J Cardiol 2000; 36: 405–410

Electrophysiological Mechanism of Combination Therapy With Disopyramide and Propranolol for Paroxysmal Atrial Fibrillation

Naoki GONDO, MD
Koichiro KUMAGAI, MD
Yoshio YAMANOUCHI, MD
Miyuki ANNOURA, MD
Keijiro SAKU, MD, FJCC

Abstract

Objectives. Combined administration of propranolol and disopyramide treatment often leads to better results in patients with atrial fibrillation refractory to only disopyramide administration. The electrophysiological mechanism of this combination therapy was investigated.

Methods. Nineteen patients with paroxysmal atrial fibrillation without organic heart disease were studied. The indices for atrial vulnerability were compared in the control state, 10 min after injection of disopyramide (2 mg/kg) and 10 min after additional administration of propranolol (0.2 mg/kg).

Results. Administration of both drugs did not significantly change the percentage fragmented atrial activity and the interatrial conduction delay. Disopyramide increased the atrial effective refractory period and the wavelength index, defined as the ratio of the atrial effective refractory period to the interatrial conduction delay and represented the length of the reentry circuit. Additional injection of propranolol caused further increases in both values.

Conclusions. Combination therapy with disopyramide and propranolol improves atrial vulnerability by increasing the wavelength.

J Cardiol 2000; 36(6): 405–410

Key Words
■ **Antiarrhythmia agents** ■ **Atrial fibrillation (paroxysmal)** ■ **Drug therapy**
■ **Electrophysiology**

INTRODUCTION

Atrial fibrillation is one of the most common types of arrhythmia. Paroxysmal and chronic atrial fibrillation could cause thrombus in the left atrium and induce cerebral infarction. Disopyramide, a class IA antiarrhythmic agent, has been employed for the treatment of atrial fibrillation. This drug certainly has a beneficial effect on atrial fibrillation[1–3]. However, some patients continue to exhibit atrial fibrillation after administration of only disopyramide. Such patients can be treated with combination therapy of disopyramide and propranolol, and improved results have been obtained. Several studies have reported the advantages of combination therapy using class IA antiarrhythmic agent and beta-blocker[4,5]. Although the additional administration of propranolol is considered to suppress the inducibility of atrial fibrillation by decreasing premature atrial contractions, the electrophysiological mechanism of this combination therapy resulting in such superiority is unclear. The

福岡大学医学部 第二内科：〒814−0180 福岡市城南区七隈7−45−1
The Second Department of Internal Medicine, School of Medicine, Fukuoka University, Fukuoka
Address for reprints: GONDO N, MD, The Second Department of Internal Medicine, School of Medicine, Fukuoka University, Nanakuma 7−45−1, Jonan-ku, Fukuoka 814−0180
Manuscript received March 27, 2000; revised July 3 and August 22, 2000; accepted August 23, 2000

purpose of this study was to clarify the mechanism of combination therapy with disopyramide and propranolol by means of an electrophysiological study.

SUBJECTS AND METHODS

Subjects

Nineteen patients, 7 men and 12 women aged from 32 to 85 years (mean age 62 ± 12.2 years), with paroxysmal atrial fibrillation without organic heart disease were studied. Paroxysmal atrial fibrillation was documented by 12-lead or Holter electrocardiography for more than 30 sec. All patients had marked symptoms such as palpitation, chest pain or dyspnea during an attack of arrhythmia. Informed consent was obtained from all patients prior to participation in the study. All cardioactive medications, including disopyramide, propranolol and other antiarrhythmic drugs, were withdrawn more than 7 days before the procedure. The patients were studied in the fasting and nonsedated state.

Methods

The method of the electrophysiological study was described in our previous report[6]. Briefly, catheter electrodes were placed in the high right atrium, the His bundle and the coronary sinus as a substitute for the left atrium. Stimulation was applied from the high right atrium. Electrograms were recorded in all 3 locations. We used square impulses of 2 msec duration and an intensity of twice the threshold delivered by programmable stimulation. The intracardiac signals were filtered to record frequencies of 50−700 Hz. All patients underwent electrophysiological studies before and 10 min after intravenous administration of disopyramide (2 mg/kg), and 10 min after propranolol (0.2 mg/kg). We did not change the strength of the stimulus and the basic cycle length because the intensity of the threshold remained unchanged.

