Quantitative assessment of cibenzoline administration for vagally mediated paroxysmal atrial fibrillation using frequency-domain heart rate variability analysis

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Antiarrhythmic drug;
Anticholinergic action;
Muscarinic receptor;
Cibenzoline

Summary
Background: Cibenzoline (CBZ), a class I antiarrhythmic drug, has been widely used to maintain sinus rhythm in patients with paroxysmal atrial fibrillation (P-AF). This agent has an anticholinergic action and will become the drug of first choice for vagally mediated P-AF. We assessed its efficacy quantitatively by analyzing the frequency-domain heart rate variability (FD-HRV) of the Holter electrocardiogram (ECG) in patients with vagal P-AF.
Methods: We enrolled 65 consecutive patients with vagal P-AF, but 31 patients were excluded because of the occurrence of significant arrhythmias during the 24-h Holter recordings. Accordingly, CBZ was administered to the remaining 34 patients. After administration, a Holter ECG recording was made again. High frequency (HF) components, i.e., vagal tone index, on the FD-HRV analysis from 00:00 h to 06:00 h were used for assessment. In 14 patients, the treatment was changed to disopyramide (DSP) and the same analyses were performed.
Results: In two patients, the FD-HRV analysis was not utilized after administration. Finally, 32 patients were available for evaluation. CBZ was considered effective for vagal P-AF in 24 patients (75%). After administration, the HF component levels decreased (1589 ± 795 ms² vs. 850 ± 524 ms², p < 0.0001). Comparison of the
pre-administration HF component levels between the CBZ-responsive group and the CBZ-non-responsive group showed higher levels in the CBZ-responsive group (1766 ± 758 ms² vs. 1058 ± 690 ms², p = 0.026). Although no significant difference in the reduction of the HF component levels was found between CBZ and DSP, DSP had anticholinergic side effects in two patients (14%).

Conclusions: In vagal P-AF patients, larger HF components on the FD-HRV analysis could be a hallmark of the antiarrhythmic action of CBZ. The reduction in the HF component levels after drug administration is useful for a quantitative assessment of anticholinergic action.

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Introduction

Paroxysmal atrial fibrillation (P-AF) is one of the most common arrhythmias seen in daily practice. In general, P-AF is not an arrhythmia with a poor prognosis, particularly in patients with normal cardiac function, but it is an arrhythmia that may lower quality of life by causing certain symptoms such as palpitations, or occasionally lead to serious complications such as cerebral infarction. For the treatment of P-AF, either pharmacological treatment or catheter ablation is used, with the former treatment being carried out in most patients.

P-AFs are classified into three types depending on the pattern of onset: (1) vagal type; (2) sympathetic type and (3) mixed type [1—3]. Among these types, with respect to vagal P-AF, as stated in the guidelines in America, Europe, and Japan [1,2] class I antiarrhythmic drugs such as cibenzoline (CBZ) or disopyramide (DSP) should be the pharmacological treatment of first choice to inhibit P-AF.

One method used for quantitative assessment of vagal nerve activity is the frequency-domain (FD) method [4]. This method, which measures heart rate variability (HRV) by means of a 24-h Holter electrocardiogram (ECG), is used in clinical practice [5,6]. High frequency (HF) components obtained from the FD-HRV analyses are known to accurately reflect vagal nerve activity [4—6].

The purpose of the present study was to evaluate quantitatively the effect of CBZ on vagal P-AF using FD-HRV analyses with Holter ECG. In some patients in whom the treatment could be changed from CBZ to DSP, the anticholinergic actions of both drugs were compared.

Methods

Patient enrollment

Sixty-five consecutive patients with vagal P-AF were enrolled at Kyorin University Hospital from January 2005 to August 2008. Patients with P-AF of sympathetic or mixed type were excluded from the study. These definitions of P-AF were made by a symptom logbook recorded by the patient [7]. They initially sought medical consultation for subjective symptoms such as palpitations. These patients had no underlying heart diseases, endocrine disorders including thyroidal dysfunction, and/or other pathological conditions such as anemia, indicating lone AF. Vagal P-AF was defined as AF that initiated at nighttime, at rest, and/or after taking meals, and which terminated spontaneously within 24 h after onset. All patients desired drug treatment and had not received antiarrhythmic drugs for at least 1 month or more prior to their enrollment. Patients with implanted pacemakers or a medical history of invasive treatments such as catheter ablation were not included. Among all the patients, a P-AF episode was recorded two or more times within 1 month prior to their enrollment.

