Effect of Aprindine on Heart Rate Variability Indices in Patients with Ischemic Heart Disease

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Summary

Background: Decreased heart rate variability indices (HRV) are associated with untoward outcome of patients with ischemic heart disease (IHD). Most class I antiarrhythmic agents decrease HRV, but aprindine (a new class I antiarrhythmic agent) is reported to increase HRV in patients without ischemia.

Hypothesis: The study was undertaken to determine whether aprindine might increase HRV in patients with IHD.

Methods: To investigate the effect of aprindine on HRV in patients with IHD, we performed 24-h ambulatory electrocardiogram (ECG) at the end of placebo and aprindine (60 mg daily) treatment phases on 38 patients with IHD and at least isolated premature ventricular contractions (PVC). The study protocol utilized a single blind, 4-week, placebo-controlled design. Heart rate variability from ambulatory ECG included SDNN (ms), SDANN (ms), SD (ms), rMSSD (ms), pNN50 (%); frequency analysis of HRV consisting of total (ms, 0.01–1.00 Hz), low (ms, 0.04–0.15 Hz), and high (ms, 0.15–0.40 Hz) components.

Results: Study patients were divided into three groups according to the severity of IHD and antiarrhythmic efficacy of aprindine. Group 1 consisted of 15 patients with angina with single-vessel disease, and Group 2 was composed of 10 patients with either multivessel disease or post myocardial in-

farction; PVCs decreased in both groups as a result of aprindine treatment. Group 3 consisted of 13 patients who showed no decreased PVC after aprindine treatment. RMSSD increased, and pNN50 and high-frequency spectra tended to increase in Group 1, while SD, rMSSD, pNN50, and total and low-frequency spectra decreased in Group 3; no significant changes were observed in Group 2. Aprindine significantly augments vagal activity, as reflected by the increase of rMSSD, pNN50, and high-frequency spectra in mild IHD.

Conclusion: These salutary effects are less in more severe IHD, but aprindine does not aggravate HRV. Thus, if there are salutary effects on arrhythmias and no proarrhythmic effects, aprindine could be prescribed to patients with IHD without concern about decreasing HRV.

Key words: aprindine, heart rate variability, ischemic heart disease

Introduction

Class I antiarrhythmic drugs reportedly have no salutary effects on the prognosis of patients post myocardial infarction,¹ and it is suspected that impaired autonomic balance is reflected by decreased heart rate variability (HRV) indices or proarrhythmic effects.² The low values of HRV indices are associated with lethal arrhythmic and/or ischemic events,^{3–6} which lead to untoward outcomes in patients with ischemic heart disease.

Aprindine, a new class I antiarrhythmic agent not yet available in the USA, increases HRV indices in patients without ischemic heart disease.^{7,8} However, there are no studies evaluating the effect of aprindine on HRV indices in patients with ischemic heart disease. Therefore, the purposes of the present study are to determine whether or not aprindine increases HRV indices in patients with ischemic heart disease, and to determine whether the effect, if any, differs according to the severity of ischemic heart disease or to the efficacy of this agent.

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Methods

Study Population

Thirty-eight patients (17 men, 21 women) with coronary artery disease, ages 44–83 years (mean 70 ± 10 years) were enrolled in the study; informed consent was obtained from all. Each patient met both of the following criteria: (1) diagnosed coronary artery disease [the criteria used for diagnoses were (a) angiographically documented coronary artery disease with $\geq 70\%$ reduction in luminal diameter in one or more major coronary arteries; (b) a well-documented previous myocardial infarction meeting World Health Organization (WHO) criteria;⁹ or (c) a positive thallium-201 exercise test manifested by a significant exercise-induced reversible defect or an exercise-induced myocardial ischemia [positive electrocardiogram (ECG) obtained in treadmill exercise testing] while not taking any antianginal medications (except sublingual nitroglycerin) for at least 2–3 days prior to the test, and terminated because of positive ischemic ECG changes (ST-segment depression 80 ms after J points, ≥ 1 mm) with typical anginal symptom; (2) a 24-h ambulatory ECG revealing at least isolated premature ventricular contraction (PVC).

