Prospective Randomized Trial of Transthoracic Versus Low-Energy Internal Cardioversion in Persistent Atrial Fibrillation

Long Term Follow-up

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SUMMARY

Low energy internal cardioversion (ICV) is a relatively new method. This report describes the long-term follow-up results of a prospective randomized comparison of low energy ICV and transthoracic cardioversion (TT CV) in patients with persistent atrial fibrillation (AF).

Fifty-two patients (mean age, 60.6 ± 10.1 years, 23 males) with persistent AF were randomly assigned to either TT (n = 26) or ICV (n = 26). The baseline characteristics of the 2 groups were similar. Transthoracic CV was performed under sedation with hand-held electrodes in the apex-anterior position and high energy (100-360 J) monophasic shocks. ICV was performed by a dedicated balloon-directed catheter utilizing truncated, biphasic shocks of low energy (1-15 J).

Sinus rhythm (SR) was restored in 24/26 (92%) patients in the ICV group and in 22/26 (85%) patients in the TT CV group (P > 0.05). Immediate recurrence of AF (IRAF), defined as reappearance of AF within 2 minutes of successful CV, occurred in 5 patients (21%) in the ICV group and in 1 patient (4.5%) in the TT group (P > 0.05). Successfully cardioverted patients in whom no IRAF occurred were followed-up for 18 months under both warfarin and Class 1 or 3 antiarrhythmic drugs, as guided by the current ACC/AHA/ESC Guidelines. The rate of SR at 1, 3, 6, 12, and 18 months of follow-up was not significantly different between the 2 groups, and in an intention-to-treat analysis at 18 months, SR was present in 6 patients (23%) in the ICV group and in 10 patients (38%) in the TT group (P > 0.05). The majority of AF recurrences occurred within a month of successful CV in both groups (8/12 [67%] in the TT group and 15/18 [83%] in the ICV group, P > 0.05). The mortality, thromboembolic, and bleeding complication rates were similar in the 2 groups.

In this prospective randomized comparison of TT and low energy ICV in patients with persistent AF, the 18-month rates of SR and major adverse clinical events were found to be similar. (Int Heart J 2006; 47: 753-762)

Key words: Atrial fibrillation, Low energy internal cardioversion

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ALTHOUGH recent large-scale randomized trials\(^1\)\(^-\)\(^3\) have questioned the benefit of restoring and maintaining normal sinus rhythm (SR) in patients with AF, there may still be a need to cardiovert AF into SR for various reasons.

Of the 2 ways of performing cardioversion (CV), electrical CV utilizes direct current (DC) shocks synchronized to the QRS complex on the surface electrocardiogram. There are basically 2 ways of performing electrical CV. Transthoracic (TT) CV utilizes monophasic high energy shocks delivered through large surface electrodes. Internal CV (ICV), a rather new technique, is performed by intracardiac electrodes introduced transvenously and especially with biphasic shock waveforms, allows successful CV with very low energy levels.\(^4\)\(^-\)\(^9\)

We have previously published data regarding a comparison of these 2 methods of CV with respect to immediate success.\(^10\) This report describes the long-term follow-up of this prospective randomized comparison.

**METHODS**

Patients of either sex, aged 18-75 years, who had persistent AF were randomly assigned to undergo CV with either TT or ICV. Both procedures were performed under transesophageal echocardiography guidance. Antiarrhythmic drugs were discontinued for at least 3 half-lives before CV in each arm. Verapamil, diltiazem, and beta-blockers were allowed for rate control.

Transthoracic CV was performed in the fasting state under conscious sedation with the hand-held paddle electrodes in the apex-anterior position. The initial energy was 100 joules and in cases in which AF persisted, the energy level was increased to 200, 300, and to a maximum of 360 joules in a stepwise fashion as necessary using monophasic damped sinusoidal waveform DC shocks synchronized to the surface QRS.