When the 24-h Holter ECG was performed without any antiarrhythmic drug treatment in all 65 patients, P-AFs or atrial premature contractions (APCs) >10 beats/h were found sporadically during recording in 31 patients. Since HRV analysis is used to measure the interval between normal beats, when such arrhythmias occur during recording, an assessment using FD-HRV analysis becomes impossible. Thus, those 31 patients were excluded from the study. As a result, the remaining 34 patients (mean age 58 ± 16 years, 28 males and 6 females) were evaluated in this study (Table 1). The average heart rate at rest was 72 ± 17 beats/min. On echocardiography, the left atrial diameter was found to be 36 ± 2 mm and the left ventricular ejection fraction was 63 ± 5%. These levels were all within normal ranges. Concomitant drugs were warfarin anticoagulation in two patients (6%), aspirin in five (15%), β-blockers for inhibition of heart rate in two (6%), and verapamil in one (6%).

The protocol was approved by the ethical committee of Kyorin University Hospital. Informed consent was obtained from all patients prior to enrollment into the study.
**Table 1** Clinical background of the study patients.

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<table>
<thead>
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</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>34</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58 ± 16</td>
</tr>
<tr>
<td>Men</td>
<td>28 (82%)</td>
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<tr>
<td>Underlying heart diseases</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Lone atrial fibrillation</td>
<td>34 (100%)</td>
</tr>
<tr>
<td>Heart rate at rest (beats/min)</td>
<td>72 ± 17</td>
</tr>
<tr>
<td>Left atrial diameter (mm)</td>
<td>36 ± 2</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>63 ± 5</td>
</tr>
<tr>
<td>Thromboprophylaxis drugs</td>
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<tr>
<td>Warfarin</td>
<td>2 (6%)</td>
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<tr>
<td>Aspirin</td>
<td>5 (15%)</td>
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<tr>
<td>Rate control drugs</td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Verapamil</td>
<td>1 (1%)</td>
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</tbody>
</table>

FD-HRV analyses with 24-h Holter ECG

Before drug administration, a 24-h Holter ECG was performed in all patients. The ECG wave patterns obtained were analyzed for HRV by an ECG analyzer (SCM-6000, Fukuda Densi Co., Ltd., Tokyo, Japan). Although there are several methods used for HRV analysis including the time-domain and FD methods, the FD method, which is capable of reflecting short-term changes in autonomic nervous system activity [4], was used in this study. In the FD method, although the HF component (0.15—0.40 Hz), low frequency (LF) component (0.04—0.15 Hz), and LF/HF ratio are measured automatically, in this study, only the HF component levels, which are a reliable way of assessing vagal nerve activity, were used. To facilitate the quantitative assessment of vagal nerve activity, the mean HF component levels from 00:00 h (midnight) to 06:00 h (early morning) [8], when vagal nerve activity is considered to be higher than at other times, were used in this study.

The same analyses were performed after drug administration. When arrhythmias such as P-AF or APC occurred during the recording of the 24-h Holter ECG after drug administration, the Holter ECG was repeated as FD-HRV analysis of such recordings was considered inappropriate.

Administration of antiarrhythmic drugs

After the recording of the 24-h Holter ECG, CBZ was administered orally at a dose of 300 mg/day. However, for patients with kidney dysfunction (glomerular filtration rate <40 mL/min/1.73 m²) and elderly patients (>80 years), the dose was 200 mg/day. After a 4-week administration period, as CBZ was being administered, the Holter ECG was performed again.

In 14 of the 34 patients, after the effect of CBZ was evaluated and 1 week had elapsed from drug discontinuation, the treatment was changed to DSP, a class I antiarrhythmic drug with similar anticholinergic action to CBZ. After 4 weeks of oral administration of DSP, a 24-h Holter ECG was recorded. The dose of DSP was 300 mg/day, and 200 mg/day for patients with renal dysfunction and for elderly patients. The anticholinergic actions were compared between both drugs.

Evaluation of drug efficacy

Because all the subjects in this study were P-AF patients, drug efficacy was evaluated based on the presence/absence or disappearance of symptoms. To confirm the disappearance of symptoms, patients recorded their symptoms in a notebook. The patients were instructed to record whether symptoms were present or absent after drug administration, and if they were present, to record daily the nature, frequency, and duration of symptoms. Then, whether the symptoms induced by P-AF disappeared was evaluated.

In addition, the absence of P-AF was confirmed by 24-h Holter ECG after drug administration. Even in patients in whom symptoms had apparently disappeared, when P-AF appeared, even temporarily, as detected by the 24-h Holter ECG, the drug was evaluated as being not effective.

Statistical tests

The real numbers in the text are expressed as the mean level ± standard deviation. Comparison of the HF component levels between both drugs assessed in the same patient before and after drug administration was performed by Student’s paired t-test. Comparison of the HF component levels between the groups in which the drug was effective and not effective was performed by Student’s unpaired t-test. A level of p < 0.05 was considered to be significant in both tests.

