JACC Vol. 7, No. 5
May 1986:1121–6



# Effect of Encainide and Flecainide on Chronic Ectopic Atrial Tachycardia

KLAUS-PETER KUNZE, MD, KARL-HEINZ KUCK, MD, MICHAEL SCHLÜTER, PHD, WALTER BLEIFELD, MD, FACC

*Hamburg, West Germany*

**In the treatment of chronic ectopic atrial tachycardia, standard antiarrhythmic therapy has been shown to be ineffective in the majority of patients. The intravenous and oral effects of two class IC antiarrhythmic drugs, encainide and flecainide, in five patients with chronic ectopic atrial tachycardia were studied using exercise testing, 24 hour long-term electrocardiography and programmed electrical stimulation. All patients had been treated unsuccessfully with at least four antiarrhythmic drugs. In two patients tachycardia was persistent, and in three patients tachycardia occurred intermittently for more than 12 hours/day.**

**Intravenous encainide and flecainide at doses ranging from 0.3 to 2.0 mg/kg and from 0.5 to 1.5 mg/kg body weight, respectively, terminated atrial ectopic tachycardia in all patients. Oral encainide, 150 to 225 mg/day, completely suppressed ectopic atrial activity in four patients during a mean follow-up period of 8 ± 3 months. In the remaining patient encainide markedly reduced the number of episodes of tachycardia. In three patients encainide had to be withdrawn because of intolerable side effects. These patients were well controlled with oral flecainide, 200 to 300 mg/day, without side effects.**

**On the basis of these results, the efficacy of encainide and flecainide in the treatment of chronic ectopic atrial tachycardia appears to be not drug-specific but rather a general class IC property.**

***(J Am Coll Cardiol 1986;7:1121–6)***

Chronic ectopic atrial tachycardia is a rare rhythm disorder, especially in adults. Clinically, it may be intermittent, lasting for more than half of the day, or persistent, interrupted only by single sinus beats. It may have serious sequelae, such as cerebrovascular accident (1), congestive heart failure (2) and death (3). Congestive heart failure has been reported to be reversible when a marked slowing of tachycardia rate or even restoration of sinus rhythm can be achieved (2).

A great number of therapeutic regimens have been proposed for the treatment of chronic ectopic atrial tachycardia. Administration of antiarrhythmic drugs almost always fails to control the arrhythmia (2,4,5). Electrical cardioversion, programmed stimulation and overdrive pacing are ineffective because they suppress the focus for at most a few seconds (4,5). Promising new approaches in the treatment of these patients are surgical excision and transvenous catheter ablation of the focus (5). Both procedures may definitively cure the patient, but failures have been reported (5).

Recently, it has been shown that encainide, a class IC antiarrhythmic drug (6), is highly effective in patients with incessant supraventricular tachycardia (7). We studied the short- and long-term effects of two class IC antiarrhythmic agents, encainide and flecainide, in patients with chronic ectopic atrial tachycardia. Our aim was to elucidate whether a favorable effect of encainide on this arrhythmia is drug specific or due to a uniform response of ectopic activity to class IC antiarrhythmic drugs.

## Methods

**Clinical data.** Five patients (two men and three women) with a mean age of 37 years were studied (Table 1). All had symptomatic chronic ectopic atrial tachycardia. In each patient the arrhythmia had been refractory to at least four antiarrhythmic drugs, including amiodarone and verapamil. At the time of study all drugs had been withdrawn for at least three half-lives. Two-dimensional echocardiography showed an enlarged left ventricular end-diastolic diameter of 60 mm in Patient 3 and 65 mm in Patient 2, with moderately depressed global left ventricular contractility in both.

From the Department of Cardiology, University Hospital Eppendorf, Hamburg, West Germany. This work was supported by a grant from the Werner Otto-Stiftung, Hamburg.

Manuscript received August 20, 1985; revised manuscript received December 11, 1985, accepted December 26, 1985.

Address for reprints: Karl-Heinz Kuck, MD, Department of Cardiology, University Hospital Eppendorf, Martinistrasse 52, D-2000 Hamburg 20, West Germany.