Internal CV was performed in the fasting state using a 7.5 F, special balloon directed catheter (Alert Catheter, EP Med Systems Inc., NJ, USA) via the femoral vein approach. The method of ICV has been described in detail previously.\(^10\) In brief, low energy (up to a maximum of 15 Joules) biphasic shocks synchronized to the right ventricular intracardiac electrogram were applied through the distal and proximal arrays of electrodes with a dedicated balloon-tipped catheter situated in the left pulmonary artery - right atrium position.

Successful CV was defined as the documentation of at least 2 consecutive sinus beats after CV with either technique. Immediate recurrence of AF (IRAF) was defined as the reappearance of AF within 2 minutes after successful CV. In cases of IRAF, no further attempts at CV were made.

The patients were followed for at least 48 hours in the hospital after each procedure and discharged thereafter. The rhythm at 24 hours and at discharge was
recorded. All patients were maintained in an anticoagulated state with warfarin unless strictly contraindicated.

Those patients in whom the index AF was deemed to be the first episode and less than a month old were not prescribed any antiarrhythmic drugs for SR maintenance. On the other hand, patients in whom the index AF was either a recurrent episode or more than a month old were given prophylactic antiarrhythmic drugs for SR maintenance as guided by the most updated AF guidelines at the time the study was performed.1) Accordingly, patients with minimal or no heart disease and hypertensive patients with a left ventricular wall thickness below 14 mm were given propafenone 450 mg/day. Those with coronary artery disease were followed on sotalol 160 mg/day and those patients who had congestive heart failure and/or a left ventricular ejection fraction below 0.40 and hypertensive patients with a left ventricular wall thickness of 14 mm or higher were given amiodarone 200 mg/day after a loading dose of 800 mg/day for a week. Prophylactic medications, if given, were started at 1 hour post CV, in case CV was successful and IRAF did not occur. No intravenous loading of any of the 3 drugs was performed. Those patients in whom the rhythm at discharge was SR were kept on antiarrhythmic drugs until the occurrence of the first recurrent episode of AF or the end of follow-up, whichever came first. On the other hand, if the rhythm at discharge was AF, the antiarrhythmic medication was stopped and the patients were discharged on rate controlling drug therapy with either calcium channel blockers or beta-blockers.

Follow-up was scheduled at 1, 3, 6, 12, and 18 months. Electrocardiograms were obtained and the INR was checked and the patients were questioned with respect to the occurrence of symptoms probably ascribable to the recurrence of AF but only ECG evidence of AF was accepted as recurrence. If AF recurred, no additional attempts at CV were made. This systematic follow-up protocol was applied to all patients including those who were not in SR at hospital discharge.

Statistical analysis: Continuous variables are given as the mean ± standard deviation. The differences between groups were evaluated using Student's t-test for continuous variables and the chi-square test for categorical variables. Statistical significance was defined as a P value below 0.05.

RESULTS

The study population consisted of 52 patients (23 males, 29 females, mean age, 60.6 ± 10.1 years). Twenty-six were randomly assigned to TT and 26 to ICV after initial evaluation. The baseline characteristics of the 2 groups were similar (Table I). Likewise, the precardioversion medications used in the 2 groups were not different (Table II).
Immediate success was similar to that previously reported\textsuperscript{10} and 24 of 26 (92\%) patients in the ICV group and 22 of 26 (85\%) patients in the TT group were successfully cardioverted to SR ($P > 0.05$). The mean energy required to achieve successful CV was 246.4 ± 73.6 joules (range, 100 - 360 joules) in the TT group and 9.8 ± 4.3 joules (range, 5 - 15 joules) in the ICV group ($P < 0.05$).