No subject had experienced an event of acute myocardial infarction within the past 3 months, and none had received coronary revascularization procedures within 6 months prior to entry in the study. None had shown ECG abnormalities on the rest ECG that preclude measurement of ischemic ST- or T-wave changes and RR intervals (e.g., bundle-branch block, Wolff Parkinson-White syndrome, findings for left ventricular hypertrophy). Anti-ischemic medications and the other drugs such as angiotensin-converting enzyme (ACE) inhibitors that affect HRV indices were kept unchanged throughout the course of the study.

Study Protocol

The study protocol utilized a single-blind, 4-week placebo-controlled design. Treatment consisted of placebo for 28 days followed by 60 mg/day (20 mg t.i.d.) of aprindine daily for the next 28 days. We used the aspirin tablet of 81 mg as placebo, informing patients that it has some antiarrhythmic effects and also giving it in the aprindine phase. The 60 mg/day dose is reported to be optimal in patients with arrhythmia.¹⁰ Ambulatory ECG monitoring (24 h) was carried out on Days 27 and 28 of the placebo phase and the aprindine phase. At the end of ambulatory ECG monitoring, peripheral venous blood was withdrawn for the measurement of circulating plasma aprindine levels (determined by liquid chromatography).

Ambulatory Electrocardiographic Monitoring

Twenty-four-h 2-channel ambulatory ECG recordings were obtained on a Marquette 8500 recorder (Marquette Electronics, Milwaukee, Wisc.). The ambulatory ECG monitoring tapes were analyzed by a Marquette 8000 T analyzer (Marquette Electronics), using arrhythmia software (version 5.5)

and edited by one of the investigators. These analyzer findings were confirmed by cardiologist reviewers, all of whom were blinded with respect to medication. Numbers and severity of PVCs were determined using the arrhythmia software, with editing by a cardiologist throughout the study. If numbers of PVC decreased $> 75\%$ during the aprindine phase compared with the placebo phase, aprindine was defined as effective in decreasing PVC frequency.¹¹

Measurement of Heart Rate Variability Indices

Heart rate variability indices were measured with commercial HRV software version 002A, based on RR intervals of normal sinus beats obtained by an arrhythmia analysis program (Marquette Electronics, Version 5.5) installed in an 8000 T analyzer. Time domain and frequency domain analyses were performed using this software. For time domain analysis, mean RR (mean value of RR intervals of normal sinus beats over 24 h, ms), SDNN (standard deviation of all normal sinus RR intervals in the 24-h recordings, ms), SDANN (standard deviation of the mean of all 5 min segments of normal RR intervals of 24-h recordings, ms), SD (mean of the standard deviations of all normal RR intervals for all 5 min segments of 24-h recordings, ms), rMSSD (root mean square successive differences, the square root of the mean of the sum of the squares of differences between adjacent normal RR intervals over all the 24-h recordings, ms), and pNN50 (percent of difference between adjacent normal RR intervals that are greater than 50 ms computed over all the 24-h recordings, %) were calculated. For frequency domain analysis, the recording period was divided into small segments of contiguous 2 min periods. For each segment, time series functions were comprised of sampling RR intervals every 469 ms, and 256 data points per segment were transformed to power spectral density by fast Fourier transformation. To minimize spectral leakage, a Hanning window was applied. Data from ectopic beats and artifacts were excluded and replaced by maintaining the previous coupling interval levels. This system provides spectral plots as amplitudes (ms) instead of power (ms^2). The amplitude method is identical to modification of power by the logarithm function. At first, total spectra (0.01–1.00 Hz), low-frequency spectra (0.04–0.15 Hz), and high-frequency spectra (0.15–0.40 Hz) were calculated at each segment; thereafter, these values were averaged over 24 h to obtain 24-h mean values of total spectra, low-frequency spectra, and high-frequency spectra. The latter values were used for analysis.

If the analysis of ambulatory ECG monitoring revealed more than 2% artifact beats per total beats, the tapes were to be excluded from the analysis. However, in the present study none of the recorded tapes met this exclusion criterion.

Statistical Analysis

All normally distributed data are expressed as mean $\pm$ standard deviation. Data with skewed distributions, such as those dealing with PVC and HRV indices, are expressed as median and range. In the present study, mainly the nonparametric

FIG. 1 Effects of aprindine on the frequency of premature ventricular contractions (PVC) in the three groups. Pre = before aprindine phase, Post = at the end of the aprindine phase. □ = Group 1, ○ = Group 2, △ = Group 3. Median with range (75–25%). * $p < 0.05$ vs. Pre.