0735-1097/86/$3.50

**Table 1.** Clinical Data in Five Patients With Chronic Ectopic Atrial Tachycardia

| Case | Age (yr) & sex | NYHA Functional Class | Cardiothoracic Ratio | Duration (yr) of Tachycardia |
|---|---|---|---|---|
| 1 | 48M | II | 0.4 | ≥ 5 |
| 2 | 45F | III | 0.6 | ≥ 20 |
| 3 | 23F | III | 0.6 | ≥ 7 |
| 4 | 48M | II | 0.4 | ≥ 11 |
| 5 | 22F | I | 0.5 | ≥ 18 |

NYHA = New York Heart Association.

These patients had a cardiothoracic ratio of 0.6 each; in all other patients no signs of organic heart disease were observed. Routine laboratory examinations revealed no abnormalities in any patient.

In all patients 12 lead electrocardiography, symptom-limited bicycle exercise testing according to a modified Bruce protocol and 24 hour ambulatory electrocardiographic (Holter) monitoring were performed before drug administration.

**Electrophysiologic study.** After informed written consent was obtained, an electrophysiologic study was performed according to a standard protocol (8). In each patient four catheters were passed through the femoral veins using the Seldinger technique. Quadripolar catheters were placed in the lateral high right atrium in all patients, in the coronary sinus in four and in the left atrium through a patent foramen ovale in one patient. Two bipolar catheters were positioned, one across the tricuspid valve to record the His bundle electrogram, and another in the apex of the right ventricle. A Siemens 16 channel electrocardiograph was used for continuous display and recording of the endocardial electrograms and of at least three body surface electrocardiograms at a paper speed of 100 mm/s. A Biotronik stimulator (ERA-S-HIS) was used to deliver rectangular pulses with a duration of 1 ms and a constant current of twice diastolic threshold.

In three patients with intermittent tachycardia (Cases 1, 4 and 5) single and double right and left atrial and right ventricular extrastimuli were delivered during sinus rhythm and at two different paced cycle lengths (510 and 440 ms). The right and left atria were also paced at increasing rates up to a maximal rate of 250 beats/min to induce tachycardia. If tachycardia could not be induced, isoproterenol was administered intravenously until ectopic atrial tachycardia occurred spontaneously or sinus rate had increased by 20%. When tachycardia had not occurred spontaneously during isoproterenol infusion, the stimulation protocol to induce tachycardia was repeated at the increased sinus rate.

During tachycardia, mapping was performed to localize the origin of ectopic atrial activity. Termination of tachycardia was attempted by single right and left atrial as well as right ventricular extrastimuli, which were introduced in 10 ms decrements after every eighth beat. In addition, both atria were paced for overdrive suppression at various rates exceeding the rate of tachycardia.

*Intravenous encainide.* During the electrophysiologic study patients received intravenous encainide at a rate of 10 mg/min until ectopic activity was completely suppressed or until a maximal dose of 2.0 mg/kg body weight was reached. Stimulation studies to initiate atrial tachycardia were then repeated as described earlier.

With one stimulation catheter remaining in the high right atrium after the initial study, all patients were restudied 2 days later in a drug-free state. If sinus rhythm was dominant, atrial tachycardia was induced as during the initial study. Then all patients received intravenous flecainide at a rate of 10 mg/min under continuous six lead ($V_1$ to $V_6$) electrocardiographic control until tachycardia was terminated or a maximal dose of 1.5 mg/kg was reached.

**Electrophysiologic data.** The electrocardiographic and electrophysiologic data of ectopic atrial tachycardia are listed in Tables 2 and 3. The electrophysiologically determined

