Favorable Effects of Flecainide in Transvenous Internal Cardioversion of Atrial Fibrillation

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OBJECTIVES
The aim of the study was to evaluate the effects of intravenous (IV) flecainide on defibrillation energy requirements in patients treated with low-energy internal atrial cardioversion.

BACKGROUND
Internal cardioversion of atrial fibrillation is becoming a more widely accepted therapy for acute episode termination and for implantable atrial defibrillators.

METHODS
Twenty-four patients with atrial fibrillation (19 persistent, 5 paroxysmal) underwent elective transvenous cardioversion according to a step-up protocol. After successful conversion in a drug-free state, atrial fibrillation was induced by atrial pacing; IV flecainide (2 mg/kg) was administered and a second threshold was determined. In patients in whom cardioversion in a drug-free state failed notwithstanding a 400- to 550-V shock, a threshold determination was attempted after flecainide.

RESULTS
Chronic persistent atrial fibrillation was converted in 13/19 (68%) patients at baseline and in 16/19 (84%) patients after flecainide. Paroxysmal atrial fibrillation was successfully cardioverted in all the patients. A favorable effect of flecainide was observed either in chronic persistent atrial fibrillation (13 patients) or in paroxysmal atrial fibrillation (5 patients) with significant reductions in energy requirements for effective defibrillation (persistent atrial fibrillation: $4.42 \pm 1.37$ to $3.50 \pm 1.51$ J, $p < 0.005$; paroxysmal atrial fibrillation: $1.68 \pm 0.29$ to $0.84 \pm 0.26$ J, $p < 0.01$). In 14 patients not requiring sedation, the favorable effects of flecainide on defibrillation threshold resulted in a significant reduction in the scores of shock-induced discomfort ($3.71 \pm 0.83$ vs. $4.29 \pm 0.61$, $p < 0.005$). No ventricular proarrhythmia was observed for any shock.

CONCLUSIONS
Intravenous flecainide reduces atrial defibrillation threshold in patients treated with low-energy internal atrial cardioversion. This reduction in threshold results in lower shock-induced discomfort. Additionally, flecainide may increase the procedure success rate in patients with chronic persistent atrial fibrillation. (J Am Coll Cardiol 1999;33:333–41) © 1999 by the American College of Cardiology

Internal cardioversion of atrial fibrillation can be performed at relatively low energies by delivering biphasic shocks through transvenous catheters positioned in right atrium and coronary sinus or left pulmonary artery (1–3). This procedure has been studied in animal models (4,5), and more recently both its efficacy and safety have been evaluated in patients with paroxysmal or chronic atrial fibrillation (1–3,6,7).

Antiarrhythmic drugs may influence defibrillation energy requirements for atrial cardioversion, although conflicting reports of drug effect on conventional transthoracic cardioversion have been published (8–13). More recently the effects of sotalol have been evaluated in patients treated with transvenous low-energy internal atrial cardioversion (14).

The aim of this study was to investigate the effects of intravenous (IV) flecainide on defibrillation energy requirements in a series of patients with atrial fibrillation treated by elective internal atrial cardioversion, evaluating the potential clinical usefulness of this drug and its safety profile.

METHODS
Patients enrolled in this study fulfilled the following selection criteria, according to a recent classification of atrial fibrillation (15): 1) patients with a history of chronic paroxysmal atrial fibrillation, with arrhythmia episodes lasting more than 3 days, undergoing electrophysiologic study for atrial fibrillation mechanism evaluation; 2) patients with a history of chronic atrial fibrillation in the persistent form where the arrhythmia persisted for at least 1 week. Arrhythmia onset was documented by electrocardiographic (ECG) recordings or by an abrupt onset of palpitations with subsequent ECG evidence of atrial fibrillation.

