Isoproterenol to Evaluate Resumption of Conduction After Right Atrial Isthmus Ablation in Type I Atrial Flutter

Ashish Nabar, MD; Luz-Maria Rodriguez, MD; Carl Timmermans, MD; Joep L.R.M. Smeets, MD; Hein J.J. Wellens, MD

Background—After radiofrequency (RF) ablation of atrial flutter (AFL), the demonstration of bidirectional isthmus conduction (BIC) block is considered the hallmark of a successful procedure. The purpose of our study was to test the persistence of BIC block after isoproterenol administration and to evaluate the importance of this finding with regard to AFL recurrences.

Methods and Results—RF ablation of AFL was performed in 44 consecutive patients with type I AFL by linear ablation of the posterior isthmus (n=29 patients), septal isthmus (n=4 patients), or both right atrial (RA) isthmi (n=11 patients). The procedural end point was complete BIC block and noninducibility of AFL. In case of noninducibility and apparent BIC block, the pacing protocol was repeated under isoproterenol infusion (1 to 3 μg/min). Reversal of apparent BIC block occurred in 7 (15.9%) of 44 patients. Six patients had bidirectional and 1 had unidirectional resumption of isthmus conduction. Counterclockwise AFL could be reinduced in 4 of these patients. Two to 24 (median, 4) additional RF applications were required to achieve permanent BIC block. At a mean follow-up of 7.3±7.6 months (range, 2 to 31 months), 2 (4.5%) of 44 patients had AFL recurrences.

Conclusions—Partial linear RF ablation could possibly aggravate preexisting nonuniform anisotropic conduction in the RA isthmus, resulting in profound conduction slowing and apparent BIC block. Isoproterenol can unmask apparent BIC block, thus providing an opportunity to assess the possibility of reversal of BIC block and completeness of isthmus ablation during the same procedure. The low incidence (4.5%) of AFL recurrences at follow-up suggests that noninducibility and BIC block under isoproterenol infusion may be a better end point for successful AFL ablation. (Circulation. 1999;99:3286-3291.)

Key Words: atrial flutter • isoproterenol • conduction • anisotropy

Linear ablation of the right atrial (RA) isthmus is an effective and curative therapy for type I atrial flutter (AFL). Presently, complete elimination of bidirectional isthmus conduction (BIC) block is accepted as the best marker of long-term success. AFL recurrences are associated with failure to achieve complete BIC block at conclusion of the ablation procedure. Repeat electrophysiological studies in patients with an AFL recurrence show regression or complete disappearance of isthmus conduction block. Therefore, certainty of the presence of permanent complete BIC block is essential. Use of isoproterenol in evaluating success, defined as noninducibility of AFL and BIC block, after radiofrequency (RF) ablation of AFL has not been reported previously.

Methods

Forty-four consecutive patients who underwent RF ablation of type I AFL for multiple symptomatic episodes were included in the study (see Table 1). At the time of RF procedure, 31 patients were taking either class IC (n=22), class III (n=8), or combination (n=1) antiarrhythmic drug (AAD) therapy. Fifteen (34%) of the 44 patients taking class IC therapy developed AFL while being treated for atrial fibrillation (AF), the so-called class IC AFL. The ablation procedure was performed with the patient in a postabsorptive state after informed written consent was obtained. BIC, both anterograde and retrograde, was documented (Figure 1, A and B), and AFL was induced. In every patient, including those with class IC AFL, the atrial endocardial activation sequence was suggestive of RA macroreentry. No entrainment studies were performed. The ablation technique involved point-by-point sequential, 90-second RF applications with the temperature preset to 55°C (Osyypa HAT 300S) or 70°C (Stockert GmbH EP Shuttle generator) while the ablation catheter was progressively withdrawn across the RA isthmus under fluoroscopic guidance. A second RF application was delivered at a particular RA isthmic site unless a significant reduction in amplitude of the local atrial electrogram (<25%) was observed. We validated BIC block by pacing alternately from the coronary sinus (CS) and low lateral RA at a 600- or 500-ms constant cycle length. A retrograde isthmus conduction block was defined by an entirely cranio-caudal activation of the lateral RA wall during proximal CS (CS7.8) pacing with terminal activation of the Halo 1.2 bipole and prolongation of the CS7.8–Halo 1.2 interval (Figure 1C). An anterograde isthmus conduction block was defined by caudocranial...
activation of the lateral RA wall and craniocaudal activation of the atrial septum with terminal activation of CS7.8 after activation of the His bundle during low lateral RA pacing (Figure 1D). After apparent BIC block and noninducibility of AFL were obtained, the atrial pacing protocol (up to 3 atrial extrastimuli at 3 pacing cycle lengths and incremental atrial pacing) was repeated under isoproterenol infusion (1 to 3 μg/min). In case of reinduction of AFL or resumption of isthmus conduction under isoproterenol infusion, further RF applications were delivered. The procedural end point was the demonstration of BIC block and noninducibility of AFL under isoproterenol infusion.