**Table 2.** Long-Term Electrocardiographic, Exercise Electrocardiographic and Electrophysiologic Data in Five Patients With Chronic Ectopic Atrial Tachycardia

| Case | Chronic Ectopic Atrial Tachycardia: Long-Term ECG | Chronic Ectopic Atrial Tachycardia: Exercise ECG | Origin of Ectopic Activity | Mode of Initiation | Intravenous Dose Resulting in Termination of Tachycardia (mg/kg): Encainide | Intravenous Dose Resulting in Termination of Tachycardia (mg/kg): Flecainide |
|---|---|---|---|---|---|---|
| 1 | Intermittent | Inducible | LA: mid anterior septally | Spontaneous | 2.0 | 1.5 |
| 2 | Persistent | Persistent | RA: low posterior septally | Persistent | 1.5 | 1.5 |
| 3 | Persistent | Persistent | RA: mid anterior septally | Persistent | 0.3 | 0.5 |
| 4 | Intermittent | Inducible | RA: low posterior septally | Spontaneous, i.v. isoproterenol | 1.0 | 1.0 |
| 5 | Intermittent | Not inducible | RA: low mid septally | Spontaneous, rapid atrial pacing | 1.0 | 1.5 |

ECG = electrocardiogram; i.v. = intravenous; LA = left atrium; RA = right atrium.

**Table 3.** Conduction Intervals During Chronic Ectopic Atrial Tachycardia in Five Patients

| Case | CL (ms) | Interval (ms) | | | | |
|---|---|---|---|---|---|---|
| | | PQ | QRS | QT | AH | HV |
| 1 | 530 | 115 | 85 | 305 | 70 | 35 |
| 2 | 440 | 115 | 105 | 360 | 60 | 45 |
| 3 | 440 | 115/210* | 95 | 320 | 100/230* | 35 |
| 4 | 310 | 150 | 100 | 320 | 90 | 50 |
| 5 | 530 | 150 | 90 | 310 | 100 | 60 |

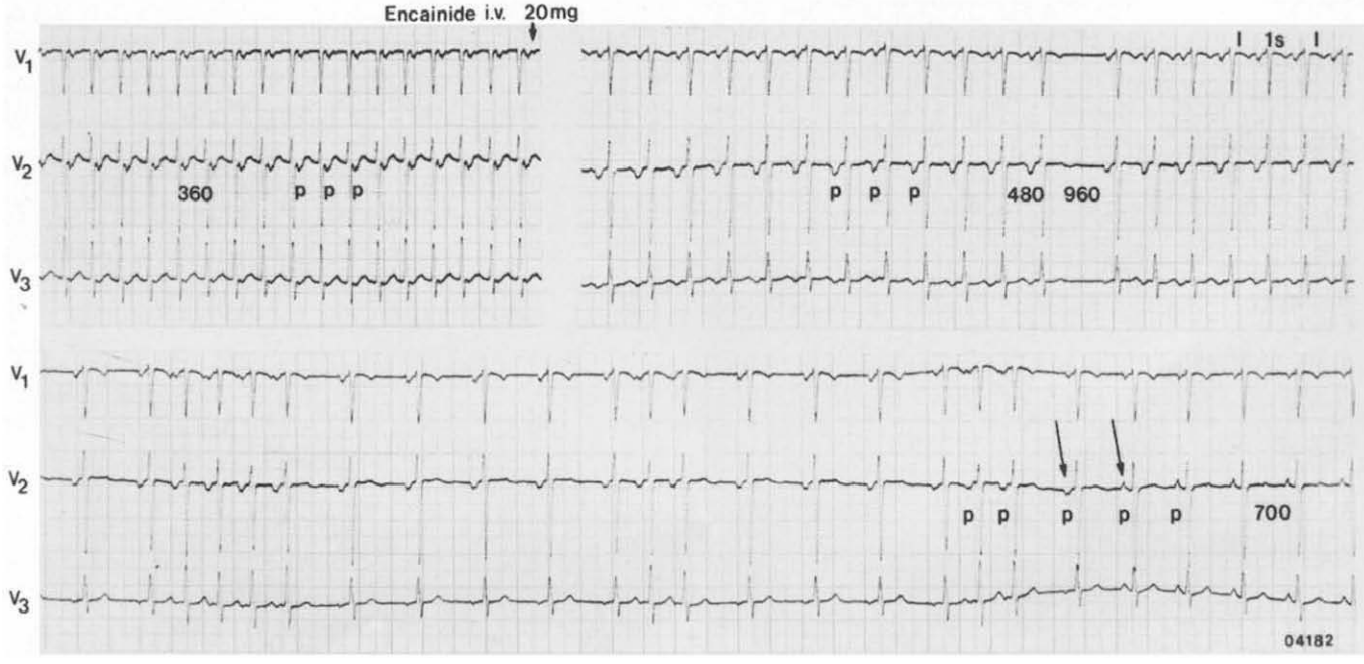
*This patient had dual atrioventricular nodal pathways in anterograde direction. CL = mean cycle length.