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Patients were excluded for the following criteria: age >80 years; heart failure, New York Heart Association (NYHA) class IV; left ventricular ejection fraction <40%; mean ventricular rate during atrial fibrillation <45 beats/min; recent (<6 months) myocardial infarction; unstable angina pectoris; ECG evidence (presence or past) of ventricular preexcitation or complete bundle branch block; previous ECG evidence of second or third degree atrioventricular block or bifascicular block; sick sinus syndrome; hypokalemia (potassium <3.5 mEq/L); severe renal or hepatic failure and severe hypoxia (partial pressure of oxygen <55 mm Hg). The study protocol was approved by our local ethics committee and all patients gave informed consent. The anticoagulation guidelines of the American College of Chest Physicians (16) were followed. Therefore, patients with atrial fibrillation lasting more than 72 h were enrolled into the study only if they received oral warfarin treatment for at least 3 to 4 weeks with an INR (international normalized ratio) in the therapeutic range (2.0 to 3.5). The procedure was performed after an antiarrhythmic drugs (including digoxin) washout period of at least 5 half-lives.

Electrophysiological study and atrial cardioversion. In the electrophysiology laboratory, catheters were positioned under fluoroscopy. Two identical 6F decapolar catheters (Electro Catheter), each with a total electrode surface area of 2.83 cm² and an electrode length of 6 cm, were inserted through left subclavian vein puncture and right femoral vein puncture for positioning into the coronary sinus and the anterolateral right atrial wall, respectively (Fig. 1). When access into the coronary sinus was unsuccessful after several attempts, the catheter was alternatively positioned in the left pulmonary artery (1). Additionally, a 6F quadripolar catheter was advanced from a femoral vein and positioned in the right ventricular apex to provide accurate R-wave synchronization and back-up ventricular pacing, if required. The decapolar defibrillation catheters were connected to an external atrial defibrillator (right atrium negative, left atrium positive). In 11 patients a Telectronics 4510 defibrillator (capacitor 120 µF) and in 13 patients a XAD defibrillator (InControl) (capacitor 90 µF) were employed. With both devices, biphasic truncated exponential shocks were delivered with two phases of 3-ms duration each. Leading-edge voltage was programmed between 20 and 400 V (up to 550 V, if necessary, when using the Telectronics device). For safety reasons, shocks were delivered only after RR intervals between 500 and 1000 ms (5).

After delivery of a test shock of 20 to 50 V to verify proper R-wave synchronization, shocks were delivered in the following sequence, with a 1-min interval between shocks: 50 V, 100 V, 120 V, 150 V, 180 V, and then further increases by steps of 40 V in patients with paroxysmal atrial fibrillation; 100 V, 150 V, 180 V, and then further increases by steps of 40 V in patients with chronic persistent atrial fibrillation up to 400 V, and then 450 V, 500 V and 550 V.

We considered a shock successful if stable sinus rhythm was restored within 3 s of a shock. In this case the sequence of shocks was terminated. Cardiac rhythm was continuously monitored during the procedure and surface ECG was recorded to paper during shock delivery.

Premedication or sedation was not routinely administered before or during the procedure; rather, shock-induced discomfort was monitored after each shock, and sedation, or general anesthesia, was administered at patient’s request. After each shock patients were requested to report the tolerability of shock-induced discomfort (scale: 1 = shock not felt; 2 = shock felt, no discomfort; 3 = mild discomfort; 4 = moderate discomfort; 5 = severe discomfort) and were given the option of requesting sedation, or anesthesia, if discomfort was intolerable.

Atrial cardioversion retesting after flecainide. Flecainide acetate was infused intravenously during 15 min (dose of 2 mg/kg), under ECG monitoring. Cuff blood pressure was checked every 5 min. In patients with successful cardioversion at baseline, atrial fibrillation was reinduced by atrial pacing, intravenous (IV) flecainide was administered and a new series of shocks was delivered 30 min after infusion end (shock delivery began with a leading-edge voltage 80 V less than the previous effective shock voltage). In patients with unsuccessful cardioversion at baseline, after shocks at maximal output had been tested twice, IV flecainide was administered and a new series of shocks was delivered after 30 min. Figure 2 shows the protocol employed in the series of patients not submitted to atrial cardioversion retesting in drug-free conditions.