Postablation Protocol
Twenty-four–hour Holter monitoring was done before discharge. Patients were followed up in the arrhythmia clinic at 8 and 12 weeks and thereafter at 3-month intervals. Holter recordings were performed at 8 and 12 weeks and additionally when symptoms suggested a recurrence. All patients with concomitant AF, including patients with class IC AFL, received AADs after ablation of the RA isthmus. At follow-up, depending on the incidence of AF recurrences, an attempt was made to discontinue AADs. However, patients with ablation of class IC AFL continued to receive propafenone or flecainide.

Statistical Analysis
All data are expressed as mean±SD or median and range.

Results
Electrophysiological Study and RF Ablation
Details of the electrophysiological study and RF ablation procedure are summarized in Table 2. The mean AFL cycle length was 250±41 ms, and a counterclockwise rotation of AFL was predominantly documented. RF applications were delivered during CS pacing (n=26 patients), AFL (n=11 patients), or both (n=7 patients) rhythms. Twenty-nine patients had linear ablation of the posterior isthmus. In 11 patients, additional ablation of the septal isthmus was performed. Ablation of the septal isthmus alone was done in 4 patients. In all patients, noninducibility of AFL and apparent BIC block were demonstrated.

Under isoproterenol infusion, noninducibility of AFL and BIC block persisted in 37 patients. Seven patients (15.9%) showed a reversal of BIC block. In these 7 patients, resumption of BIC under isoproterenol infusion was noted 23±11 minutes after the last RF application that showed apparent BIC block. In 6 patients, resumption of isthmic conduction was bidirectional (Figure 2). In 3 of these 6 patients, a counterclockwise AFL was reinduced, whereas short runs of

### Table 1. Baseline Characteristics of the 44 Patients Studied

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>55±13</td>
</tr>
<tr>
<td>Male/female, n/n</td>
<td>39/5</td>
</tr>
<tr>
<td>Mean duration of atrial flutter, y</td>
<td>5±5.3</td>
</tr>
<tr>
<td>Additional cardiac disease</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>7</td>
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<tr>
<td>Tachycardiomyopathy</td>
<td>2</td>
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<tr>
<td>Status after atrial septal defect repair</td>
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</tr>
<tr>
<td>Left atrial size, cm</td>
<td>4.5±0.4</td>
</tr>
<tr>
<td>Number of failed AADs, median (range)</td>
<td>2 (1–6)</td>
</tr>
</tbody>
</table>

Figure 1. A (Pacing at CS orifice) and B (pacing at low lateral RA) represent pacing in sinus rhythm before ablation. Dual wave front of RA activation with BIC is seen. C (Pacing at CS orifice) and D (pacing at low lateral RA) show apparent BIC block. Surface ECG lead III is shown. Intracardiac electrograms recorded include His bundle electrograms (HIS). H1.2 to H19.20 denote 10 bipoles of duodecapolar (Halo) catheter positioned around tricuspid annulus, and CS1.2 to CS7.8 represent 4 bipoles of decapolar catheter placed in CS.
clockwise AFL were induced in 2 of the other 3 patients. The remaining patient had persistent retrograde isthmus conduction block, but counterclockwise AFL could be induced, which suggests a unidirectional resumption of isthmus conduction (Figure 3). In the 4 patients with reinducible AFL, the mean AFL cycle length before RF ablation was 240 ± 8 ms. The reinduced AFL was sustained but slower, with a mean cycle length of 285 ± 60 ms. Four (median) additional RF applications (range, 2 to 24) were required to obtain complete and permanent BIC block. These additional RF applications were delivered at the same RA isthmi as those resulting in apparent BIC block.

Procedural success was achieved in a single session in every patient after a total of 24 (median; range, 4 to 43) RF applications. Mean procedure duration was 192 ± 51 minutes, with a mean fluoroscopic time of 46 ± 20 minutes.

**Follow-Up**

Follow-up (mean of 7.3 ± 7.6 months; range, 2 to 31 months) was available in all patients. At the time of the last follow-up visit, 29 patients were receiving AADs for AF recurrences. Two patients had an AFL recurrence at 3 and 7 months after the procedure, respectively, in spite of documentation of persistent BIC block under isoproterenol. During a second procedure, both patients were found to have BIC delay, suggesting regression of isthmus block. Both patients underwent a successful repeat ablation and were free of AFL recurrences at the last follow-up 8 and 10 months later, respectively.