The sinus cycle length was measured by means of body surface electrocardiography. A premature beat (S2) was introduced with a cycle length of 600 msec (S1). The S1−S2 interval was decreased in 10 msec steps until the effective refractory period of the right atrium was reached. The effective refractory period of the atrium is the longest S1−S2 interval that fails to result in atrial depolarization. The percentage fragmented atrial activity was defined as the maximal value of the ratio of A2 to A1 wave duration at the high right atrium. The interatrial conduction delay was defined as the maximal difference between the S1−A1 interval and the S2−A2 interval at the coronary sinus recording site, where A1 and A2 are atrial electrograms corresponding to S1 and S2, respectively (**Fig. 1**). In addition, the wavelength index was calculated, defined as the ratio of the refractory period to the interatrial conduction delay.

The 5 parameters were analyzed using one-factor ANOVA analysis. Three parameters, which showed a significant difference, were assessed by Fisher's PLSD. The results are expressed as mean ± SD. A p value of < 0.05 was considered significant.

RESULTS

A blood sample was taken after the completion of the last study in 3 optionally selected subjects to measure the plasma concentration of disopyramide. The values were 2.35, 2.41 and 2.77 μg/m*l*. The effective serum concentration of disopyramide is 2−4 μg/m*l*[7], so we judged that an effective serum concentration of disopyramide was maintained during the study.

Representative recordings of the indices for atrial vulnerability are shown in **Figs. 1−3**. As the basic cycle length was 600 msec in the control state, the effective refractory period was 220 msec, the percentage fragmented atrial activity was 133% and the interatrial conduction delay was 40 msec. In this case, the wavelength index was 5.5 (**Fig. 1**). After injection of disopyramide, the atrial effective refractory period increased to 260 msec. The percentage fragmented atrial activity and the interatrial conduction delay were unchanged (133% and 40 msec, respectively). The wavelength index increased from 5.5 to 6.5 (**Fig. 2**). After administration of propranolol, the atrial effective refractory period was further increased to 290 msec. The percentage fragmented atrial activity and the percentage conduction delay were unchanged at 133% and 40 msec. The wavelength index increased from 6.5 to 7.25 (**Fig. 3**).

The electrophysiological parameters of the 19 patients in the 3 states are compared in **Fig. 4**. The sinus cycle length was slightly reduced after disopyramide administration, probably due to its anticholinergic effect (from 814 ± 103.2 to 784 ± 91.7 msec; NS), and significantly prolonged after propranolol administration (from 784 ± 91.7 to 1,017 ± 105.6 msec; $p < 0.01$). The atrial effective refractory period increased after disopyramide administration (from 236 ± 20.6 to 275 ± 30.3