origin of tachycardia was always in concordance with P wave configuration in the surface electrocardiogram (9). Patient 3 had dual atrioventricular (AV) nodal pathways in the anterograde direction, responsible for changes of the PR/RP interval relation during tachycardia (Fig. 1 to 3). In Patient 5 intermittent AV nodal block occurred with perpetuation of tachycardia on the atrial level. In all patients the first tachycardia beat showed an atrial activation sequence identical to that of the subsequent tachycardia beats. In patients with intermittent tachycardia the arrhythmia could not be induced by single or double atrial or ventricular extrastimuli. In Patient 5 it was initiated by stimulation at increasing rates, and in Patient 4 tachycardia was observed after intravenous administration of isoproterenol.

During tachycardia, single atrial extrastimuli introduced at decreasing coupling intervals were followed by an atrial cycle that became progressively shorter than compensatory. The atria could never be activated retrogradely by a single ventricular extrastimulus delivered at the time of refractoriness of the bundle of His, during either sinus rhythm or tachycardia. In all patients atrial pacing at rates exceeding the tachycardia rate captured the atria, yet on termination of pacing the tachycardia immediately resumed without an intervening sinus beat. Termination could not be achieved by programmed stimulation from the atria or the right ventricle in any patient.

**Follow-up with oral encainide or flecainide.** All patients were discharged receiving oral encainide at a dose of 150 mg/day. Four weeks after initiation of this medication

**Figure 1.** Patient 3. Three lead electrocardiogram ($V_1$, $V_2$, $V_3$) of ectopic atrial tachycardia. **Upper left panel**, Ectopic atrial tachycardia at a cycle length of 360 ms with a PR interval greater than the RP interval. **Upper right** and **lower panels**, Continuous recording during encainide injection. After administration of 20 mg intravenously (i.v.), tachycardia cycle length increased to 480 ms, associated with a PR interval less than the RP interval due to a change in anterograde conduction from a slow to a fast atrioventricular nodal pathway. Note the sudden change of tachycardia cycle length from 480 to 960 ms, suggesting 2:1 exit block of the ectopic focus. P wave configuration remained constant until a stable sinus rhythm at a cycle length of 700 ms was reestablished (**arrows** indicate change in P wave configuration).