Atrial cardioversion retesting in drug-free conditions. In 10 consecutive patients (the first 2 with paroxysmal and the first 8 with chronic persistent atrial fibrillation), following atrial cardioversion of baseline atrial fibrillation, atrial fibrillation was reinduced by atrial pacing (atrial extrastimuli or atrial bursts), and after induction of an atrial fibrillation
lasting 30 min a new series of shocks was tested for assessing the reproducibility of effective shocks in a drug-free condition. In the second series of shocks the same protocol employed after flecainide administration was used (shock delivery began with a leading-edge voltage 80 V less than the previous effective shock voltage). The same patients were subsequently submitted to flecainide administration and atrial cardioversion retesting as the other patients. Figure 3 shows the protocol employed in this series of 10 patients, submitted to atrial cardioversion retesting in drug-free conditions.

Analysis of ECG and electrophysiological changes. During atrial fibrillation, intracardiac electrograms were recorded at 100 mm/s (Mingograph 7, Siemens Elema) from high right atrium (HRA) and coronary sinus (CS) with a filter setting between 30 and 500 Hz and the mean value of 100 consecutive FF intervals (mean FF) was calculated before atrial cardioversion, at baseline and after flecainide administration (17). In the same samples mean RR intervals were calculated. The QRS intervals width was measured in five consecutive intervals and averaged before atrial cardioversion, at baseline and after flecainide administration, immediately before delivery of shocks.

Results

Patients. Overall, 24 patients entered the study: 5 patients had paroxysmal atrial fibrillation, and sustained atrial fibrillation was induced during the electrophysiological study by atrial pacing (1 to 3 extrastimuli or atrial bursts) and 19 patients had chronic persistent atrial fibrillation (mean arrhythmia duration 8.5 ± 9.9 months, range 3 to 48). Patient characteristics (clinical and demographic variables) are reported in Table 1.

Efficacy of atrial cardioversion. Overall successful cardioversion was obtained at baseline in 18 patients (75%): in all 5 patients with paroxysmal atrial fibrillation and in 13 of the patients with chronic persistent atrial fibrillation (68%). The effects of IV flecainide were tested on a reinduced atrial fibrillation in 15 patients (10 with chronic and 5 with paroxysmal atrial fibrillation), on a spontaneous early recurrence of atrial fibrillation in 3 patients (all with previous persistent atrial fibrillation) and on the same arrhythmia, for unsuccessful conversion at baseline, in 6 patients.

Following flecainide, successful cardioversion was obtained in 21 patients (88%); all the patients successfully converted at baseline were also converted after flecainide, whereas 3 out of 6 nonresponder patients with persistent atrial fibrillation were successfully converted to sinus rhythm only after flecainide. Shocks were delivered between right atrial and coronary sinus electrodes in 22 patients; in 2 patients, shocks were delivered between right atrium and left pulmonary artery. In these two patients successful cardioversion was obtained both at baseline (leading-edge voltage 340 and 260 V, respectively) and after flecainide (leading-edge voltage 340 and 220 V, respectively). Overall, 183 shocks were delivered at baseline and 65 after flecainide (mean 7.6 ± 1.7 and 2.7 ± 1.1 shocks per patient, respectively).

Effects of flecainide on defibrillation energy requirements. In the 18 patients with successful cardioversion at baseline, in drug-free conditions (13 with persistent and 5 with paroxysmal atrial fibrillation), the mean leading-edge voltage of successful shocks was 283 ± 72 V (range 150 to

Serum flecainide concentrations. Blood samples of 5 ml were taken 15 and 30 min after the end of flecainide infusion. Serum flecainide concentrations were determined by fluorescence polarization immunoassay (18). The normal range of flecainide concentrations is between 200 and 1000 ng/ml (19).

Statistical analysis. Continuous variables were compared using Student t test for paired data; discrete variables were compared using chi-square analysis of contingency tables. Statistical significance was achieved at p < 0.05. Data on patients submitted to cardioversion at baseline, after rein-duction in drug-free conditions, and after flecainide were analyzed by one-way analysis of variance (ANOVA) and then by Bonferroni t test.
mean delivered energy was 3.66 ± 1.71 J (range 1.2 to 6.7 J) and mean shock impedance was 49.6 ohms (range 36 to 63 ohms). In the same patients the mean leading-edge voltage of successful shocks after flecainide administration was 241 ± 86 V (range 100 to 400 V) (p < 0.001 vs. baseline), mean delivered energy was 2.76 ± 1.77 J (range 0.6 to 6.3 J) (p < 0.001 vs. baseline) and mean shock impedance was 50 ± 6 (range 36 to 63). In Figure 4, individual values of voltage and corresponding energies at baseline and after flecainide are shown. In only one patient was an increase observed in voltage and energy of successful shock following flecainide infusion.