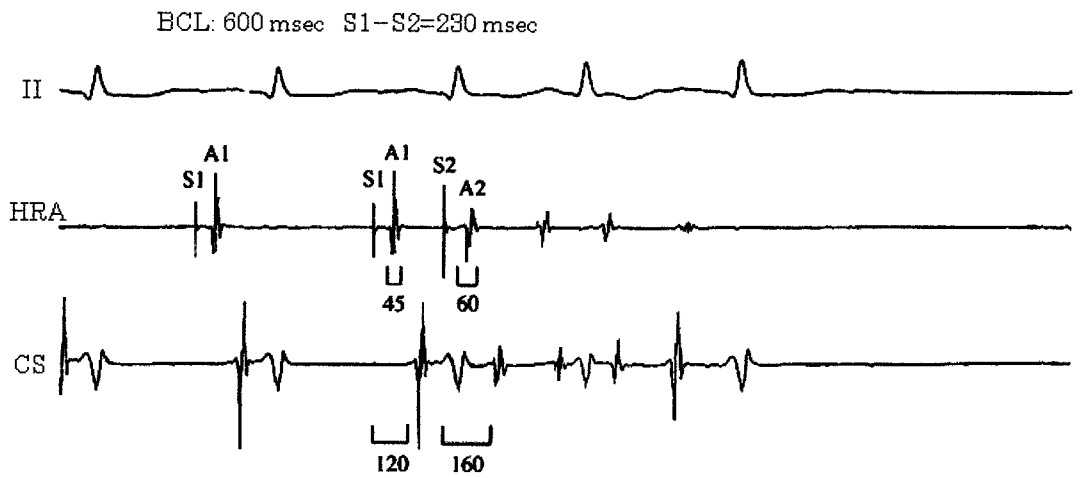

Fig. 1 Recording from a representative patient in the control state
Electrocardiographic lead II, high right atrial electrogram(HRA), and left atrial electrogram recorded from the coronary sinus(CS)are shown. The basic atrial driven cycle length was 600 msec. The atrial effective refractory period was 220 msec. Extra stimulus with a 230 msec S1−S2 interval prolonged the interatrial conduction time from 45 to 60 msec in the HRA recording(percentage fragmented atrial activity = 133%), and the interatrial conduction time from 120 to 160 msec in the CS recording(interatrial conduction delay = 40 msec). In this case, the wavelength index was 5.5.
BCL = basic cycle length.

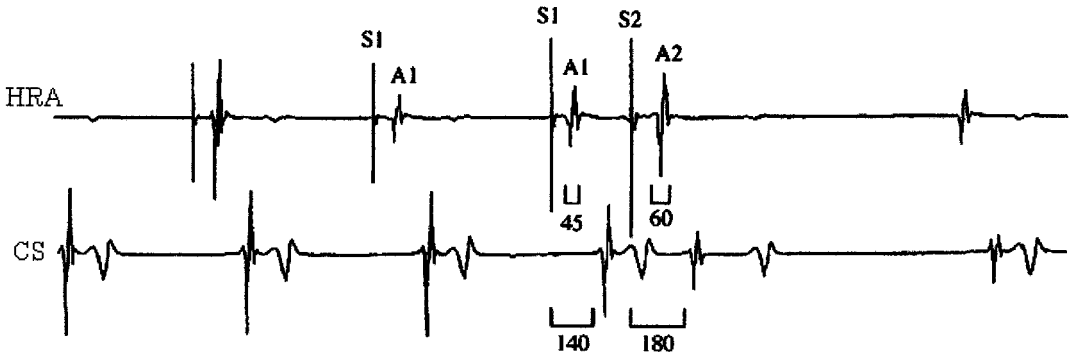

Fig. 2 Recording after intravenous administration of disopyramide
The atrial effective refractory period increased from 220 to 260 msec. The percentage fragmented atrial activity remained at 133% and the interatrial conduction delay also remained at 40 msec. The wavelength index increased from 5.5 to 6.5.
Abbreviations as in Fig. 1.

msec; $p < 0.01$), and became much larger after propranolol administration(from 275 ± 30.3 to 298 ± 40.8 msec; $p < 0.05$). One-factor ANOVA analysis proved that the percentage fragmented atrial activity and the interatrial conduction delay were not changed by administration of these drugs. The wavelength index was significantly larger after disopyramide administration than in the control state(from 5.4 ± 1.5 to 6.5 ± 1.6; $p < 0.05$). In addition, the wavelength index increased after administration of propranolol(from 6.5 ± 1.6 to 7.6 ± 1.2; $p < 0.05$).

Six patients presented with induced atrial fibrillation in the control state. However, 3 patients presented with such arrhythmia after disopyramide administration. No patient presented with such