JACC Vol 7, No 5
May 1986 1121–6

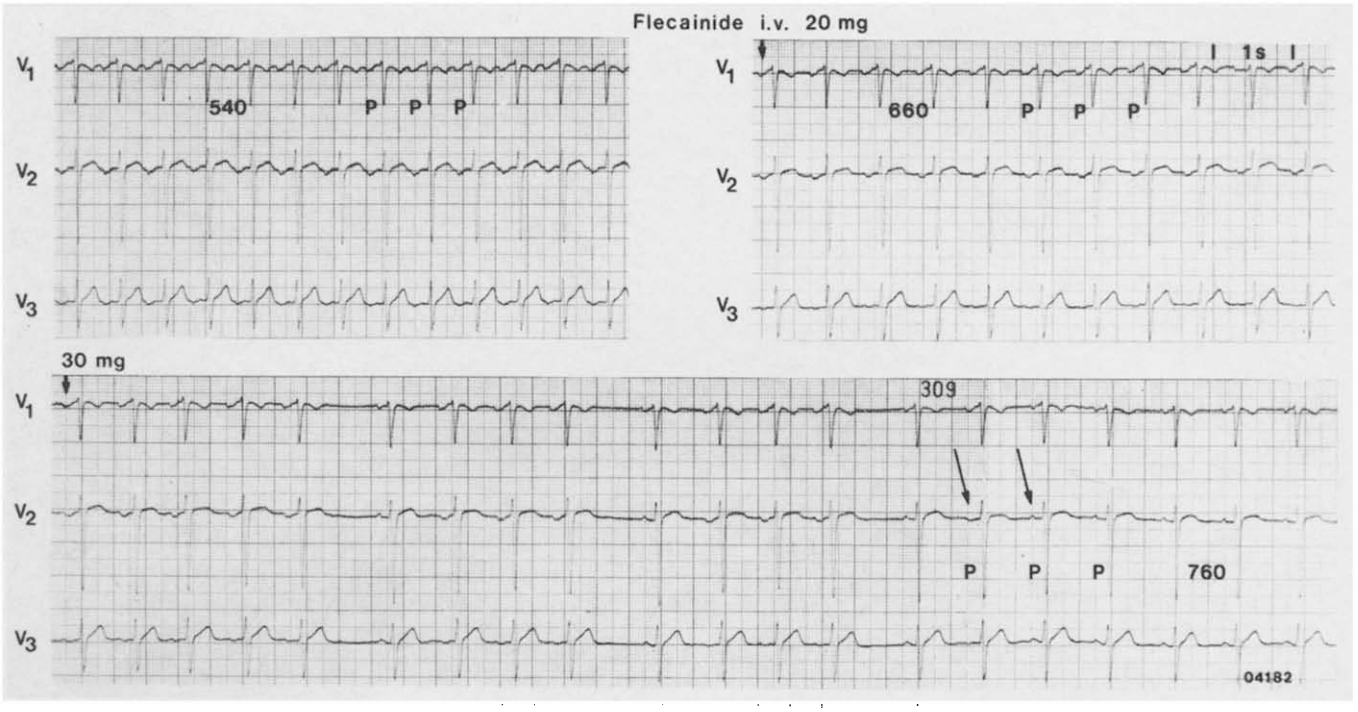



**Figure 2.** Patient 3. Three lead electrocardiogram ($V_1$, $V_2$, $V_3$) of ectopic atrial tachycardia. **Upper left panel**, Ectopic atrial tachycardia at a cycle length of 540 ms showing a PR interval less than the RP interval. **Upper right panel**, After intravenous (i.v.) injection of 20 mg of flecainide, tachycardia cycle length had increased to 660 ms. **Lower panel**, After administration of 30 mg of flecainide, tachycardia is interrupted by single sinus beats before restoration of a regular sinus rhythm at a cycle length of 760 ms (**arrows** indicate change in P wave configuration).

and every 3 months during the follow-up period, 12 lead electrocardiography, exercise testing, 24 hour Holter monitoring and routine laboratory examinations were performed. Oral drug therapy was considered to be effective if ectopic atrial tachycardia was not inducible by exercise testing and 24 hour Holter monitoring showed a reduction in duration of ectopic activity to less than 10% of the day. If the dose of 150 mg/day proved ineffective, it was increased to a maximum of 225 mg/day. Three patients (Cases 1, 3 and 5) were treated with oral flecainide, 200 mg/day, after oral encainide was withdrawn because of intolerable side effects. If this dose was ineffective, it was changed to 300 mg/day. Follow-up visits were performed as during oral encainide therapy.

## Results

**Effect of intravenous encainide on chronic ectopic atrial tachycardia.** In all patients intravenous administration of encainide initially led to a gradual increase of tachycardia cycle length before sinus rhythm emerged. In patients 1 and 3 a 2:1 exit block occurred immediately before the onset of sinus rhythm (Fig. 1). The doses necessary for termination ranged from 0.3 to 1.5 mg/kg (Table 2). After drug administration ectopic tachycardia was not inducible.

