Flecainide Augments Muscle Sympathetic Nerve Activity in Humans

Yoshiki Nagata, MD

The Cardiac Arrhythmia Suppression Trial has shown that treatment with flecainide is associated with an increased incidence of cardiac death in patients following myocardial infarction. It is believed that there is a complex mechanism involving an interaction between flecainide, sympathetic activation, and acute ischemia that is responsible for the increased risk of sudden death. The purpose of this study was to determine the effects of flecainide on muscle sympathetic nerve activity (MSNA) in humans. We measured MSNA using microneurography and cardiac output using the dye dilution method in 30 healthy individuals. Measurements were made at rest and after the oral administration of flecainide (200 mg, n=12) or placebo (n=9), or intravenous administration of propranolol (0.2 mg/kg, n=9). Flecainide significantly increased heart rate and decreased the cardiac index (both $p<0.01$). Flecainide increased the burst rate from 16.7 ± 3.5 to 23.3 ± 4.1 bursts/min and the burst incidence from 26.6 ± 5.1 to 34.7 ± 5.6 bursts/100 heartbeats (both $p<0.01$). For all of the hemodynamic parameters except heart rate, the effects of propranolol were similar to those of flecainide. Propranolol also increased the burst rate by $52\pm34\%$ and the burst incidence by $106\pm39\%$. These results suggest that flecainide suppresses myocardial contractility and produces reflex-mediated increases in sympathetic nerve firing in humans. (*Circ J* 2002; **66**: 377–381)

Key Words: Flecainide acetate; Muscle sympathetic nerve activity; Negative inotropic action; Propranolol hydrochloride

The Cardiac Arrhythmia Suppression Trial (CAST) was designed to test the hypothesis that suppression of ventricular ectopy after myocardial infarction decreases the incidence of arrhythmic death. However, an increased incidence in the number of deaths due to arrhythmia as well as deaths due to shock after recurrent myocardial infarction in patients treated with flecainide or encainide has been reported.¹ Although the underlying mechanism for these adverse outcomes is unknown, subgroup analysis found that the total death and cardiac arrest rates were significantly higher in patients with non-Q-wave myocardial infarction, suggesting that ischemia plays an important role in the increased anti-arrhythmic drug risk.²

Several subgroup analyses of the CAST data have also provided evidence supporting an additional contribution from sympathetic activity. These data demonstrated that the time of arrhythmic death in the group treated with flecainide or encainide displayed a bimodal variation, with significant peaks in the midmorning and late afternoon.³ Furthermore, CAST patients treated with both anti-arrhythmic drugs and β -blocker therapy had significantly better long-term survival than patients who received only anti-arrhythmic drugs.⁴ Recently, Cragun et al have reported that β -adrenergic stimulation in the setting of membrane depolarization potentiated flecainide-induced conduction slowing, and have suggested that the synergy between catecholamines

and flecainide facilitates arrhythmogenesis in the presence of underlying ischemia.⁵ It has also been shown in animal studies^{6,7} and clinical studies⁸ that propranolol prevents the proarrhythmic effect of flecainide. These studies suggest an interaction between flecainide and the sympathetic nervous system in the development of arrhythmias.

The evaluation of the effects of anti-arrhythmic drugs on the sympathetic nervous system has received little attention. Certain anti-arrhythmic drugs have been shown to influence muscle sympathetic nerve activity (MSNA) directly or via reflex mechanisms.^{9,10} Although flecainide has been shown to produce a significant and marked reduction in heart rate variability,^{11,12} there have been no studies of the direct effects of flecainide on MSNA in humans.

In the present study, we hypothesized that flecainide suppresses myocardial contractility^{13,14} and might produce reflex-mediated increases in sympathetic nerve firing in humans. Therefore, we directly recorded efferent postganglionic sympathetic nerve activity in the peroneal nerve before and after oral administration of flecainide. Sympathetic nerve activity recorded after flecainide administration was then compared with propranolol administration producing comparable negative inotropic effects and placebo.