Results

Drug efficacy

The dose of CBZ was 300 mg/day in 31 patients (91%) and 200 mg/day in the remaining 3 patients. In 2 of the 34 patients who received CBZ, because APCs appeared sporadically during the two record-
The effects of cibenzoline (CBZ) and disopyramide (DSP) on vagally mediated paroxysmal atrial fibrillation (P-AF).

ings of the Holter ECG, the FD-HRV could not be analyzed and these patients were excluded from assessment. Accordingly, the effect of CBZ on HF component levels was assessed in 32 patients. The administered CBZ brought about complete elimination of the symptoms without any P-AF detected by the 24-h Holter ECG in 24 of the 32 patients (75%) (Fig. 1A). These patients were classified into the CBZ-responsive group and the remaining patients into the CBZ-non-responsive group. During the oral administration of CBZ, no side effects such as anticholinergic effects on organs other than the heart were found in any of the patients.

In 14 patients whose treatment was changed to DSP, FD-HRV analyses could be carried out on all patients. The dose was 300 mg/day in 13 patients (93%) and 200 mg/day in 1 (7%). DSP was effective in 10 of the 14 patients (71%) (Fig. 1B). As for side

![Figure 1](image1.png)  
**Figure 1** The effects of cibenzoline (CBZ) and disopyramide (DSP) on vagally mediated paroxysmal atrial fibrillation (P-AF).

![Figure 2](image2.png)  
**Figure 2** Comparison of high frequency (HF) component levels before and after the administration of cibenzoline (CBZ) for vagal paroxysmal atrial fibrillation (P-AF).

![Figure 3](image3.png)  
**Figure 3** Actual frequency-domain heart rate variability (FD-HRV) analyses in a patient whose high frequency (HF) component levels decreased after oral administration of cibenzoline (CBZ). LF, low frequency.
effects, with DSP, anticholinergic effects on organs other than the heart, such as a dry mouth and frequent urination, which do not appear with CBZ, were reported in 2 of the 14 patients (14%). Consequently, the change from CBZ to DSP resulted in termination of treatment in more patients than was the case with CBZ, owing to substantial side effects.

FD-HRV analyses pre- and post-drug state

The mean level of the HF components from 00:00 h to 06:00 h according to FD-HRV analyses performed before drug administration was $1589 \pm 795 \text{ ms}^2$. After administration of CBZ, the mean level decreased to $850 \pm 524 \text{ ms}^2$, indicating that CBZ decreased HF component levels significantly ($p < 0.0001$) (Fig. 2). Fig. 3 shows actual FD-HRV analyses of a patient in which CBZ decreased HF component levels. When the HF component levels before drug administration were compared between the CBZ-responsive group ($n = 24$) and the CBZ-non-responsive group ($n = 8$), the CBZ-responsive group had a significantly higher level than the CBZ-non-responsive group ($1766 \pm 758 \text{ ms}^2$ vs. $1058 \pm 690 \text{ ms}^2$, respectively, $p = 0.026$) (Fig. 4). On the other hand, after drug administration, no significant difference was found between the CBZ-responsive group and the CBZ-non-responsive group ($864 \pm 510 \text{ ms}^2$ vs. $810 \pm 599 \text{ ms}^2$, respectively, $p = \text{N.S.}$). When the reduction levels for the HF components were calculated, they were $-902 \pm -648 \text{ ms}^2$ in the CBZ-responsive group and $-248 \pm -369 \text{ ms}^2$ in the CBZ-non-responsive group, with the difference being significant ($p = 0.011$).

The mean level of the HF components from 00:00 h to 06:00 h after administration of DSP was $989 \pm 528 \text{ ms}^2$. Similar to CBZ, DSP decreased the HF component levels significantly ($p = 0.002$). When the HF component levels and reduction levels before drug administration were compared between the DSP-responsive group and the DSP-non-responsive group, no significant difference was found. However, the levels in the DSP-responsive group tended to be higher than in the DSP-non-responsive group ($1731 \pm 806 \text{ ms}^2$ vs. $1490 \pm 485 \text{ ms}^2$, respectively) and the reduction levels of HF components in the former group also tended to be higher ($-834 \pm 531 \text{ ms}^2$ vs. $-270 \pm -764 \text{ ms}^2$, respectively).

Comparison of HF component levels between CBZ and DSP

To compare the effects on the HF component levels between CBZ and DSP, the reduction levels of the HF components were compared in the 14 patients who received both drugs. No significant difference was found for either drug (Fig. 5).