The rate of IRAF was 1 in 22 (4.5\%) and 5 in 24 (21\%) patients in the TT and ICV groups, respectively ($P > 0.05$). All incidences of IRAF in the ICV group occurred while the catheter was still in the left PA-RA position. However, no further attempts at CV were made. Therefore, 21 patients in the TT and 19 patients in the ICV group were in SR at 1 hour post CV and these patients were

### Table I. Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Internal CV ($n = 26$)</th>
<th>Transthoracic CV ($n = 26$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>59.1 ± 12.3</td>
<td>62 ± 7.3</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>14/12</td>
<td>9/17</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index</td>
<td>27.6 ± 3.3</td>
<td>28.5 ± 3.8</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>4 (15)</td>
<td>8 (30)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>14 (54)</td>
<td>20 (77)</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>3 (11)</td>
<td>4 (15)</td>
<td>NS</td>
</tr>
<tr>
<td>Valvular disease (%)</td>
<td>6 (23)</td>
<td>4 (15)</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dilated (%)</td>
<td>2 (8)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Ischemic (%)</td>
<td>0</td>
<td>2 (8)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertrophic (%)</td>
<td>0</td>
<td>1 (4)</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of AF (months)</td>
<td>15.1 ±17.1</td>
<td>26.6 ± 26.7</td>
<td>NS</td>
</tr>
<tr>
<td>Lone AF (%)</td>
<td>7 (27)</td>
<td>3 (11)</td>
<td>NS</td>
</tr>
<tr>
<td>Prior heart surgery (%)</td>
<td>3 (11)</td>
<td>2 (8)</td>
<td>NS</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>63.4 ± 12</td>
<td>62.6 ± 11.8</td>
<td>NS</td>
</tr>
<tr>
<td>LA diameter (mm)</td>
<td>46 ± 6.9</td>
<td>44.9 ± 6.8</td>
<td>NS</td>
</tr>
<tr>
<td>PAP (mmHg)</td>
<td>33.3 ± 8.4</td>
<td>34 ± 10.5</td>
<td>NS</td>
</tr>
<tr>
<td>LASEC/thrombus on TEE (%)</td>
<td>14 (54)</td>
<td>10 (38)</td>
<td>NS</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; LA, left atrial; PAP, pulmonary artery pressure; LASEC, left atrial spontaneous echo contrast; and TEE, transeophageal echocardiography.

### Table II. Precardioversion Medication

<table>
<thead>
<tr>
<th>Drug</th>
<th>Internal CV ($n = 26$)</th>
<th>Transthoracic CV ($n = 26$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diltiazem (%)</td>
<td>10 (38)</td>
<td>14 (54)</td>
<td>NS</td>
</tr>
<tr>
<td>Verapamil (%)</td>
<td>3 (11)</td>
<td>5 (19)</td>
<td>NS</td>
</tr>
<tr>
<td>Beta-blocker (%)</td>
<td>8 (31)</td>
<td>5 (19)</td>
<td>NS</td>
</tr>
<tr>
<td>Aspirin (%)</td>
<td>20 (77)</td>
<td>24 (92)</td>
<td>NS</td>
</tr>
<tr>
<td>Warfarin (%)</td>
<td>18 (69)</td>
<td>19 (73)</td>
<td>NS</td>
</tr>
</tbody>
</table>
started on prophylactic oral antiarrhythmic drugs as described. Accordingly, 30 patients (75%) received propafenone, 3 (7.5%) sotalol, 5 (12.5%) amiodarone, and 2 (5%) none (Table III).

One patient in the TT group and 5 patients in the ICV group relapsed into AF within 24 hours and the rhythm at discharge from the hospital at 48 hours was SR in 20 of 26 (77%) and 14 of 26 (54%) patients initially assigned to undergo CV with either the TT and ICV methods, respectively ($P > 0.05$).

No patient was lost to follow-up. A total of 3 patients died. Two patients in the ICV group died between 12-18 months and 1 in the TT CV group died between 6-12 months due to extra-cardiac causes. The rhythm recorded at the last visit before death in these 3 patients was SR in 1 and AF in 2.

