A Randomized Comparison of External and Internal Cardioversion of Chronic Atrial Fibrillation

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Background. Delivery of shocks within the right atrium has been reported to be more effective than conventional external shocks in converting atrial fibrillation (AF), but these two cardioversion techniques have never been compared prospectively. The purpose of this study was to compare the efficacies of external and internal cardioversion in patients with chronic AF unresponsive to prior attempts at electrical and/or pharmacological cardioversion. Low-dose amiodarone was used in all patients after cardioversion to suppress recurrences of AF.

Methods and Results. One hundred twelve patients with AF of at least 1 month in duration were randomly assigned to undergo external cardioversion with 300–360-J shocks or internal cardioversion with 200–300-J shocks delivered through a standard electrode catheter within the right atrium. The patients were treated with amiodarone (200 mg/day 5–7 days/week) for 1 month before electrical cardioversion and afterward if the cardioversion was successful. The patients were evaluated at regular intervals during 1 year of follow-up. The efficacy of internal cardioversion was significantly greater than that of external cardioversion (91% versus 67%, \( p = 0.002 \)). The only variable that was associated with the outcome of cardioversion was body weight. Among patients in whom sinus rhythm was restored, AF recurred as often after internal and external cardioversion; at 1 year of follow-up, 37% of patients in whom external or internal cardioversion had been effective were still in sinus rhythm. Patients who had undergone an attempt at electrical cardioversion before entry into this study were less likely to remain in sinus rhythm after cardioversion. The only complications of cardioversion were one instance of cerebral thromboembolism after external cardioversion and one instance of transient pulmonary edema after internal cardioversion. Therapy with amiodarone was discontinued because of an adverse drug effect in only three patients.

Conclusions. Internal cardioversion is more effective than external cardioversion in restoring sinus rhythm and is as safe as external cardioversion in patients with chronic AF. The recurrence rate of AF is the same after both types of cardioversion. If conventional electrical cardioversion is ineffective, internal cardioversion should be attempted. The combination of low-dose amiodarone and internal cardioversion may result in maintaining sinus rhythm long-term in patients with refractory AF.

(Circulation 1992;86:1415–1420)

Key Words • atrial fibrillation • cardioversion • amiodarone

Internal cardioversion has been reported to be effective in converting atrial fibrillation (AF) and restoring sinus rhythm for long periods of time in patients who have failed conventional external cardioversion.1,2 However, these two cardioversion techniques have never been compared in a prospective study. The purpose of the present study was to compare external and internal cardioversion in a randomized fashion. The acute efficacies of these two techniques in restoring sinus rhythm were compared in patients with chronic AF who had failed attempts at pharmacological conversion. Low-dose amiodarone was used in an attempt to maintain sinus rhythm after successful cardioversion, and the incidence of recurrent AF after both types of cardioversion were compared during 1 year of follow-up.

Methods

Selection of Subjects

This study was performed according to a protocol used at the University of Marseille and the University of Michigan. Informed consent was obtained under a study protocol approved by the Human Research Committee at both institutions.
The following criteria were used to select the subjects for this prospective study: 1) chronic AF of at least 1 month in duration, documented by serial ECG 1 month apart and by a 24-hour ambulatory ECG recording; 2) failure of AF to convert to sinus rhythm after at least one drug trial with quinidine, procainamide, disopyramide, or amiodarone; 3) no history of amiodarone toxicity or other contraindications to the use of amiodarone. Other factors such as the duration of AF beyond 1 month or left atrial size were not taken into consideration in selecting subjects for this study.

Patients who met the selection criteria and who consented to participate in this study underwent a chest x-ray and measurement of liver and thyroid function tests. M-mode and two-dimensional echocardiograms were performed in each patient for measurement of left atrial size and left ventricular ejection fraction.