Wilcoxon signed rank test was applied for comparison of data before (placebo) and after (therapy) because most of the data were not normally distributed. Paired Student's *t*-tests were utilized for the comparison of the normally distributed data. Frequency distributions were tested by chi-square test or Fisher's exact probability test. Pearson product-moment correlation coefficient was calculated to investigate the relationship between HRV indices and the change of PVC. Differences were considered significant if $p \leq 0.05$.

Results

In the entire patients studied, aprindine significantly ($p < 0.05$) decreased the frequency of a nonsustained ventricular tachycardia per patient from 0.4 ± 0.7 to 0.2 ± 0.5 . Aprindine also decreased the frequency of PVC per patient from 92 (8–530) to 35 (3–420), expressed as median with range (25–75%), but this decrement did not reach statistical significance. Further, in this study population, only 25 patients met the defi-

nition of effective in decreasing PVC. Thus, after the effect of aprindine on the frequency of PVC was gauged in each patient, the study population was divided into three groups according to the severity of stenosis in the coronary artery, the presence of prior myocardial infarction, and the efficacy of aprindine administration on PVC. Group 1 consisted of 15 patients (4 men, 11 women; age 44–80 years, mean 68 ± 10) who were characterized as having mild ischemic heart disease; they had no prior myocardial infarction or single-vessel disease, and aprindine effectively decreased the number of PVCs (Fig. 1). After aprindine treatment, only 2 of the 15 patients in this group showed nonsustained ventricular tachycardia, whereas 5 had shown nonsustained ventricular tachycardia before the treatment. Mean frequency of the nonsustained ventricular tachycardia per patient significantly decreased (0.5 ± 0.7 vs. 0.2 ± 0.6 , $p < 0.05$). Group 2 consisted of 10 patients (7 men, 3 women; age 53–83 years, mean 74 ± 9) who were characterized as having moderate to severe ischemic heart disease; they had either prior myocardial infarction or angiographically proved multivessel disease. As in Group 1 patients, aprindine decreased the frequency of PVC in Group 2 patients (Fig. 1). After aprindine treatment, none of the 10 patients in Group 2 showed nonsustained ventricular tachycardia, whereas 3 had shown nonsustained ventricular tachycardia before treatment. Because of the small number of nonsustained ventricular tachycardia, its mean frequency decreased with a marginal statistical significance (0.3 ± 0.5 vs. 0.0 ± 0.0 , $p = 0.08$). Group 3 consisted of 13 patients, 6 of whom met the entry criteria of Group 1 while 7 met the entry criteria of Group 2. However, aprindine was not effective in decreasing PVC in Group 3 by definition. As a result, aprindine significantly increased the number of PVC in patients in this group (Fig. 1), and the number showing nonsustained ventricular tachycardia and its frequency per patient (0.3 ± 0.9 vs. 0.3 ± 0.6 , NS) was unchanged. Only one of the 13 patients in Group 3 was defined as showing a proarrhythmic response to aprindine, according to criteria proposed by Morganroth *et al.*;¹² the other 12 members of Group 3 simply showed no salutary effects of aprindine on PVC frequency by definition.

Selected clinical characteristics of each group are listed in Table I. Prevalences of organic diseases which could affect the

TABLE I Clinical characteristics of the patients divided into three groups on the basis of their response to aprindine treatment

	Male No.	MVD No.	Prior MI No.	HTN No.	Smoking No.	HL No.	DM No.	Medications		
								NTG No.	BB No.	CB No.
Group 1 (age 68 ± 10 ; $n = 15$)	4	0 ^a	0 ^a	9	2	8	6	11	1	9
Group 2 (age 74 ± 9 ; $n = 10$)	7	7 ^b	7 ^b	7	5 ^b	5	3	9	0	8
Group 3 (age 71 ± 10 ; $n = 13$)	6	4	2	5	1	5	3	12	5 ^c	8

^a $p < 0.05$ vs. Group 3.

^b $p < 0.05$ vs. Groups 1 and 3.

^c $p < 0.05$ vs. Groups 1 and 2.

Abbreviations: MVD = multivessel disease, MI = myocardial infarction, HTN = hypertension ($\geq 160/95$ mmHg), HL = hyperlipidemia (total cholesterol ≥ 230 mg/dl), DM = diabetes mellitus (fasting blood glucose ≥ 110 mg/dl), NTG = nitrates, BB = beta-blocking agents, CB = calcium-channel blockers, No. = number of patients in each group.