Table III. Drugs Given for Sinus Rhythm Maintenance in Patients in Whom SR Was Present at 1 Hour Post CV

<table>
<thead>
<tr>
<th>Drug</th>
<th>Transthoracic CV ($n = 21$)</th>
<th>Internal CV ($n = 19$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>2</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>1</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Sotalol</td>
<td>3</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Propafenone</td>
<td>15</td>
<td>15</td>
<td>NS</td>
</tr>
</tbody>
</table>

Figure. Sinus rhythm rate at follow-up in the TT and ICV groups.
One patient in the TT group experienced an episode of transient ischemic attack (TIA) which resolved spontaneously within 24 hours of CV. Another patient in the TT group experienced peptic ulcer bleeding at 15 months and a cerebrovascular event was recorded in 1 patient in the TT group at 9 months. In the ICV group, 3 patients experienced peptic ulcer bleeding and 1 patient had a TIA during follow-up. None of these bleeding and thromboembolic complications were fatal.

The antiarrhythmic drugs were well tolerated in both groups and in no case was drug discontinuation necessary.

The SR rates at 1, 3, 6, 12, and 18 months of follow-up in the 2 groups are shown in the Figure. In an intention-to-treat analysis, of the 26 patients who were assigned to undergo CV with the ICV method, 9 (35%), 8 (31%), 8 (31%), 6 (23%), and 6 (23%) were still alive and in SR at 1, 3, 6, 12, and 18 months of follow-up, respectively. Among the 26 patients who were assigned to undergo CV with the TT method, 14 (54%), 12 (46%), 11 (42%), 11 (42%), and 10 (38%) were still alive and in SR at 1, 3, 6, 12, and 18 months of follow-up, respectively. The rate of SR at any time point was not significantly different between the 2 groups ($P > 0.05$). The majority of AF recurrences occurred within a month of successful CV in both groups (8/12 [67%] in the TT group and 15/18 [83%] in the ICV group).

**DISCUSSION**

In this prospective randomized comparison of TT and ICV for persistent AF, we were unable to demonstrate any difference between the 2 modalities with respect to 18-month SR rates when the patients were prescribed prophylactic antiarrhythmic drugs as guided by the most recent ACC/AHA/ESC guidelines for the management of AF. Total mortality, bleeding complications, and thromboembolic complications occurred at similar rates in the 2 groups.

Immediate recurrence of AF was observed almost 5 times more frequently in the ICV group, though the difference did not reach statistical significance. The rate of IRAF was reported to be 12% in 135 patients with persistent AF undergoing TT CV.$^{12}$ Among patients with persistent AF undergoing ICV, the rate of IRAF was reported to range from 5% to 31%.$^{13-17}$ Our finding of a nonsignificant but 5 times higher rate of IRAF with ICV as compared to TT CV needs confirmation using a larger population trial, since the small population size in our study may be the most probable explanation for this unexpected finding. The low energy levels utilized with ICV as compared to TT CV may be a factor that could explain the higher frequency of IRAF with ICV. Theoretically, IRAF can be precipitated with atrial premature beats provoked by mechanical trauma at the atrial
wall while the ICV catheter is pulled back after successful CV. This definitely was not the case in our study, as all IRAF episodes were observed while the catheter was stable at the left PA-RA position. Atrial premature complexes with short coupling intervals not originating from the defibrillation catheter have been shown to be the most frequent cause of IRAF. Increasing defibrillation energy levels has not been able to decrease the rate of IRAF. Repeated CV may theoretically overcome IRAF but this issue is still debatable.