Therapy with amiodarone was initiated on an outpatient basis at a dose of 400 mg/day for 1 week followed by 200 mg/day 5–7 days per week. Amiodarone was chosen for use in this study because it was available both in France and the United States, because its low risk of proarrhythmic effects allowed initiation of therapy on an outpatient basis, and because it was felt that a low dosage would be well tolerated during 1 year of follow-up. Each patient was reevaluated after 4 weeks of therapy with amiodarone and if AF was still present, the patient was randomly assigned to undergo either external or internal cardioversion.

**Anticoagulation**

The patients in Ann Arbor were treated with warfarin sodium for at least 4 weeks before the attempt at electrical cardioversion. The dosage was adjusted to maintain a prothrombin time of 15–18 seconds (control range, 10–13 seconds). Treatment with warfarin sodium was discontinued 3 days before cardioversion, then continued for at least 4 weeks after cardioversion. If there was a contraindication to the use of warfarin sodium, aspirin was used at a dosage of 300–600 mg/day.

The patients in Marseille were anticoagulated with heparin starting at least 3 days before the cardioversion attempt. Heparin was administered subcutaneously at a dosage of 7,000–12,000 IU t.i.d. The dosage was adjusted to maintain a coagulation time of 1.5 to 2 times the control value and a serum heparin concentration of 1 to 2 mg/l.

Therapy with warfarin sodium or aspirin was continued indefinitely in patients who did not have a successful cardioversion and for at least 3 months after cardioversion in patients in whom sinus rhythm was restored.

**Cardioversion Protocol**

Cardioversions were performed in the fasting state. Either methylhexital, etomidate, or midazolam was used for induction of anesthesia or an amnestic state. In patients randomly assigned to undergo external cardioversion, the defibrillator paddles were positioned over the ventricular apex and in the right infraclavicular area and a 300-J shock was delivered in a synchronized fashion. If sinus rhythm was not restored, a second shock 360 J in strength was delivered.

In patients randomly assigned to undergo internal cardioversion, a previously unused 6F quadripolar USCI catheter with 1-cm interelectrode spacing was inserted into a femoral vein and positioned in the right atrium such that the tip of the catheter was resting on the tricuspid annulus and the most proximal electrode was in the cavity of the right atrium. A second electrode catheter positioned in the right ventricle was used for ventricular pacing in the event of atrioventricular block after internal cardioversion. A 200-J shock was delivered in synchronized fashion in the right atrium using the proximal electrode of the cardioversion catheter as the cathode and a back plate on the left posterior chest as the anode. If sinus rhythm was not restored, a second shock 300 J in strength was delivered. These shock strengths were selected because prior studies demonstrated their safety and efficacy for internal cardioversion.

The acute efficacy of external or internal cardioversion was evaluated based on whether or not sinus rhythm was present 10 minutes after the last external or internal shock. If sinus rhythm was still not successfully restored acutely by the method of cardioversion to which the patient had been randomly assigned, cardioversion was then attempted using the alternative method.

The plasma concentrations of amiodarone and desethylamiodarone were measured from a blood sample drawn upon completion of the cardioversion procedure. The patients underwent continuous ECG monitoring and were observed for a minimum of 1–3 hours before being discharged home.

**Evaluation of Long-term Results**

The patients were examined by one of the authors, and a 12-lead ECG was obtained at 1, 3, 6, 9, and 12 months of follow-up or if the patient experienced symptoms suggestive of recurrent AF. A 24-hour Holter monitor recording was performed at 6 months of follow-up to rule out asymptomatic recurrences of AF. Amiodarone therapy was continued for a minimum of 1 year or until AF recurred. Thyroid function tests, liver function tests, and a chest x-ray were obtained at 6 and 12 months of follow-up to monitor for amiodarone toxicity.

**Statistical Analysis**

Statistical comparisons were performed by contingency table analysis or using the Student’s t test. Multivariate analysis of variables associated with the outcome of cardioversion and the maintenance of sinus rhythm after cardioversion was performed by multivariate logistic regression. The recurrence rate of AF after cardioversion was analyzed by life table analysis using the Kaplan-Meier method.