In the 13 patients with persistent atrial fibrillation, shocks delivered after flecainide resulted successful at lower voltages (284 ± 54 vs. 321 ± 38 V, p < 0.005) and lower energies compared to baseline cardioversion (3.50 ± 1.51 vs. 4.42 ± 1.37 J, p < 0.005). Even in the subgroup of five patients with paroxysmal atrial fibrillation, shocks delivered after flecainide resulted successful at lower voltages (130 ± 34 vs. 184 ± 27 V, p < 0.005) and lower energies compared to baseline cardioversion (0.84 ± 0.26 vs. 1.68 ± 0.29 J, p < 0.01). In the three patients who resulted to be nonresponders at baseline (lack of cardioversion at 400 V), who were successfully converted to sinus rhythm only after flecainide, leading-edge voltage was 400 V for successful shocks and 400 V for previous ineffective shocks at baseline, and delivered energy was 6.00 ± 0.17 J for successful shocks and 6.10 ± 0.10 J for previous ineffective shocks at baseline.

Sedation was required in six patients (25%) at baseline and after flecainide administration. In the other 18 patients sedation was not required at baseline nor after flecainide. In patients not requiring sedation and with successful conversion either at baseline and after flecainide (14 patients), the reduction in leading-edge voltage and delivered energy of effective shocks obtained after flecainide (278 ± 74 to 235 ± 91 V, p < 0.001 and 3.69 ± 1.83 to 2.76 ± 1.94 J, p < 0.002) was associated with a significant reduction in reported subjective score for shock-induced discomfort (4.29 ± 0.61 to 3.71 ± 0.83, p < 0.005).

**Reproducibility of effective shocks and effects of flecainide.** Data concerning effective shocks in the group of 10 patients (2 with paroxysmal atrial fibrillation, 8 with chronic persistent atrial fibrillation) submitted to atrial cardioversion at baseline, after atrial fibrillation reinduction in a drug-free condition, and after flecainide are reported in Table 2.
flecainide, conversion to sinus rhythm was obtained at significantly lower leading-edge voltage and delivered energy compared to baseline, while no statistically significant differences were found in these parameters between baseline cardioversion and repeated cardioversion in a drug-free state (Table 2).

Electrocardiographic and electrophysiological changes. The effects of flecainide on mean FF intervals, mean RR and QRS width are shown in Table 3. After flecainide, mean FF intervals lengthened significantly either in high right atrium (HRA) or coronary sinus (CS) (Fig. 5) and the average change was +56.5% in HRA (range 12% to 100%) and +58.5% in CS (range 22% to 91%).

The sinus pause at sinus rhythm resumption was 994 ± 432 ms in basal conditions (18 patients) and 1452 ± 810 ms after flecainide (21 patients). In the 18 patients with successful cardioversion either at baseline or after flecainide, a significant lengthening of sinus pause at sinus rhythm resumption was observed (Table 3).

Serum flecainide concentrations. Mean serum flecainide concentrations were 1335 ± 550 (range 500 to 2000) ng/ml after 15 min and 455 ± 177 (range 250 to 800) ng/ml 30 min after IV infusion.

Adverse effects. No ventricular arrhythmia was observed after atrial cardioversion, either at baseline or after flecainide. Transient bradycardia requiring support ventricular pacing was observed in two patients. In no patient, pauses >3 s were observed at sinus rhythm resumption, at baseline cardioversion or after flecainide. Two patients had transient, asymptomatic hypotension after flecainide infusion, and one patient reported transient dizziness and lightheadedness in absence of rhythm abnormalities.

DISCUSSION
This is the first study showing that IV flecainide may reduce energy requirements in transvenous low-energy atrial cardioversion, without significant adverse effects. This reduction in defibrillation requirements may be associated with

![Figure 4.](image)

**Figure 4.** Leading-edge voltage (top) and delivered energy (bottom) for effective shocks in patients with paroxysmal or persistent atrial fibrillation (AF) at baseline and after flecainide administration.