Methods

Study Population

The study included 30 healthy volunteers (20 men and 10 women; mean age 27 ± 2 years; range 19–54 years). Subjects were screened by physical examination, biochemical and hematological analysis, and electrocardiogram. All subjects were of average physical fitness, and none were taking medication at the time. The experimental protocol and its purpose were explained in detail to each subject, and informed written consent was obtained. The study protocol

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Department of Cancer Gene Regulation, Gastroenterology and Nephrology, Graduate School of Medical Science, Kanazawa University, Kanazawa, Japan

Mailing address: Yoshiki Nagata, MD, Department of Cancer Gene Regulation, Gastroenterology and Nephrology, Graduate School of Medical Science, Kanazawa University, 13-1 Takara-machi, Kanazawa 920-8641, Japan. E-mail: drnagata@nsknet.or.jp

Table 1 Baseline Clinical and Hemodynamic Characteristics

Variable	Control group	Flecainide group	Propranolol group
No. of subjects	9	12	9
M/F	6/3	9/3	5/4
Age (years)	24±2	31±4	24±3
Heart rate (beats/min)	65±4	62±4	65±3
Systolic arterial pressure (mmHg)	123±3	136±4	138±5
Diastolic arterial pressure (mmHg)	73±3	77±2	79±3
Cardiac index (L·min ⁻¹ ·m ⁻²)	2.91±0.22	3.14±0.27	3.02±0.17
SVRI (units)	2,565±183	2,577±187	2,679±204

Results are expressed as the mean±SEM. SVRI, systemic vascular resistance index.

was approved by the ethical panel of the Department of Cancer Gene Regulation, Gastroenterology and Nephrology, Graduate School of Medical Science, Kanazawa University.

Measurements

All experiments were carried out in a quiet room with subjects in a supine position. Arterial pressure was recorded directly from a polyethylene catheter inserted into the brachial artery and connected to a pressure transducer (Baxter UK1000; Baxter, Tokyo, Japan). Another polyethylene catheter was inserted into the antecubital vein for drug infusion. Heart rate was determined from a continuous recording of the electrocardiogram. Cardiac index was measured by the dye dilution method using a cuvette (TL-430S; Nihon Kodan, Tokyo, Japan). Systemic vascular resistance index was calculated by dividing the mean arterial pressure (diastolic pressure plus one-third of the pulse pressure) by the cardiac index.

Multiunit postganglionic MSNA was recorded from a muscle nerve fascicle in the peroneal nerve at the level of the fibular head using tungsten microelectrodes (FHC Inc, Brunswick, USA) and microneurographic techniques.^{15,16} The electrodes were connected to a preamplifier at a gain of 1,000 and an amplifier at a gain of 70. The signal was fed through a band-pass filter (700–2,000 Hz) and a resistance-capacitance integrating circuit with a time constant of 0.1 s, producing a mean voltage neurogram. The signal was fed through a loudspeaker, displayed on an oscilloscope, and recorded by a paper chart recorder (Nihon Kodan). The MSNA was identified based on its relationship to cardiac and respiratory activity, its tendency to increase during the Valsalva maneuver, and its lack of change during arousal stimuli and skin stroking. Sympathetic bursts were determined by inspection of the filtered and mean voltage neurogram. Nerve activity was expressed as both bursts/min (burst rate) and bursts/100 heartbeats (burst incidence).

Study Protocol

After placement of the intra-arterial catheter and microelectrodes for nerve activity recording, subjects were allowed to rest for 15 min. Baseline data were recorded for 5 min, and baseline values for arterial pressure, heart rate, and MSNA were averaged over the 5-min period. At least 2 measurements of cardiac output were obtained for each subject and an average value was used for comparison. All subjects performed a sustained handgrip exercise at 30% of maximal voluntary contraction for 3 min.