**Results**

**Characteristics of Subjects**

One hundred twenty-three patients met the selection criteria of this study and were treated with amiodarone. After 1 month of therapy, nine patients were found to be in sinus rhythm and were excluded from the study. An additional two patients remained in AF but became asymptomatic after initiation of therapy with amiodarone and declined cardioversion, so these two patients also were excluded. The remaining 112 patients (62 in Ann Arbor, 50 in Marseille) were randomly...
TABLE 1. Characteristics of Patients Randomly Assigned to Undergo External and Internal Cardioversion

<table>
<thead>
<tr>
<th></th>
<th>External</th>
<th>Internal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>57</td>
<td>55</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63±12</td>
<td>64±11</td>
</tr>
<tr>
<td>Male/female ratio</td>
<td>35/22</td>
<td>36/19</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>78±18</td>
<td>75±15</td>
</tr>
<tr>
<td>Underlying heart disease</td>
<td></td>
<td></td>
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<tr>
<td>Coronary</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Valvular</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>DCM</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>HCM</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Miscellaneous*</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>None</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>20 (35%)</td>
<td>25 (45%)</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>36</td>
<td>26</td>
</tr>
<tr>
<td>II</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>III</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Duration of current episode of AF (months)</td>
<td>27±43</td>
<td>20±33</td>
</tr>
<tr>
<td>Prior attempts at pharmacological conversion (No.)</td>
<td>1.6±0.8</td>
<td>1.6±0.7</td>
</tr>
<tr>
<td>History of electrical cardioversion</td>
<td>21 (36%)</td>
<td>23 (41%)</td>
</tr>
<tr>
<td>Prior electrical cardioversions (No.)</td>
<td>0.6±0.9</td>
<td>0.8±1.8</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>0.50±0.15</td>
<td>0.49±0.16</td>
</tr>
<tr>
<td>Left atrial size (mm)</td>
<td>46±7</td>
<td>45±7</td>
</tr>
<tr>
<td>Amiodarone concentration (mg/l)</td>
<td>0.5±0.2</td>
<td>0.5±0.2</td>
</tr>
<tr>
<td>Desethylamiodarone concentration (mg/l)</td>
<td>0.4±0.2</td>
<td>0.4±0.2</td>
</tr>
</tbody>
</table>

*There was no significant difference between the two groups. Values are mean±SD. DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; NYHA, New York Heart Association; AF, atrial fibrillation.

| Miscellaneous* | 2 | 1 |
| None | 17 | 12 |
| Congestive heart failure | 20 (35%) | 25 (45%) |
| NYHA functional class |
| I | 36 | 26 |
| II | 12 | 18 |
| III | 9 | 11 |
| Duration of current episode of AF (months) | 27±43 | 20±33 |
| Prior attempts at pharmacological conversion (No.) | 1.6±0.8 | 1.6±0.7 |
| History of electrical cardioversion | 21 (36%) | 23 (41%) |
| Prior electrical cardioversions (No.) | 0.6±0.9 | 0.8±1.8 |
| Left ventricular ejection fraction | 0.50±0.15 | 0.49±0.16 |
| Left atrial size (mm) | 46±7 | 45±7 |
| Amiodarone concentration (mg/l) | 0.5±0.2 | 0.5±0.2 |
| Desethylamiodarone concentration (mg/l) | 0.4±0.2 | 0.4±0.2 |

*Cor pulmonale, pulmonary hypertension, status after repair of atrial septal defect.

assigned to undergo external cardioversion (57 patients) or internal cardioversion (55 patients).

The characteristics of the subjects randomly assigned to undergo external and internal cardioversion are compared in Table 1. There were no significant differences between the two groups in age, male/female ratio, body weight, underlying heart disease, presence of congestive heart failure, New York Heart Association functional class, left ventricular ejection fraction, left atrial size, time of first onset of AF, duration of the most recent episode of AF, number of prior attempts at external cardioversion, number of antiarrhythmic drugs used for prior attempts at pharmacological conversion, or in the mean amiodarone or desethylamiodarone plasma concentrations at the time of the cardioversion in this study. Of note is that the duration of the most recent episode of AF was greater than 2 years in 44% of the patients randomly assigned to undergo external cardioversion and in 48% of the patients randomly assigned to undergo internal cardioversion.