**Effect of oral encainide on chronic ectopic atrial tachycardia.** During a mean follow-up period of 8 ± 3 months, two patients (Cases 2 and 4) tolerated oral encainide without side effects and showed no recurrence of ectopic atrial tachycardia. In Patient 1 the dose of 150 mg/day was reduced after 2 weeks of treatment to 100 mg/day because of headache and nightmares, which the patient related to encainide ingestion. At a control visit he complained of palpitation. Holter monitoring showed recurrences of tachycardia lasting for maximally 30 minutes, and tachycardia was still inducible on exercise testing. Oral encainide therapy was therefore discontinued. In Patients 3 and 5 encainide, 150 mg/day, completely suppressed ectopic atrial tachycardia (Fig. 2), but both patients complained of intolerable orthostasis and blurred vision. Because of these side effects the drug was withdrawn.

**Effect of intravenous flecainide on chronic ectopic atrial tachycardia.** In all patients flecainide, at a dose ranging from 0.5 to 1.5 mg/kg (Table 2), led to a gradual slowing of tachycardia rate before a stable sinus rhythm was reestablished and ectopic activity was completely suppressed (Fig. 3).

**Effect of oral flecainide on chronic ectopic atrial tachycardia.** Three patients (Cases 1, 3 and 5) received oral flecainide during a mean follow-up period of 7 ± 5 months. In Patient 1 a dose of 200 mg/day reduced the