### Table 2. Data on Effective Shocks in the Group of 10 Patients Submitted to Atrial Cardioversion at Baseline, After Atrial Fibrillation Reinduction in a Drug-Free Condition and After Flecainide

<table>
<thead>
<tr>
<th>Pt. Number</th>
<th>Leading-Edge Voltage (volts)</th>
<th>Delivered Energy (joules)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline AF</td>
<td>Reinduced AF</td>
</tr>
<tr>
<td>1</td>
<td>120</td>
<td>140</td>
</tr>
<tr>
<td>2</td>
<td>180</td>
<td>140</td>
</tr>
<tr>
<td>6</td>
<td>340</td>
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<tr>
<td>7</td>
<td>260</td>
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<td>13</td>
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<td>Mean</td>
<td>272</td>
<td>264</td>
</tr>
<tr>
<td>SD</td>
<td>70</td>
<td>71</td>
</tr>
</tbody>
</table>

*p < 0.05 vs. baseline AF. †p < 0.05 vs. reinduced AF.
AF = atrial fibrillation.
either an increase in defibrillation efficacy or patient tolerance or both.

Preliminary data showed reduction in defibrillating energies with IV sotalol in humans (14), a finding not confirmed in another animal study (20), and with IV procainamide in animals (20). No significant changes in atrial defibrillation threshold have been reported for flecainide in the canine sterile pericarditis model (21). No data are available in the literature on the effects of a class 1C drug administered during internal low-energy cardioversion of atrial fibrillation in humans, despite the fact that flecainide and propafenone are the most effective agents, apart from amiodarone, in terminating recent-onset atrial fibrillation (22–24) and in preventing paroxysmal atrial fibrillation recurrences (25,26).

In ventricular defibrillation, flecainide and encainide increased defibrillation energy requirements (27,28) and conflicting data were reported on propafenone in animal studies (29,30). The use of class 1C agents is usually avoided in patients with ventricular tachyarrhythmias (31).

Van Gelder et al. (10) evaluated the effects of an IV loading of flecainide in a randomized placebo-controlled study performed on patients with long-standing atrial fibrillation, who submitted to conventional transthoracic cardioversion; the authors described a trend toward an increase in defibrillation energy requirements in drug-treated patients, who more often required shocks at relatively high energies (200 or 400 J). In an observational study (32), patients with chronic atrial fibrillation treated with oral flecainide required higher energies for successful transthoracic cardioversion, in comparison with patients treated with class 1A drugs or with amiodarone, but the success rate of cardioversion was the same in all the groups.

In the present report, IV flecainide significantly reduced cardioversion energy requirements: the percent reduction in mean delivered energy was 50% in paroxysmal atrial fibrillation and 21% in chronic persistent atrial fibrillation and associated reductions in leading-edge voltage were 29% and 12%, respectively. Moreover, in half the patients with persistent atrial fibrillation resistant to cardioversion at baseline, conversion to sinus rhythm was achieved after drug infusion. Energy requirements for atrial cardioversion were reproducible in the drug-free state, after atrial fibrillation reinduction, and only after flecainide administration was a significant reduction in energy requirements compared to baseline found, thus excluding a potential bias due to lack of reproducibility.

The favorable effects of IV flecainide on defibrillation energy requirements were associated with a marked increase in mean FF intervals, either in HRA or CS (Fig. 5), as a result of flecainide pharmacodynamic effects (33). A lengthening of mean FF intervals usually implies a reduction in the number of circulating wavelets in the atria (34,35), thus leading to a more organized arrhythmia where interruption may be easier, even by defibrillation (35). Indeed, even spontaneous termination of paroxysmal atrial fibrillation in humans is associated with a lengthening of mean FF intervals (17). In conscious dogs, lengthening of atrial fibrillation cycle after administration of a new class 1C drug (36) was correlated with lengthening of the shortest possible atrial wavelength, and the antifibrillatory effects of the drug, measured by these electrophysiological changes, were related to a reduction of the number of circulating wavelets (36). Wang et al. (37) demonstrated in a dog model that flecainide causes organization of atrial fibrillation, reduces the number of reentry circuits, and may terminate atrial fibrillation by increasing the wavelength of atrial fibrillation to the point that the arrhythmia can no longer sustain itself.