TABLE II Effect of aprindine on heart rate variability indices

	Mean RR (ms)	SDNN (ms)	SDANN (ms)	SD (ms)	rMSSD (ms)	pNN50 (%)	Total spectra (ms)	Low-frequency spectra (ms)	High-frequency spectra (ms)
Total (n = 38)	844 ± 95	126 (103–157)	117 (99–154)	40 (32–50)	22 (17–36)	3.4 (1.2–12.0)	23 (16–32)	12 (8–16)	9 (6–12)
Pre	892 ± 110 ^a	127 (105–146)	118 (97–136)	36 (26–44) ^a	25 (17–32)	4.7 (0.7–8.7)	20 (15–24) ^a	9 (6–13) ^a	8 (5–11)
Post	849 ± 111	127 (106–145)	116 (103–129)	39 (33–50)	22 (17–24)	3.7 (2.7–6.4)	22 (18–27)	11 (8–14)	9 (7–10)
Group 1 (n = 15)	931 ± 96 ^a	139 (115–151)	123 (106–145)	40 (30–54)	27 (22–54) ^a	6.4 (2.6–9.0)	22 (17–27)	11 (7–16)	10 (6–11)
Pre	837 ± 74	114 (67–137)	104 (67–137)	32 (27–50)	18 (16–31)	1.2 (0.5–10.6)	16 (15–29)	8 (7–16)	7 (5–12)
Post	907 ± 102 ^a	114 (89–141)	86 (75–110)	34 (25–42)	24 (15–27)	5.0 (0.6–8.6)	19 (13–23)	8 (6–10)	8 (5–10)
Group 3 (n = 13)	843 ± 97	149 (116–192)	142 (105–165)	49 (33–51)	28 (21–40)	7.4 (2.3–13.7)	31 (22–32)	14 (10–19)	9 (7–15)
Pre	836 ± 97	127 (108–148)	122 (101–142)	36 (28–41) ^a	23 (15–30) ^a	2.7 (0.5–6.5) ^a	20 (15–23) ^a	9 (8–13) ^a	7 (5–11)
Post									

Mean ± standard deviation or median with range (25–75%).

^a p < 0.05 vs. Pre.

For abbreviations, see text under "Measurement of Heart Rate Indices."

values of HRV indices are not significantly different among these groups, except for the number of smokers and the incidence of prior myocardial infarction, both of which were significantly greater in Group 1. With regard to the prevalence of antianginal agents used in each group, beta-blocking agents were significantly more frequently prescribed in Group 3 because of the severity of ischemic heart disease.

Plasma concentrations of aprindine reached therapeutic levels¹³ of 1.0 ± 0.9 , 1.0 ± 0.4 , and 1.0 ± 0.4 ng/ml in Groups 1, 2, and 3, respectively. In all patients studied, aprindine significantly prolonged mean RR interval and significantly decreased SD, total spectra, and low-frequency spectra (Table II). Aprindine significantly prolonged mean RR interval in Groups 1 and 2, whereas no significant change in mean RR was noted in Group 3 (Table II); it also significantly increased rMSSD in Group 1. Although pNN50 and high-frequency spectra, which reflect parasympathetic activity,¹⁴ increased after aprindine administration in Group 1 patients, these increments did not reach statistical significance. However, aprindine decreased rMSSD in Group 3 (Table II) and significantly decreased SD, pNN50, total spectra, and low-frequency spectra in Group 3 (Table II) despite the therapeutic plasma concentration of aprindine. A marked decrease of these indices was especially noted in the patient who showed a proarrhythmic response and had a new nonsustained ventricular tachycardia on aprindine treatment. No other significant effects on other indices of HRV were observed. The changes of mean RR interval and any HRV indices did not significantly correlate with the changes of PVC in any groups.