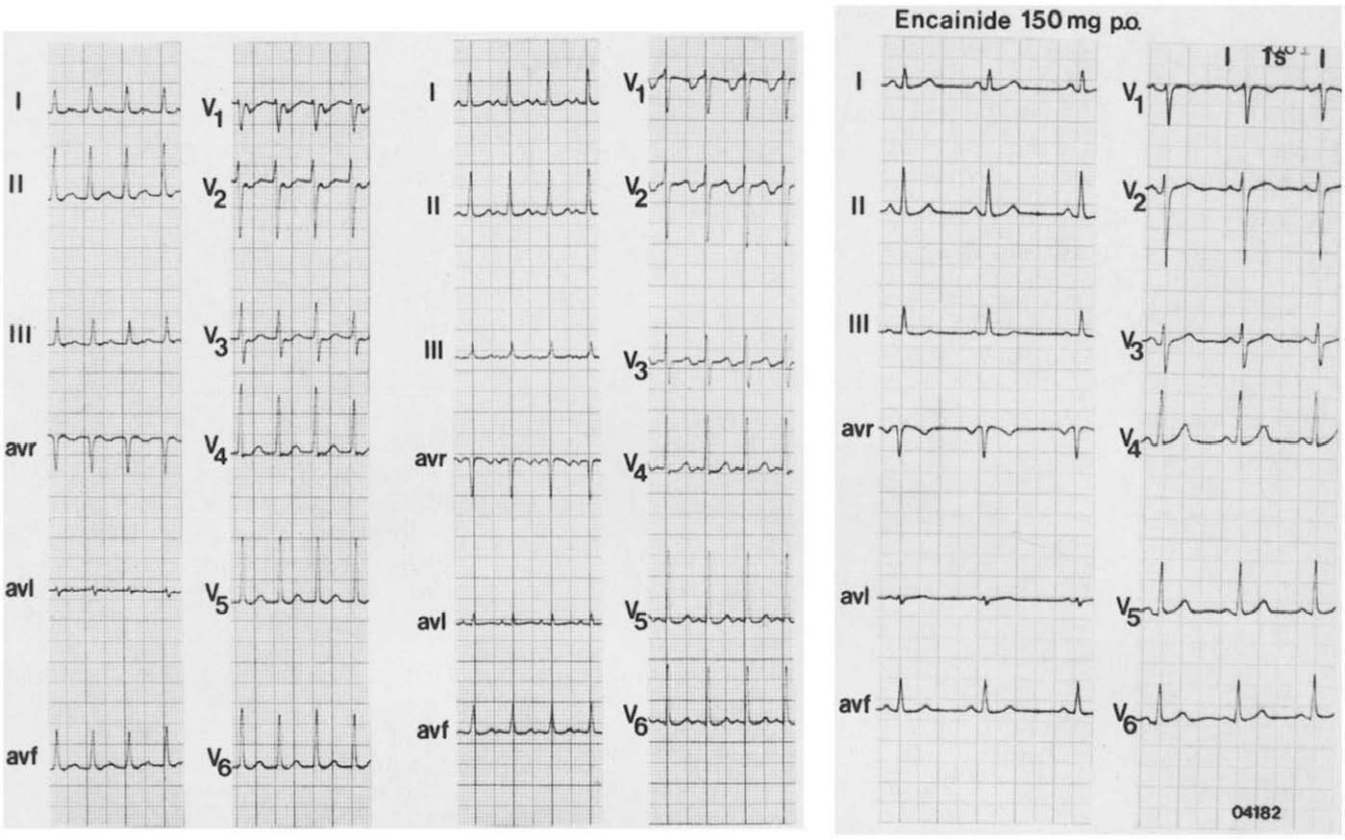



**Figure 3.** Patient 3. Twelve lead electrocardiograms before and during oral (p.o.) encainide therapy at a dose of 150 mg/day. The electrocardiograms show the same ectopic atrial tachycardia with a PR interval greater than the RP interval (**left panels**) or with a PR interval less than the RP interval (**middle panels**). See text for explanation. Sinus rhythm is shown in the **right panels** (note change of P wave configuration).

duration of ectopic activity from 70 to 40% of the day, as shown by Holter monitoring. Atrial tachycardia was still inducible by exercise testing. After an increase of the dose to 300 mg/day only short episodes of tachycardia with a maximal duration of 2 minutes were observed on Holter monitoring. Clinically, the patient was free of symptoms. Oral flecainide, 200 mg/day, successfully inhibited palpitation in Patient 3. The Holter electrocardiogram showed occasional short runs of tachycardia lasting up to 30 seconds. However, ectopic activity recurred 9 to 10 hours after drug ingestion. Tachycardia was not inducible by exercise testing. This patient, who was initially in New York Heart Association functional class III, improved to class II. Patient 5 did not have any recurrences of atrial tachycardia at an oral dose of flecainide, 200 mg/day. Drug-related side effects were not observed with oral flecainide therapy.

## Discussion

**Differential diagnosis.** The diagnosis of chronic ectopic atrial tachycardia in our patients was based on the electrocardiographic and electrophysiologic data listed earlier. In the differential diagnosis of a supraventricular tachycardia showing a PR interval shorter than the RP interval, AV nodal tachycardia of the "fast-slow" type or AV reciprocating tachycardia using retrogradely an accessory pathway with a long conduction time must be considered. However, apart from the positive findings for atrial tachycardia, none of our patients met the criteria for intranodal or extranodal reentrant tachycardia (10,11).

**Efficacy of encainide and flecainide.** In our five patients, the class IC agents encainide and flecainide, administered intravenously as well as orally, effectively suppressed chronic ectopic atrial tachycardia. Recently it was shown in a large number of patients that encainide terminated incessant supraventricular tachycardia due to a variety of mechanisms and originating from various sites (7). In two of these patients, each with atrial tachycardia, both intravenous and oral encainide were successful in terminating and preventing the arrhythmia. Our data support the efficacy of encainide in such patients, who are known to be refractory to the majority of antiarrhythmic drugs.

In a patient with incessant atrial tachycardia occurring after successful cryoablation of a left-sided accessory pathway, flecainide suppressed ectopic activity (12). In our study

JACC Vol 7, No 5
May 1986:1121–6

flecainide proved to be as effective as encainide in the treatment of this arrhythmia. We may therefore infer that the beneficial effect on chronic ectopic tachycardia of both drugs is not drug specific but a general response to class IC antiarrhythmic properties. Class IC agents have been shown to slow phase zero of the action potential, but have little or no effect on its duration (13).

**Mechanism of drug action.** Encainide as well as flecainide have been reported to depress automaticity of ectopic pacemakers significantly in in vitro studies (13,14). Suppression of ectopic atrial automaticity may also explain the efficacy of these drugs in patients with chronic ectopic atrial tachycardia. The increase in tachycardia cycle length during intravenous drug administration may give evidence for a direct effect on automaticity. Another drug mechanism that may also be in effect is exit block formation between the ectopic focus and the adjacent atrial tissue. During intravenous injection of encainide in two patients, a sudden increase of tachycardia cycle length to twice the previous value was observed. This observation is more consistent with the occurrence of a 2:1 exit block than with a depression of automaticity.