Results of Primary Attempts at Cardioversion

Sinus rhythm was restored in 38 of 57 patients (67%) randomly assigned to undergo external cardioversion compared with 50 of 55 patients (91%) randomly assigned to undergo internal cardioversion ($p=0.002$). A single external shock of 300 J was effective in restoring sinus rhythm in 31 patients, and a second external shock of 360 J was effective in seven patients. Among the patients who underwent internal cardioversion, a single shock of 200 J was effective in restoring sinus rhythm in 40 patients, and a second internal shock of 300 J was effective in 10.

Results of Secondary Attempts at Cardioversion

Among the 19 patients randomly assigned to undergo external cardioversion in whom AF was present 10 minutes after the delivery of two external shocks, internal cardioversion was effective in restoring sinus rhythm in 12 (63%). Among the five patients randomly assigned to undergo internal cardioversion in whom AF was present 10 minutes after delivery of two internal shocks, external cardioversion was effective in restoring sinus rhythm in two (40%).

Overall Acute Results

Combining the primary and crossover attempts, internal cardioversion was significantly more effective than external cardioversion in restoring sinus rhythm. Sinus rhythm was restored in 62 of a total of 74 patients (84%) who underwent an attempt at internal cardioversion compared with 40 of a total of 62 patients (64%) who underwent an attempt at external cardioversion ($p=0.01$).

Recurrences of Atrial Fibrillation

There was no significant difference in the recurrence rate of AF between the 62 patients in whom sinus rhythm initially was restored by internal cardioversion and the 40 patients in whom sinus rhythm was restored by external cardioversion (Figure 1). At 1 year of follow-up, 37% of both groups of patients remained in sinus rhythm.

Based on an intention-to-treat analysis, there was no difference in the proportion of patients in sinus rhythm 1 year after external and internal cardioversion. Fourteen of the 57 patients (24%) randomly assigned to
undergo external cardioversion were in sinus rhythm 1 year later compared with 21 of 55 patients (38%) randomly assigned to undergo internal cardioversion (p=0.1).

Variables Associated With Outcome

The patients in whom either external or internal cardioversion was and was not effective in converting AF to sinus rhythm are compared in Table 2. The mean weight of patients in whom cardioversion was effective (76±16 kg) was significantly lower than that of patients in whom cardioversion was ineffective (93±18 kg, p<0.01). The body weight that best discriminated patients with and without successful cardioversion was 75 kg; cardioversion was effective in 57 of 58 patients (98%) who weighed 75 kg or less compared with 45 of 54 patients (83%) who weighed more than 75 kg (p=0.01). None of the other variables listed in Table 2 were associated with the outcome of cardioversion.

The patients who were and were not in sinus rhythm at 1 year of follow-up are compared in Table 3. The mean number of electrical cardioversions attempted before entry into this study was significantly lower in the patients who were in sinus rhythm at 1 year of follow-up (0.3±0.6 attempts per patient) than in patients who were in AF (1.0±1.7 attempts per patient, p=0.02). Among 67 patients who never had an attempt at electrical cardioversion before entry into this study, 30 (45%) were in sinus rhythm at 1 year of follow-up compared with 10 of 45 patients (22%) who had had one or more attempts at cardioversion before entry into this study (p=0.01). None of the other variables listed in Table 3 were associated with the presence of sinus rhythm at 1 year of follow-up.

Complications

Among the patients who underwent an attempt at external cardioversion, the only complication was the
occurrence of a transient right hemiparesis in a 73-year-old woman 3 days after successful conversion to sinus rhythm. This patient had not been treated with warfarin sodium because of a recent history of gastrointestinal bleeding and instead had been taking aspirin for 4 weeks before the cardioversion.