After a 10-min recovery period, 12 subjects were given 200 mg of flecainide orally. All measurements were repeated 60 min after the administration of flecainide. The same measurements were repeated 30 min after the intravenous administration of propranolol (0.2 mg/kg) in 9 subjects, and

30 min and 60 min after the oral administration of placebo in 9 subjects. This dosing regimen has been shown to produce significant hemodynamic effects and significant increased plasma drug levels of flecainide¹⁴ and propranolol.^{17,18}

Statistical Analysis

Results are expressed as the mean±SEM. Student's *t*-test was used for paired comparisons. Repeated measures analysis of variance was used to compare within-group measurements. A value of *p*<0.05 was considered statistically significant.

Results

Subject Characteristics

Table 1 summarizes the clinical characteristics of the 3 groups. The mean age of the flecainide group was slightly but insignificantly greater than that of the control group and the propranolol group. There was no significant difference in gender, resting heart rate, systolic and diastolic arterial pressure, cardiac index, or systemic vascular resistance index among the 3 groups.

Hemodynamic Effects of Flecainide and Propranolol

Table 2 summarizes the hemodynamic effects of flecainide and propranolol. Flecainide increased heart rate and diastolic arterial pressure (both *p*<0.01) significantly, but did not affect systolic arterial pressure. After the oral administration of flecainide, the cardiac index decreased by 14±2% (*p*<0.01), and was associated with a 17±6% increase in the systemic vascular resistance index. For all of the hemodynamic parameters except heart rate, the effects of propranolol were similar to those of flecainide. Propranolol decreased heart rate by 12±3% (*p*<0.01). After the administration of placebo, there were no significant changes for any of the hemodynamic parameters.

Effects of Flecainide and Propranolol on Muscle Sympathetic Nerve Activity

Fig 1 shows a representative integrated neurogram, arterial pressure, and electrocardiogram. After the oral administration of flecainide, a marked increase in muscle sympathetic nerve bursts is noted. Flecainide significantly increased the burst rate by 98±56% (*p*<0.01; Table 3) and the burst incidence by 79±46% (*p*<0.01). Propranolol also increased the burst rate by 82±34% (*p*<0.05; Table 3) and the burst incidence by 106±39% (*p*<0.01). Placebo did not affect MSNA.

Muscle Sympathetic Nerve Activity Responses to Handgrip Exercise

During handgrip exercise (Fig 2), the increase in burst

Table 2 Hemodynamic Effects of Flecainide, Propranolol and Placebo

	Control group			Flecainide group		Propranolol group	
	Baseline	30 min	60 min	Baseline	Flecainide	Baseline	Propranolol
Heart rate (beats/min)	65±4	62±3	63±3	62±4	67±4 [†]	65±3	57±2 [†]
Systolic arterial pressure (mmHg)	123±3	122±2	125±2	136±4	139±5	138±5	139±4
Diastolic arterial pressure (mmHg)	73±3	71±2	75±3	76±3	81±2 [†]	79±3	83±2*
Cardiac index (L·min ⁻¹ ·m ⁻²)	2.91±0.22	2.75±0.21	2.97±0.23	3.14±0.27	2.69±0.21 [†]	3.02±0.17	2.31±0.10 [†]
SVRI (units)	2,565±183	2,690±223	2,612±219	2,577±187	3,121±263 [§]	2,679±204	3,591±206 [§]

Results are expressed as the mean±SEM. SVRI, systemic vascular resistance index. **p*<0.05, [†]*p*<0.01, [§]*p*<0.001 compared with values at baseline.