Discussion

In patients in whom aprindine decreased PVC (Groups 1 and 2), it also increased mean RR. In addition, aprindine increased rMSSD in Group 1, in which patients showed relatively mild ischemic heart disease. This HRV index mainly reflects parasympathetic activity.¹⁴ In contrast, in patients in whom aprindine increased PVC (Group 3), HRV indices decreased. Proarrhythmic effects were suspected in only one patient in this group; in the others, aprindine simply had no effect on PVC despite the fact that the plasma concentration of aprindine reached therapeutic levels. In Group 3 patients, the effects of aprindine on hormonal or autonomic activities, which decrease some indices of HRV but lack effect on PVC, might be the reason for a significant decrease of HRV indices in the group. The potential deteriorating effect of aprindine, particularly when it shows no effect on PVC, should be considered when prescribing aprindine to patients with coronary artery disease. Decreased HRV indices relate to increased sympathetic activity which can prevent a decrease in the numbers of PVC and also cause proarrhythmic effects on PVC.

Generally, increased parasympathetic activity provides a protective effect on cardiac arrhythmia. The incremental effect of rMSSD indicates that aprindine has a salutary effect on autonomic activity in patients with mild ischemic heart disease. Aprindine did not decrease any indices of HRV in Group 2.

suggesting that the drug might safely be prescribed to patients with moderate to severe ischemic heart disease when its effects are confirmed. However, the caution based on the Cardiac Arrhythmia Suppression Trial (CAST) study¹⁵ should dictate that, in 28 days of therapy, we cannot recognize all of the proarrhythmic events that might occur in patients taking aprindine. Before we make a conclusion about the safety of aprindine, we need to perform a further long-term follow-up study to confirm it.

The prolonged mean RR interval is a favorable prognostic finding in ischemia, and it might subsequently improve HRV indices. Also, there is a strong correlation between mean RR interval and HRV indices.¹⁴ The effects of aprindine on PVC might be caused by these effects. However, there was no significant correlation between the changes in PVC and either mean RR interval or HRV indices. The salutary effect of aprindine on PVC in Groups 1 and 2 of the present study could be considered as being direct.

The incremental effects of aprindine on HRV indices are in agreement with Otsuka *et al.*⁷ and Nakanishi *et al.*⁸ In their papers, aprindine decreased frequency of PVC. Their populations are similar to both Groups 1 and 2 in the present study, except for the existence of ischemic heart disease. In the present study, we used a single-blind study protocol so that the stability or the reproducibility should be considered before drawing conclusions. The weak study protocol is a major limitation of the present study. However, Kautzer *et al.*¹⁶ reported that HRV indices derived from 24-h ambulatory ECG monitoring in patients post myocardial infarction was generally stable and that the variability was <20%. In Group 1, aprindine increased rMSSD by 23%, which exceeds the above values.

Heart rate variability indices have recently been recognized as possible prognostic indicators for patients with coronary artery disease. After the wide use of revascularization therapy, HRV indices were still independent risk predictors for both mortality and arrhythmic events.^{17,18} Kleiger *et al.*³ reported that SDNN and SDANN are both powerful indices for predicting adverse outcomes in patients recovering from acute myocardial infarction. Although the predictive power of HRV indices for prognosis in patients with chronic stable angina is still not fully investigated, the decremental effect of antiarrhythmic agents on HRV indices is perhaps not yet feasible for patients with prior myocardial infarction and serious arrhythmia, since decreased HRV indices are associated with arrhythmic cardiac sudden death and life-threatening ventricular tachycardia and ventricular fibrillation.¹⁹ Thus, generally prescribing class I antiarrhythmic drugs to patients with coronary artery disease complicated with potential serious arrhythmia should be approached cautiously. In the present study, however, aprindine did not significantly decrease either SDNN or SDANN and it significantly increased rMSSD in the selected patients with coronary artery disease. The salutary effect of beta-blocking agents on survivors of acute myocardial infarction has generally been proven. Molgaard *et al.*²⁰ reported that metoprolol significantly increased HRV indices in patients recovering from acute myocardial infarction. It is speculated that any antianginal or antiarrhythmic agents that improve

HRV indices might be associated with improvement of prognosis in patients with coronary artery disease.

Conclusion

Aprindine might improve quality of life by decreasing PVC associated with symptoms such as palpitations, without the worsening effects on HRV indices when it does show an effect on PVC. However, the effect of aprindine on the long-term prognosis of ischemic heart disease cannot be evaluated from this study. Since our findings were anecdotal in a relatively small number of study patients, this study should be duplicated in larger sets of populations to see whether aprindine, at a daily dose of 60 mg, can be safely used in patients with ischemic heart disease with respect to effects on long-term prognosis.

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