Table 3. Effects of IV Flecainide on ECG and Electrophysiological Parameters

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>After IV Flecainide</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean FF interval HRA (ms)</td>
<td>168 ± 24</td>
<td>261 ± 35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean FF interval CS (ms)</td>
<td>163 ± 27</td>
<td>259 ± 44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean RR interval (ms)</td>
<td>674 ± 192</td>
<td>633 ± 108</td>
<td>0.236</td>
</tr>
<tr>
<td>QRS interval width (ms)</td>
<td>80 ± 11</td>
<td>105 ± 18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pause at SR resumption (ms)</td>
<td>994 ± 432</td>
<td>1398 ± 812</td>
<td>0.015</td>
</tr>
</tbody>
</table>

HRA = high right atrium; CS = coronary sinus; SR = sinus rhythm.

**Figure 5.** Surface ECG recordings (leads aVR and D1) and intracavitary bipolar recordings (HRA = high right atrium; CS = coronary sinus) in a patient at baseline (top) and after flecainide IV infusion (bottom). A lengthening of atrial fibrillation cycle is evident in either HRA or CS recordings.
These effects may explain how flecainide makes electrical cardioversion of atrial fibrillation easier.

In conventional transthoracic cardioversion of long-standing atrial fibrillation, Van Gelder et al. (10) found that IV loading of flecainide was followed by a trend toward an increase in defibrillation energy requirements, but many differences exist in the design of that study compared to the present one (parallel study vs. sequential study) and in the methodology of shock delivery (transthoracic monophasic shocks vs. biphasic endocardial shocks) and it could be matter of speculation to consider how the different methodologies may condition the results.

Bianconi et al. (12), in a randomized controlled study on the effects of propafenone pretreatment in transthoracic cardioversion, found that the beneficial effects of propafenone were associated with transformation of the atrial fibrillation pattern into a flutter-like ECG pattern. This finding indeed is consistent with our observation of a marked lengthening of mean FF intervals after flecainide, but in our view analyses of surface ECGs have major limitations in studying the electrophysiological pattern of atrial fibrillation and its dynamic changes (17,38).

The electrophysiological effects of flecainide at the atrial level include a marked slowing of conduction and a rate-dependent increase in refractoriness, which is therefore particularly enhanced during atrial fibrillation (37,39). Our study did not allow us to determine which of these changes are responsible for obtaining a reduction in defibrillation energy requirements, but the final result is clearly related to a pharmacological effect, as demonstrated by QRS widening and attainment of serum concentrations within the therapeutic range (19).

Implications in clinical practice. According to the results of the present study, intravenous administration of flecainide may have several useful indications in patients with chronic persistent atrial fibrillation treated with electrical cardioversion. The first indication is related to the ability of this drug to increase the likelihood of restoring sinus rhythm (half of the nonresponders at baseline were converted after flecainide in this study) and this may be of great importance in chronic persistent atrial fibrillation of long duration, provided that patients with left ventricular dysfunction are excluded. As reported in the literature, transvenous endocardial cardioversion may be successful in patients with previous ineffective transthoracic cardioversion (6,7); however, cardioversion efficacy is only 70% in chronic persistent atrial fibrillation if a maximal output of 400 V is delivered (3). Therefore, in patients with unsuccessful transvenous cardioversion, a possible method by which to restore sinus rhythm is via a pharmacological effect on the substrate. Antiarrhythmic drugs like flecainide may be indicated for preventing early recurrences after electrical cardioversion, which have been reported in 7% to 30% of the cases (8,10,40). Flecainide administration may be a good choice in this situation because, according to the results of the present study, this drug, when administered intravenously, has a favorable effect on defibrillation energy requirements, and the overall safety profile is favorable.

A reduction in atrial defibrillation threshold may be helpful in patients who are candidates for an implantable atrial defibrillator (2,3,41) but in whom defibrillation threshold is nearly the maximum output of the device. In these cases flecainide may be an optimal drug because of the ability to prevent atrial fibrillation recurrences (25), thus limiting the device’s need to deliver therapy, coupled with the ability to reduce defibrillation energy requirements. However, a prospective study confirming the positive effects of flecainide on defibrillation energies even during long-term oral administration is required.