Among the patients who underwent an attempt at internal cardioversion, the only complication was in a 75-year-old man with coronary artery disease and a left ventricular ejection fraction of 0.50 who developed pulmonary edema 12 hours after successful conversion to sinus rhythm. The pulmonary edema cleared rapidly with pharmacological therapy, and there was no evidence of a myocardial infarction. He remained in sinus rhythm during and after the episode of pulmonary edema.

Transient second- or third-degree atrioventricular nodal block lasting 2–15 seconds occurred after internal cardioversion in seven patients. There were no instances of persistent atrioventricular block among the patients who underwent attempts at internal cardioversion.

The only patient who died during the study period was a 62-year-old man with coronary artery disease and a left ventricular ejection fraction of 0.38 who died of complications related to chronic congestive heart failure 3 months after successful internal cardioversion.

Complications Related to Amiodarone

Two patients developed symptomatic hypothyroidism after 3 months of therapy with amiodarone, and one patient experienced visual disturbances after 6 months of therapy. Treatment with amiodarone was discontinued in these three patients; two of them subsequently reverted from sinus rhythm to AF and one patient remained in sinus rhythm during the 1-year follow-up. There were no other instances of side effects or adverse reactions related to amiodarone.

Discussion

Main Findings

The results of this study demonstrate that direct current shocks are more effective in converting AF to sinus rhythm when delivered directly within the right atrium than when delivered to the chest wall in conventional fashion. In this prospective comparison of the two cardioversion techniques in patients who had had AF for a mean of approximately 2 years, AF was successfully converted to sinus rhythm in 91% of patients randomly assigned to undergo internal cardioversion compared with 67% of patients randomly assigned to undergo external cardioversion. Delivery of 200–300-J shocks within the right atrium was found to be safe, with no instances of myocardial perforation or persistent atrioventricular block.

To maximize the probability of remaining in sinus rhythm, the patients in this study who underwent successful cardioversion then were treated with amiodarone. AF was found to recur as often after successful internal cardioversion as after successful external cardioversion, with sinus rhythm being present in 37% of patients 1 year after both effective external and effective internal cardioversion. Therefore, the advantage of internal cardioversion appears to be limited to a higher acute efficacy in restoring sinus rhythm, and there is no evidence that the probability of a recurrence of AF is affected by whether cardioversion is performed internally or externally.

Intracavity Cardioversion

In prior studies in which high-energy shocks were used for internal cardioversion, it was suggested that intracavity shocks might exert some effect on the atrial myocardium that is helpful in maintaining sinus rhythm and delaying a recurrence of AF.1,2 However, the randomized comparison of conventional and intracavity cardioversion in the present study demonstrates convincingly that there is no difference in the incidence or time course of recurrent AF after the two types of cardioversion. Therefore, because it is an invasive procedure, internal cardioversion should be reserved for patients in whom conventional cardioversion is ineffective.

Experimental studies in dogs have demonstrated that transeptal shocks of 0.01–5 J delivered in the right atrial appendage or in the right atrial cavity often are effective in converting AF or atrial flutter.3,4 However, internal cardioversion with shocks of similar strength have been found to be ineffective in humans.5 In the present study, a high conversion rate was achieved with intracavity shocks of 200–300 J. Because shocks of lower strength were not tested, the minimum energy needed for successful intracavity cardioversion was not identified and remains to be determined.

Predictors of Successful Cardioversion

Among many variables examined, the only variable that was significantly associated with the outcome of cardioversion was body weight, with patients weighing more than 75 kg having a significantly lower probability of successful cardioversion than patients who weighed 75 kg or less. The association between body weight and the outcome of cardioversion is consistent with the probability of successful cardioversion being dependent on the amount of energy delivered to the heart. This would explain the higher efficacy of internal cardioversion compared with external cardioversion. The association between body weight and the outcome of cardioversion also suggests that the efficacy of external cardioversion in this study may have been improved by using shocks stronger than 300 J.

