p = 0.029$) (Fig. 5). Consequently, an increasing HR might better reflect increasing sympathetic activity and decreasing parasympathetic activity in the P-PVC patients. The HRV analysis is widely used to assess cardiac autonomic activity [24], however, in the present study, an HRV analysis was not performed. To confirm the validity of these results, it might be necessary to clarify the relationship among the mean HR, percent improvement in the PVC count, and HRV indices in patients with P-PVCs by a correlation analysis. Moreover, an estimate of the balance between the sympathetic activity and parasympathetic activity when the P-PVCs occurred may be useful to more accurately predict the effects of the bisoprolol patch.

Approximately 70% of patients experienced an improvement in their subjective symptoms. However, the improvement rate did not differ between the P-PVC and NP-PVC groups. The improvement rate of subjective symptoms was almost at the same level as the responder rate in the P-PVC group, whereas it reached 75.0% in spite of a low responder rate (15.0%) in the NP-PVC group. A randomized, placebo-controlled trial demonstrated that a placebo improved the subjective symptoms to the same extent as atenolol, but had no effect on the PVC count in patients with symptomatic VAs without SHD [4]. Considering this result, the improvement in the subjective symptoms may not be related to the suppression of PVCs.

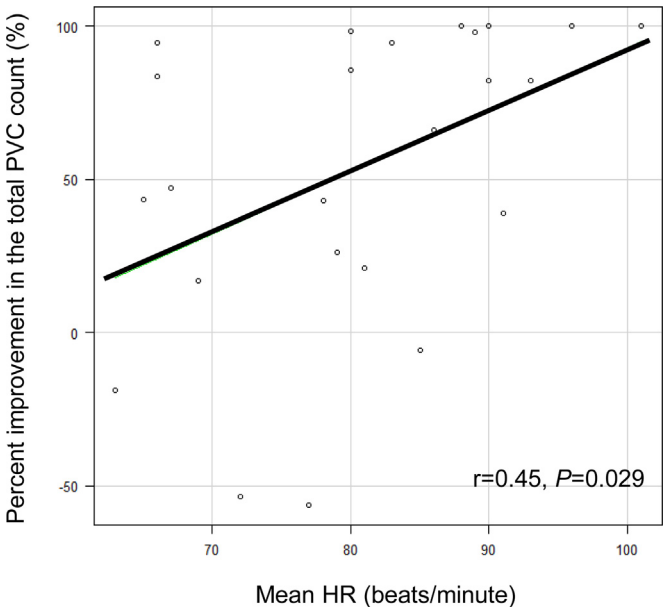

Fig. 5. Relationships between the mean HR and percent improvement in the total PVC count over 24-hours in the P-PVC patients. The mean HR and percent improvement in the total PVC count over 24-hours was found to have a positive relationship in the P-PVC patients ($r = 0.45$, 95% CI: 0.051–0.72, $p = 0.029$). HR, heart rate; PVC, premature ventricular contraction; P-PVC, positive heart rate-dependent premature ventricular contraction.

Characteristics of the bisoprolol patch

The bisoprolol patch was designed to maintain a sustained plasma concentration of bisoprolol by lower peak plasma bisoprolol concentrations and higher through concentrations than oral bisoprolol, therefore demonstrating the same area under the curve for plasma concentrations as that of oral bisoprolol [9]. The half-life of the bisoprolol patch was about twice as long as that of oral bisoprolol, and was approximately 18 hours. The bisoprolol patch is considered to be clinically suitable for treating arrhythmias during 24-hour periods because of a sustained stable plasma concentration.

In the present study, the bisoprolol patch decreased the PVCs during both the day-time and night-time. Moreover, significant reductions were observed during each time period for changes in the PVC count from baseline in those with P-PVCs during a 24-hour period. This result suggested that P-PVCs might be facilitated by sympathetic activation during the 24-hour period, and the bisoprolol patch could reduce P-PVCs all day because of its long-acting β1-antagonist effect. Matsuoka *et al.* demonstrated that both the bisoprolol patch and oral bisoprolol demonstrated stable HR-reducing effects during the 24-hour period. However, the morning (each 3 hours before and after waking up) HR decreased significantly in the bisoprolol patch group compared to the oral bisoprolol group [9]. This finding may have indicated that the bisoprolol patch was more useful for treating P-PVCs during the 24-hour period than oral bisoprolol. In the future, a detailed study should be conducted on the differences in the effects between the bisoprolol patch and oral bisoprolol for the 24-hour profiles of the P-PVCs.

Adverse events

Although adverse events at the application site were observed in 3 patients, all were relatively mild. Bradycardia (HR <45 beats/minute) was observed in 1 patient with light headedness. Bradycardia is an adverse event frequently associated with

β-blockers. A careful follow-up is necessary with the clinical use of the bisoprolol patch even if its dose is mid-range.

Limitations

This study had some potential limitations. First, we did not perform an HRV analysis to estimate the cardiac autonomic activity. We need further studies using the HRV analysis to clarify the effects of the bisoprolol patch for treating PVCs in more detail. Second,this study did not compare the results with those of patients with a placebo or other β-blockers as a control. Third, this study had a small sample size, which might have resulted in a statistical bias. Further research is necessary with more patients. Nevertheless, the results were found to be clear and statistically significant.

Conclusions

The transdermal bisoprolol patch at a daily dose of 4 mg was useful for treating frequent PVCs in patients without SHD. It seemed to be more effective for reducing PVCs in the P-PVC patients, particularly in those with faster mean HRs. Furthermore, the bisoprolol patch resulted in a stable PVC-reduction effect during the 24-hour period when treating P-PVCs.

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