Discussion

It is known that P-AF is likely to occur in conjunction with basic underlying heart diseases such as valvular disorders, ischemic heart diseases, cardiomyopathies, and hypertensive heart disease. However, P-AF may occur in the normal heart, and may be induced by modulation of autonomic nervous functions. Thus, autonomic nervous activity is also an important factor in the occurrence of P-AF [1,2]. In fact, there have been many reports stating that $\beta$ receptor and muscarinic receptor antago-
nists are effective therapy for P-AF induced by autonomic nervous activity [7,9,10]. P-AFs induced by autonomic nervous activity are classified into two types: vagal P-AF, which is likely to appear in association with sleep, rest, and after meals and sympathetic P-AF, which is likely to appear in association with exercise, tension, and stress [4]. When P-AFs are classified according to the time of onset, either nighttime or daytime, the former corresponds to the vagal type and the latter to the sympathetic type [5]. In younger patients (aged 60 years or less) without underlying heart diseases, it is reported that vagal P-AFs occur more often [11]. The mean age of the patients in this study was 58 years, which is relatively young, in keeping with previous studies.

One mechanism by which the tensional vagal nerves induce P-AFs is assumed to be as follows: acetylcholine is released from the terminal parts of the vagal nerves, binds to M₃ muscarinic receptors, and then activates the Iᵥ,ACh channels through G₁ proteins to reduce the action potential duration of the atrial myocardium [12,13]. Many experiments have demonstrated that stimulation of the vagal nerves induces a typical P-AF [14,15]. On the other hand, it has been demonstrated that the elimination of the influence of the vagal nerves does not induce P-AF [16].

CBZ and DSP are class I antiarrhythmic drugs with anticholinergic actions. However, the mechanisms of the anticholinergic actions of both drugs are somewhat different. Although both drugs have antagonistic actions against the M₂ muscarinic receptors of the atrial myocardium, CBZ also directly blocks the Iᵥ,ACh channels [17]. The Iᵥ,ACh channels do not exist in the ventricular myocardium, but are abundant in the sinus node cells and atrial myocardium. In the atrium, the Iᵥ,ACh plays an important role in determining the atrial action potential duration [13]. If the Iᵥ,ACh channels are directly blocked in addition to M₂ muscarinic receptors, theoretically, it can be inferred that the inhibitory action of CBZ on the vagal nerve functions in P-AF patients is more potent than that of DSP. Compared with DSP, CBZ is reported to have weaker anticholinergic actions on the brain (M₁ muscarinic receptors), and glands and smooth muscle (M₃ muscarinic receptors) other than those of the heart [18], and is thus recommended in order to reduce side effects.

In this study, the HF component levels identified by the FD-HRV analyses were used as indices to reflect vagal nerve activity. These component levels are the indices that most accurately reflect vagal nerve activity among the many HRV analysis indices [4–6]. The results of this study indicate that the HF component levels decreased in patients in whom CBZ was effective. The HF component levels before administration were significantly higher in the CBZ-responsive patients than in the CBZ-non-responsive group. In considering indications for antiarrhythmic drugs with anticholinergic action, the FD-HRV analyses were considered useful. Another advantage is that the FD-HRV analyses allow the effects of these drugs on vagal nerve activity to be evaluated quantitatively.

In this study, after administration of DSP, FD-HRV analyses were performed and the results were compared with those of CBZ. Because the number of patients was low, the superiority of CBZ in terms of anticholinergic action on the heart could not be proved. However, anticholinergic side effects on organs other than the heart which did not occur with CBZ occurred in 14% of patients taking DSP. In terms of reducing or avoiding side effects, CBZ is considered to be superior.

Study limitations

This study had a number of limitations. First, the effects of the antiarrhythmic drugs were evaluated mainly based on the disappearance of symptoms, not by a prolonged period of continuous ECG recording. Thus, it may be difficult to state that P-AF could be inhibited completely [19]. However, in this study, because the subjects were only those patients with clear P-AF symptoms, the reliability of the results is considered to be high.

Second, patients with sympathetic P-AF or mixed type P-AF were not enrolled and not used as a control group. To state that CBZ is effective for vagal P-AF, it may be necessary to perform controlled studies.

The third issue is that the quantitative evaluation of the HF component levels by FD-HRV analyses was conducted within a limited period (00:00—06:00 h). Because there are periods during the day when vagal nerve activity increases, such as after meals or at rest, measurements at other times might be necessary. However, as the patients enrolled in this study had P-AF episodes at night, an analysis limited to the specific period chosen for this study appears to be appropriate.

Conclusions

The HF component levels obtained from FD-HRV analyses of Holter ECGs were useful as indices to quantitatively assess the effects of antiarrhythmic drugs with anticholinergic action. CBZ was shown
to have marked antiarrhythmic effects on patients with symptomatic lone P-AF occurring at night. It was also found that CBZ is less likely to have anticholinergic actions on organs other than the heart, compared to DSP.

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