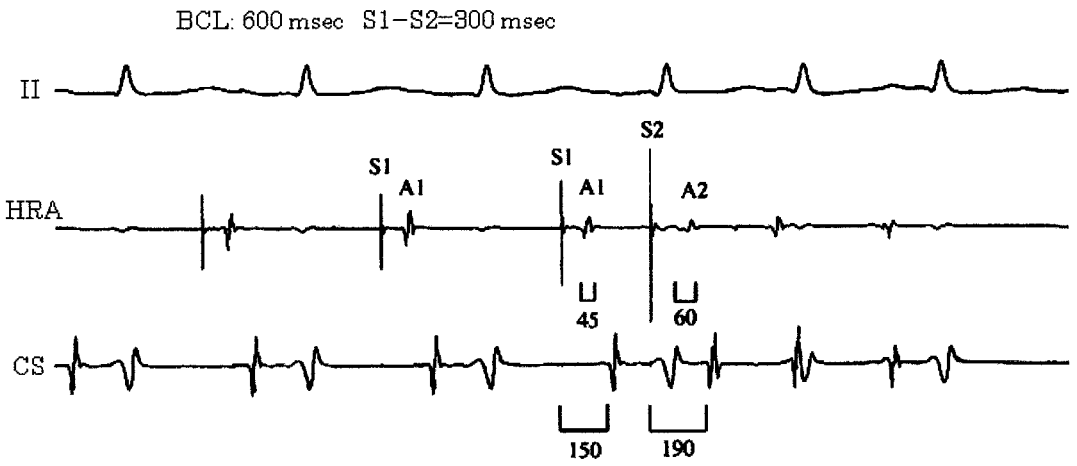

Fig. 3 Recording after intravenous administration of disopyramide and propranolol
The atrial effective refractory period increased from 260 to 290 msec. The percentage fragmented atrial activity and the interatrial conduction delay remained at 133% and 40 msec, respectively. The wavelength index increased from 6.5 to 7.25.
Abbreviations as in Fig. 1.

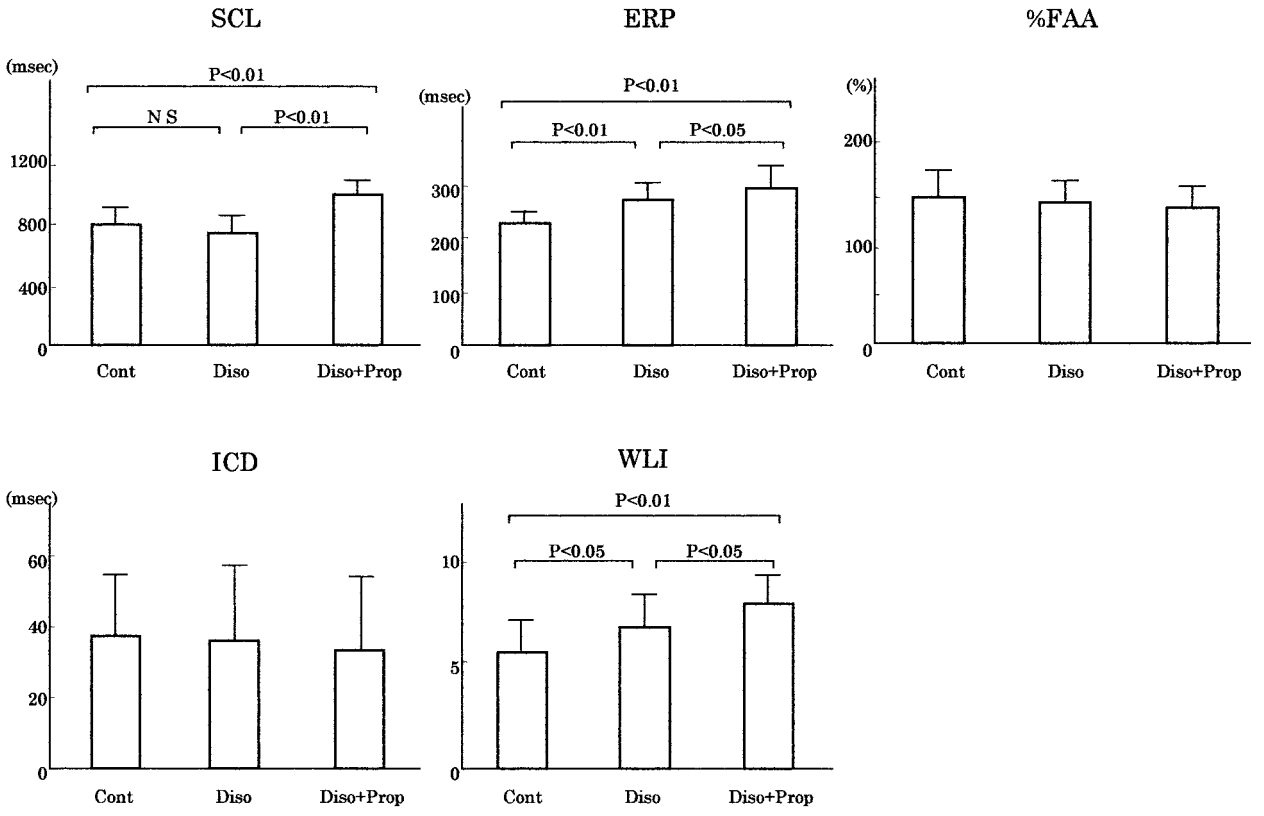

Fig. 4 Comparison of electrophysiological parameters in the 3 states
SCL = sinus cycle length; ERP = atrial effective refractory period; %FAA = percentage fragmented atrial activity; ICD = interatrial conduction delay; WLI = wavelength index; Cont = control; Diso = disopyramide; Prop = propranolol.

arrhythmia after administration of both disopyramide and propranolol.