**Side effects.** Side effects have been observed with oral encainide therapy (7,8). Two of our five patients developed blurred vision, headache and orthostasis, necessitating the discontinuation of encainide therapy. Another patient complained of frequent nightmares that disappeared after withdrawal of the drug. The high incidence in our patients of intolerable encainide-related side effects, despite commonly used dosage, is not understood. All three patients received flecainide, which was well tolerated by all. Previously unrecognized atrial or ventricular arrhythmias were not induced by either drug.

**Clinical implications.** Chronic ectopic atrial tachycardia is a rare rhythm disorder that may have serious sequelae. The therapeutic efficacy of encainide and flecainide shown by our study is of clinical importance to patients with this disorder, and indicates that medical treatment with class IC drugs in such patients offers an alternative to surgery or catheter ablation.

## References

1. Shachnow N, Spellman S, Rubin I. Persistent supraventricular tachycardia. Circulation 1954;10:232–6.
2. Packer D, Bardy GH, Gallagher JJ, Worley SJ, Smith MS, German LD. Tachycardia induced cardiomyopathy: a reversible form of left ventricular dysfunction (abstr). J Am Coll Cardiol 1984;3:521.
3. Keane JF, Plauth WH, Nadas AS. Chronic ectopic tachycardia of infancy and childhood. Am Heart J 1972;84:748–57.
4. Gillette PC, Garson A. Electrophysiologic and pharmacologic characteristics of automatic ectopic atrial tachycardia. Circulation 1977; 56:571–5.
5. Gillette PC, Wampler DG, Garson A, Zinner A, Ott D, Cooley D. Treatment of atrial automatic tachycardia by ablation procedures. J Am Coll Cardiol 1985;6:405–9.
6. Harrison DC, Winkle RA, Sami M, Mason JW. Encainide: a new and potent antiarrhythmic agent. In: Harrison DC, ed. Cardiac Arrhythmias. A Decade of Progress. Boston: G. K. Hall Medical Publishers, 1981:315–30.
7. Brugada P, Abdollah H, Wellens HJJ. Suppression of incessant supraventricular tachycardia by intravenous and oral encainide. J Am Coll Cardiol 1984;4:1255–60.
8. Kunze KP, Kuck KH, Schlüter M, Kuch B, Bleifeld W. Electrophysiologic and clinical effects of intravenous and oral encainide in accessory atrioventricular pathway. Am J Cardiol 1984;54:323–9.
9. MacLean WAH, Karp RB, Kouchoukos NT, James TN, Waldo AL. P waves during ectopic atrial rhythms in man. A study utilizing atrial pacing with fixed electrodes. Circulation 1975;52:426–34.
10. Brugada P, Bär FWHM, Vanagt EJ, Friedman PL, Wellens HJJ. Observations in patients showing A-V junctional echoes with a shorter P-R than R-P interval. Distinction between intranodal reentry or reentry using an accessory pathway with a long conduction time. Am J Cardiol 1981;48:611–22.
11. Brugada P, Farre J, Heddle B, Roy D, Wellens HJJ. Observations in patients showing a supraventricular tachycardia with a shorter P-R than R-P interval. Distinction between atrial tachycardia or tachycardia using an accessory pathway with long conduction time. In: Brugada P, ed. New Observations on the Role of the A-V Junction in Tachycardias in Man. Schrijen-Lippertz BV, 1982:99–117.
12. Creamer JE, Nathan AW, Camm AJ. Successful treatment of atrial tachycardias with flecainide acetate. Br Heart J 1985;53:164–6.
13. Gibson JK, Somani PB, Bassett AL. Electrophysiologic effects of encainide (MJ 9067) on canine Purkinje fibres. Eur J Pharmacol 1978;52:161–9.
14. Hodess AB, Follansbee WP, Spear JF, Moore EN. Electrophysiological effects of a new antiarrhythmic agent, flecainide, on the intact canine heart. J Cardiovasc Pharmacol 1979;1:427–39.