Predictors of Maintenance of Sinus Rhythm

The probability of remaining in sinus rhythm throughout the 1-year follow-up in this study was two-fold greater in patients who had never had an attempt at electrical cardioversion before entry into this study than in patients who had undergone one or more prior attempts at electrical cardioversion (45% versus 22%). This observation indicates that patients who have had a recurrence of AF after electrical cardioversion, either with or without pretreatment with an antiarrhythmic drug, are less likely to benefit from another attempt at cardioversion combined with pretreatment and maintenance therapy with amiodarone.

Comparison With Prior Studies

Several prior studies have examined the variables that predict successful cardioversion of AF and/or maintenance of sinus rhythm after cardioversion. Whereas Van
Gelder et al\textsuperscript{6} reported that the duration of AF and age were significantly associated with the outcome of cardioversion, Dittrich et al\textsuperscript{7} in concert with the results of the present study, found that no historical or clinical variables correlated with the results of cardioversion. Regarding body weight, the only variable in the present study that was associated with the outcome of cardioversion, no prior studies evaluated this variable.

The results of studies that have examined the variables associated with the maintenance of sinus rhythm after cardioversion have also differed widely. Variables that have been reported to be associated with the maintenance of sinus rhythm in some studies but not in others have included the duration of AF, the type of underlying heart disease, functional class, and left atrial size.\textsuperscript{6-11} The differing results among these prior studies and the present study may be attributable to different patient selection criteria, differences in the type of pharmacological therapy used after cardioversion, variable durations of follow-up, and the retrospective nature of some of the studies.

In the present study, the only variable associated with the maintenance of sinus rhythm was whether or not the patient had undergone a prior attempt at electrical cardioversion; however, this variable was not examined in any of the prior studies.

**Complications of Cardioversion**

Internal cardioversion, using the technique previously described by Levy et al,\textsuperscript{1} was found in this study to be as safe as conventional external cardioversion. Although 95\% of patients who underwent internal cardioversion developed second- or third-degree atrioventricular block, this was always short-lived and never persistent or recurrent. The absence of any other barotraumatic complications such as myocardial perforation may be explained by delivery of shocks within the right atrial cavity instead of against the atrial wall. The only two complications of cardioversion in this study were cerebral thromboembolism and transient pulmonary edema, and it is unlikely that either of these complications was related to the technique used for cardioversion.

**Efficacy and Safety of Amiodarone**

Prior reports have demonstrated that amiodarone may be effective in preventing recurrences of AF after class I antiarrhythmic agents have failed.\textsuperscript{12-14} Because all patients in the present study were treated with amiodarone and no control groups were present, this study provides no data on the efficacy of amiodarone either in facilitating the electrical conversion of AF or in maintaining sinus rhythm after cardioversion. Amiodarone therapy was discontinued because of an adverse effect in only three of the 112 patients in this study. This low incidence of adverse drug effects related to low-dose amiodarone compares favorably with that of class I agents.\textsuperscript{15} Of particular note is that there was only one death among the patients in this study, and this was caused by heart failure. The absence of clinically significant proarrhythmic effects suggests that low-dose amiodarone may have a major advantage over other drugs used to maintain sinus rhythm after cardioversion such as quinidine, which may be associated with a threefold increase in mortality.\textsuperscript{16}

**Conclusions**

An attempt at electrical cardioversion combined with pretreatment and maintenance therapy with low-dose amiodarone may be worthwhile in patients with chronic AF who have not responded to prior attempts at cardioversion. If shocks delivered to the thorax in conventional fashion are not effective in restoring sinus rhythm, an attempt at internal cardioversion may be appropriate. Using this approach, it may be possible to maintain sinus rhythm long-term in a significant proportion of patients who previously may have been considered inappropriate candidates for cardioversion because of long-standing AF or because of a dilated left atrium.

**Acknowledgment**

The authors are grateful to Marion Maguire for her excellent secretarial assistance.

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A randomized comparison of external and internal cardioversion of chronic atrial fibrillation.

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Circulation. 1992;86:1415-1420
doi: 10.1161/01.CIR.86.5.1415

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1992 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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