Table 3 Effects of Flecainide and Propranolol on Muscle Sympathetic Nerve Activity and Electrocardiographic Parameters

	Control group			Flecainide group		Propranolol group	
	Baseline	30 min	60 min	Baseline	Flecainide	Baseline	Propranolol
Burst rate (bursts/min)	15.1±2.0	13.9±2.0	14.6±2.6	16.7±3.5	23.3±4.1 [†]	10.8±2.3	17.1±2.7*
Burst incidence (bursts/100 heartbeats)	23.8±3.3	22.8±3.7	23.9±4.9	26.6±5.1	34.7±5.6 [†]	17.5±4.1	30.9±5.2 [†]
PR interval (s)	0.15±0.01	0.16±0.01	0.16±0.01	0.15±0.01	0.16±0.01	0.16±0.01	0.16±0.01
QRS duration (s)	0.081±0.003	0.081±0.003	0.084±0.003	0.090±0.005	0.103±0.005*	0.090±0.005	0.090±0.005
QT interval (s)	0.39±0.01	0.39±0.01	0.40±0.01	0.39±0.01	0.39±0.01	0.41±0.01	0.39±0.01 [†]

Results are expressed as the mean±SEM. **p*<0.05, [†]*p*<0.01 compared with values at baseline.

Fig 1. Typical example of experimental records showing the effects of oral administration of flecainide on muscle sympathetic nerve activity, arterial pressure, and electrocardiogram (ECG).

incidence under basal conditions was 7.2 ± 2.0 bursts/100 heartbeats, which was similar to that after the administration of flecainide (9.7 ± 2.5 bursts/100 heartbeats). In the propranolol and placebo group, handgrip exercise led to similar increases in burst incidence under basal conditions and after drug administration.

Electrocardiogram

Flecainide significantly increased the QRS duration ($p < 0.05$; Table 3), but did not affect the PR or QT intervals. After propranolol infusion, the QT interval decreased ($p < 0.01$; Table 3), but the QRS duration and PR interval did not change. There was no significant change in the electrocardiographic parameter after the administration of placebo.

Discussion

The present study is the first to demonstrate that flecainide enhances sympathetic outflow in humans from direct measurements of sympathetic nerve activity in the peroneal nerve.

Anti-Arrhythmic Drugs and Sympathetic Nerve Activity

The sympathetic nervous system is an important regulator of cardiovascular function. Activation of the sym-

Fig 2. Increases in burst incidence during handgrip exercise at () baseline, and () after administration of placebo, flecainide, and propranolol. Values are expressed as the mean±SEM. NS, not significant.

thetic nervous system plays an important role in the pathophysiology and prognosis of cardiovascular disorders such as heart failure, coronary heart disease, hypertension, and arrhythmias.^{19–23} Clinical trials of short-acting calcium channel antagonists have yielded disappointing results, particularly in patients with acute myocardial infarction and unstable angina.²⁴ A potential mediator of these untoward effects is activation of the sympathetic nervous system.²⁵ Therefore, an analysis of the interaction between

cardiovascular drugs and the sympathetic nervous system is important.

Certain anti-arrhythmic drugs have been shown to influence MSNA, either directly or via a reflex mechanism. Rea et al have reported that the intravenous administration of procainamide decreases postganglionic sympathetic nerve activity in humans directly and that the vasodilator effects of the drug may be because of withdrawal of the sympathetic vasoconstrictor tone.⁹ Mariano et al have demonstrated that quinidine, unlike procainamide, causes vasodilation directly and is associated with baroreflex-mediated increases in sympathetic nerve activity.¹⁰ Furthermore, Ellenbogen and colleagues have demonstrated that therapeutic doses of lidocaine do not have a direct effect on MSNA during sustained ventricular tachycardia or during programmed electrical stimulation with single ventricular extrastimuli.²⁶ The results of the present study demonstrate, for the first time, that flecainide increases sympathetic outflow in humans. In addition, flecainide increases the heart rate and systemic vascular resistance index, suggesting cardiac and peripheral sympathetic augmentation.