One of the issues associated with transvenous cardioversion is shock-induced discomfort (2,3,7,41,42), which is unpredictable and shows wide intersubject variability (42). Flecainide, by reducing defibrillation energy requirements and the score of shock-related discomfort, may have a substantial positive impact on patients’ ability to tolerate internal atrial cardioversion, performed during electrophysiological study or by an implanted atrial defibrillator, with a positive effect on patients’ acceptance of this therapy (2,41,42). The positive effects of flecainide on shock-induced discomfort do not seem to be biased by the number of shocks delivered in sequence; indeed, if a series of shocks lowers the patient’s tolerability of the shocks, this bias will be against flecainide, thus enhancing the strength of our findings. Nevertheless, a prospective trial is required for evaluating, in a prospective, controlled manner, the impact of flecainide treatment on these issues.

Risk-benefit ratio. A positive risk-benefit ratio is required for antiarrhythmic drugs (43) and according to our experience, acute IV administration of flecainide, under ECG and blood pressure monitoring, did not cause ventricular proarrhythmic effects or hemodynamic deterioration. Two patients had periods of transient bradycardia after successful cardioversion requiring temporary pacing, at baseline and after flecainide, and mean pause after cardioversion was longer following flecainide, even though no complications occurred. Sinus pauses or sinus bradycardia may occur at spontaneous sinus rhythm resumption after a period of atrial fibrillation (44) and may be increased in duration when pharmacological cardioversion is performed with flecainide (22) or when transthoracic electrical cardioversion is performed during oral flecainide (32) or oral propafenone treatment (12). In clinical practice, the ability to conduct temporary pacing is required when cardioversion is performed, especially after acute drug administration.

Study limitations. Evaluation of defibrillation energy requirements in humans implies a different approach in comparison to animal studies where curves of response can be obtained using multiple sequences of atrial fibrillation inductions followed by shock delivery (4,5,20,21). Indeed, for limiting the number of delivered shocks, studies in
humans have typically employed a step-up protocol (2,3,7,42,45,46). This technique implies some obvious approximation and some potential problems of reproducibility. Moreover evaluation of the effects of flecainide on defibrillation energy requirements in patients with chronic persistent atrial fibrillation requires a first cardioversion at baseline and a subsequent cardioversion, after flecainide administration, on a reinduced atrial fibrillation. Because of the potential bias of comparing cardioversion of a long-standing atrial fibrillation with a reinduced atrial fibrillation, we analyzed in 10 patients energy requirements at baseline, after atrial fibrillation reinduction in a drug-free condition and after flecainide. The lack of significant differences in defibrillation energy requirements in sequential cardioversions performed in a drug-free condition, coupled with statistical evidence of favorable effects of flecainide in this subgroup of patients, strongly supports our findings of the positive effects of flecainide on defibrillation.

In the literature, conflicting data have been reported on defibrillation energy reproducibility (45,46). In the study by Lok et al. (45) atrial defibrillation threshold was reproducible if shocks were delivered within 2 min, whereas an increase in defibrillation threshold was found if shocks were delivered after a pause of 20 min. Conversely, in the study by Santini et al. (46) lower defibrillation thresholds were found for the second cardioversion sequence.

According to our protocol, after IV flecainide administration, cardioversion sequence began at 80 V under previous effective shocks; therefore, it can be argued that the beneficial effects on defibrillation energy requirements can be underestimated in some cases, because the maximum detectable reduction was 80 V.

Conclusions. Intravenous flecainide has favorable effects when used during low-energy internal atrial cardioversion because it lowers defibrillation energy requirements for patients with either chronic persistent atrial fibrillation or paroxysmal atrial fibrillation and secondarily lowers shock-induced discomfort. Moreover, flecainide increases the procedure success rate in chronic persistent atrial fibrillation. This effect on defibrillation energy requirements might be associated with a marked prolongation of atrial fibrillation mean cycle. The employment of this drug under ECG and blood pressure monitoring proved to be safe during cardioversion, without any ventricular proarhythmia.

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REFERENCES

sinus rhythm in patients without structural heart disease or with only systemic hypertension. Am J Cardiol 1992;70:69–72.