DISCUSSION

The atrial effective refractory period and its dispersion have been used as indices for atrial vulnerability. Several investigators reported that patients with atrial fibrillation had shorter atrial effective refractory period[8,9]. We also obtained the same findings in our previous study[6]. According to the wavelength theory, a shorter refractory period is compatible with the occurrence of reentry in the atrium. A longer refractory period would prolong the wavelength and hinder the initiation of atrial fibrillation unless the conduction became slower. In the present study, we demonstrated that disopyramide increased the atrial refractory period, and that additional injection of propranolol caused a further increase. Propranolol suppresses the sympathetic nerve system, and thereby could increase the effect of disopyramide. Another hypothesis is that the prolongation of the atrial refractory period might be due to the potassium channel blocking effects of both drugs[10,11]. In other words, disopyramide blocks the muscarinic acetylcholine receptor-operated potassium channel, the transient outward potassium channel and the rapid component of the delayed rectifier potassium channel. Propranolol suppresses the slow component of the delayed rectifier potassium channel current.

Several studies have reported that the percentage fragmented atrial activity was larger in patients with atrial fibrillation than in control subjects[8,12]. In this study, neither drug had any effect on this value. Therefore, improvement of increased fragmented atrial activity does not seem to be the mechanism involved in the superiority of this combination therapy.

Interatrial conduction delay is accepted as an index illustrating the conduction time between the right and left atria[13,14]. Our findings demonstrated that disopyramide and propranolol did not influence the interatrial conduction delay. The wavelength for circus movement in the heart corresponds to the distance traveled by the depolarization wave in the refractory period[15,16]. When the wavelength is shortened, multiple reentering wavelets may begin to wander in various directions, resulting in atrial fibrillation[16]. Therefore, we defined the wavelength index as the ratio of the refractory period to the interatrial conduction delay. Also, in our previous report, we demonstrated that the wavelength index was a more reliable index for atrial vulnerability than the atrial effective refractory period[17].

Disopyramide increased the atrial effective refractory period and the wavelength index. Additional administration of propranolol caused further increase in both values. On the basis of this study, we conclude that combination therapy with disopyramide and propranolol improves the enhanced atrial vulnerability by increasing the wavelength.

CONCLUSION

Combination therapy with disopyramide and propranolol improves atrial vulnerability by increasing the wavelength.

要　　約

発作性心房細動に対するジソピラミドおよびプロプラノロールの併用療法の電気生理学的機序

権藤　直樹　　熊谷浩一郎　　山之内良雄　　案浦　美雪　　朔　啓二郎

目　的: 発作性心房細動に対する治療において，ジソピラミド単独では無効であった患者に，プロプラノロールを併用すると有効である場合が少なからずあるが，その詳細な機序については，いまだ明らかではない．

方　法: 孤立性発作性心房細動の患者19例に対し，電気生理学的検査を施行し，心房受攻性の各指標を，薬剤投与前，ジソピラミド(2mg/kg)静注10分後，プロプラノロール(0.2mg/kg)静注10分後の各時点において比較検討した．

結　果: Percentage fragmented atrial activityおよび左右心房間の伝導遅延は，この2つの薬物投与では有意な変化はみられなかった．一方，心房有効不応期は，薬剤投与前と比較して，ジソピラミ

ド静注後に有意に延長し，プロプラノロール静注後にはさらに延長した．心房有効不応期を左右心房間の伝導遅延で除した値であるwavelength indexは，リエントリー回路の大きさを表す指標の一つであるが，この値はジソピラミド静注後に増大し，プロプラノロール静注後にはさらに大きな値となった．

結　論：ジソピラミドとプロプラノロールの併用療法は，いわゆるwavelengthをより大きくすることにより，発作性心房細動に対して効果を発揮するものと考えられる．

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