Maintenance of SR after successful CV of AF is a major problem both after TT and ICV. With a single shock and no antiarrhythmic drug approach, the SR rate at 1 year after TT CV is around 20%. The proportion of patients remaining in SR after TT CV rises to around 40-50% at 1 year when prophylactic class I or class III drugs are utilized. Among these drugs, amiodarone seems to be the most promising. In our study, we followed the most recent ACC/AHA/ESC guideline recommendations regarding the selection of antiarrhythmic drugs for the maintenance of SR and in a way, we attempted to disclose how such a policy would work. Our 18 month SR rate of 38% in the TT group compares favorably with the literature. The rate of SR maintenance after low-energy ICV has varied from 32% to 71% at 6 to 15 months. The variation in these numbers is due to the different types of antiarrhythmic drugs utilized and the different patient populations studied. Our 23% rate of SR at 18 months in the ICV group is lower than these figures. One reason for this discrepancy may be due to the fact that in most of the studies cited above, the SR rate at follow-up was calculated by taking into account the number of patients successfully cardioverted, not the number of patients initially assigned to CV with the ICV method. Therefore, these figures overestimate the follow-up SR rates as compared to the intention-to-treat analysis that we performed in our study. Moreover, this discrepancy may also reflect an inadequacy of the prophylactic drug regimen that we utilized in our study, but this is far from being valid as the same drug regimen seems to have worked well in the TT CV group of the same study. Almost all (83%) AF recurrences in the ICV group occurred during the first month after successful CV. This is in accordance with the results of a study by Tse, et al, where among 50 patients undergoing low-energy ICV, 63% of the recurrences of AF occurred within one week after CV. In another study of 48 patients with persistent AF undergoing low-energy ICV, 71% of AF recurrences were noted within the first week of successful CV.

Transvenous ICV has been performed in various manners since first described. In the earlier reports, high-energy (200-300 joules) monophasic truncated shocks were applied between a quadripolar intra-atrial catheter and a back plate. With the introduction of biphasic shocks and special intracardiac elec-
trode catheters, ICV can now be performed by using low energies in the order of 5-15 joules under only light sedation.

Two randomized trials have compared high-energy ICV to TT CV in patients with chronic\textsuperscript{24} and lone\textsuperscript{25} AF. In the trial by Levy \textit{et al},\textsuperscript{24} among 112 patients with chronic AF, the SR rate at 1 year of follow-up was 42\% and 38\% in the TT and ICV groups, respectively ($P > 0.05$). Likewise, in the other trial comparing high-energy ICV to TT CV in patients with lone AF, the long-term AF recurrence rates were found to be similar.\textsuperscript{25}

The only trial that compared low-energy ICV to TT CV in a prospective fashion included 187 patients with chronic AF.\textsuperscript{9} It is important to note that this trial was not randomized and the initial CV modality was left to the patient's choice and crossover to the alternative strategy was allowed in case of CV failure with the initial strategy. The acute success was significantly greater with the ICV modality (93\% versus 79\%, $P < 0.05$). Likewise, at a mean follow-up of 12.5 $\pm$ 6.4 months, the SR rate was superior in the ICV group (48\% versus 38\%, $P < 0.05$). Among patients in whom CV was successful, the follow-up SR rates were similar (53\% versus 51\%, $P > 0.05$). Therefore, the difference in the long-term follow-up SR rates stems from the difference in the initial acute CV success rates in this study\textsuperscript{9} and the advantage of ICV seems to be limited to a higher acute efficacy in terminating AF and the probability of recurrence of AF is most likely independent of the CV modality.\textsuperscript{24,27}

In our prospective randomized comparison, we found no significant difference between low-energy single catheter transvenous internal and TT CV techniques with respect to either acute CV success or 18-month SR rates. Our study is unique in that it prospectively and randomly compares low energy ICV with TT CV modalities for treating persistent AF. We allowed no cross-over between groups, so that our results reflect a direct comparison of low-energy ICV and TT CV. Although statistically not significant, the 5-fold higher rate of IRAF with low-energy ICV as compared to TT CV deserves further evaluation in a larger study population.

Based on our findings and those in the literature, low-energy ICV cannot be recommended as an alternative to TT CV in routine daily clinical practice. We suggest that low-energy ICV should be reserved as an alternative strategy when CV of AF is clinically mandatory and TT CV fails to achieve this goal.

\textbf{REFERENCES}