The autonomic effects of flecainide have not been investigated in great detail. It has been shown that flecainide decreases heart rate variability.^{11,12} The potential importance of the interaction between flecainide and activation of the sympathetic nervous system has also been suggested by the observation that the proarrhythmic effect of flecainide can be prevented by β -blocking agents.⁶⁻⁸

Potential Mechanisms

Although the exact mechanisms by which flecainide enhances sympathetic nerve activity remain unclear, the following 2 mechanisms should be considered: (1) suppression of afferent vagal nerve activity through negative inotropic actions, and (2) direct action on the central nervous system.

Cardiopulmonary mechanoreceptors with C-fiber vagal afferents have been shown to inhibit sympathetic vasomotor outflow tonically in animal studies.^{27,28} Studies in open-chest, anesthetized cats have indicated that the 2 main mechanical determinants of ventricular C-fiber activity are left ventricular end-diastolic pressure and contractility.²⁷ Decreases in ventricular contractility by acute β -adrenergic blockade attenuate the increase in C-fiber activity caused by increases in end-diastolic pressure.^{27,28} In the present study, we hypothesized that flecainide decreases myocardial contractility^{13,14} and might produce reflex-mediated increases in sympathetic nerve firing. Therefore, we compared sympathetic nerve activity after flecainide administration with that after the intravenous infusion of propranolol at a dose that produced comparable negative inotropic effects. In the present study, flecainide decreased the cardiac index to an extent similar to propranolol. The degree of activation of the muscle sympathetic nervous system between flecainide and propranolol was similar. These results suggest that flecainide causes increased reflex in sympathetic nerve activity through an inhibition of cardiopulmonary baroreceptor discharge. Jacobsen et al have found no increase in muscle sympathetic activity in humans following the intravenous injection of propranolol at a dose of 0.15 mg/kg.²⁹ However, recent laboratory studies of the spectral analysis of heart rate, arterial pressure, and muscle sympathetic activity in normal humans found that propranolol (0.2 mg/kg iv) increases burst incidence from 19.0 ± 2.7 to 28.1 ± 2.3 bursts/100 heartbeats.³⁰ The discrepan-

cies between studies of the effect of propranolol are likely to be related to differences in propranolol dosage.

The direct stimulation of the sympathetic nervous system through a central mechanism by flecainide is unlikely. This is based indirectly on the finding that flecainide had no effect on the response of MSNA to handgrip exercise. Furthermore, there are no previously published experimental data supporting such an interaction.³¹

Study's Limitations

The present study has several limitations. First, we measured MSNA but did not evaluate cardiac sympathetic activity. However, there is evidence indicating that in healthy normotensive individuals, there is a close relationship between resting MSNA in the peroneal nerve and cardiac norepinephrine spillover.³² In the present study we found that flecainide increased heart rate; therefore, flecainide may enhance cardiac sympathetic drive as well as muscle.

Second, the study does not determine whether these sympathetic effects persist during chronic oral flecainide treatment in patients with cardiovascular diseases. Further studies are necessary to assess this aspect of the effects of flecainide.

Clinical Implications

Despite the fact that the results of this short-term study were obtained in healthy volunteers, the treatment strategies used may be relevant to patients with cardiovascular disease in whom sympathetic activation is the major determinant of prognosis. Previous studies have demonstrated circadian rhythms in the onset of sudden cardiac death, myocardial infarction, and transient myocardial ischemia, and have suggested that increased sympathetic activity associated with awakening and rising may be involved.^{20,33-37} In the CAST, the time of onset of arrhythmic death in the active treatment group displayed a bimodal variation, with significant peaks in the midmorning and late afternoon/early evening.³ It is likely that flecainide-induced sympathetic activation produced the detrimental effects in this group. Based on the results of the present study, the selection of anti-arrhythmic drugs for the treatment of arrhythmias in patients with myocardial infarction should also take into consideration their effects on the sympathetic nervous system.

Conclusions

The results suggest that flecainide suppresses myocardial contractility and produces reflex-mediated increases in sympathetic nerve firing in humans. This sympathetic excitation is likely to be a result of diminished cardiac output.

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