**Discussion**

The RA isthmus is a slow conduction zone. The tricuspid annulus and crista terminalis are the anterior and posterior barriers of the AFL reentrant circuit that are impervious to transversal conduction. Morphological studies of the RA isthmus by Cabrera et al revealed a typical oblique

| TABLE 2. Results of Electrophysiology Study and RF Ablation in the 44 Patients Studied |
|---------------------------------|-----------------|
| **AFL cycle length, ms**        | 250 ± 41        |
| **Rotation of AFL, n**          |                 |
| Clockwise                       | 39              |
| Counterclockwise                | 2               |
| Both                            | 3               |
| **Rhythm during RF ablation, n**|                 |
| CS pacing                       | 26              |
| AFL                             | 11              |
| Both                            | 7               |
| **RA isthmus ablated, n**       |                 |
| Posterior                       | 29              |
| Septal                          | 4               |
| Both                            | 11              |
| **RF pulses/procedure, median (range)** | 24 (4–43) |
| **Mean fluoroscopy time, min**  | 46 ± 20         |
| Mean procedure time, min        | 192 ± 51        |
| **Mean follow-up duration, mo** | 7.3 ± 7.6       |
| **AFL recurrences, n (%)**      | 2 (4.5)         |

**Figure 2.** Recordings from same patient as in Figure 1 obtained during pacing in sinus rhythm after isoproterenol infusion. A (Pacing at CS orifice) shows dual wave fronts of RA activation with resumption of retrograde isthmus conduction. B (Pacing at low lateral RA) also shows dual wave fronts of RA activation. Electrogams in CS9.10 and CS7.8 show double potential, whereas those in other distal CS bipoles (CS5.6, CS3.4, and CS1.2) show single-component atrial electrogram. Proximal components of atrial double potential, in CS9.10 and CS7.8, are earlier than the atrial electrogram in HIS catheter. This suggests resumption of antegrade isthmus conduction through partially ablated RA isthmus with sequential activation of the 2 proximal CS bipoles (CS9.10 and CS7.8). Distal components of atrial electrogram in CS9.10 and CS7.8, as well as atrial electrograms recorded in CS5.6, CS3.4, and CS1.2, follow atrial activation in HIS catheter and are simultaneous. This sequence suggests activation by craniocaudal wave front. Only the proximal 2 bipoles of the CS catheter (CS9.10 and CS7.8) are activated by paced impulse conducting antegradely through the isthmus, whereas distal CS bipoles (CS5.6, CS3.4, and CS1.2) are activated by craniocaudal wave front. This suggests slow isthmus conduction in antegrade direction with faster conduction of craniocaudal wave front.
orientation of the subendocardial myocardial fibers in 57% of their normal heart specimens, with a narrow zone of intersection of the subendocardial fibers in 79%. Fiber orientation and direction of excitation are important determinants of nonuniform anisotropy\(^\text{10}\) and could provide a basis for clinical AFL. The use of class IC or III AADs in 70.5% patients in the present study could have worsened the preexisting nonuniform anisotropy in the RA isthmus.\(^\text{11}\) RF energy application causes focal necrosis, which may not always be transmural considering the variation in thickness of the RA isthmus (3 to 6 mm).\(^\text{9}\) Microscopically, there is a loss of side-to-side connections between groups of fibers and intercellular clefts with shrinkage of contractile elements.\(^\text{12}\) Presumably, an incomplete ablation of the RA isthmus aggravates preexisting nonuniform anisotropy and slows the conduction velocity further.\(^\text{13}\) The low effective conduction velocity through the RA isthmus can make it difficult to distinguish between slow conduction and conduction block.\(^\text{13,14}\) The decremental nature of nonuniform anisotropic conduction is greatest at slower pacing cycle lengths,\(^\text{13}\) as were used (600 and 500 ms) to validate BIC block. We believe that the initial apparent BIC block noted in 7 patients (15.9%) who showed a reversal of BIC block under isoproterenol infusion represents profound conduction slowing in the partially ablated isthmus and not failure of impulse conduction. Both class I and III AADs are known to preferentially slow isthmus conduction, particularly in the setting of nonuniform anisotropy,\(^\text{11}\) and could have contributed to apparent BIC block in 4 patients who were taking AADs (amiodarone, sotalol, and flecainide) during the study. However, 27 (72.9%) of the 37 patients who did not show reversal of BIC block were also taking these types of AADs. Recent studies advocate monitoring the amplitude of local electrograms at the ablation site and double potentials along the ablation line.\(^\text{15,16}\)

Isoproterenol, via its β-adrenergic–stimulating action, increases the level of intracellular cAMP,\(^\text{17}\) This decreases intercellular resistance\(^\text{18}\) and increases the rate of rise of the zero phase of the action potential,\(^\text{19}\) thereby increasing conduction velocity in the AV node, the atria, and the ventricles.\(^\text{20}\) Repetition of the postablation pacing protocol under isoproterenol (1 to 3 \(\mu g/\text{min}\)) infusion at the same or faster pacing cycle lengths as at baseline resulted in reversal of apparent BIC block in 7 (15.9%) of 44 patients. In 6 patients, there was evidence to suggest resumption of BIC. In 3 of these 6, a counterclockwise AFL was reinduced, and in addition, short runs of clockwise AFL were induced in 2 of the remaining 3 patients. The remaining patient had a persistent retrograde isthmus conduction block but an inducible counterclockwise AFL, suggesting a unidirectional resumption of isthmus conduc-

\[\text{Figure 3. Example of unidirectional resumption of isthmus conduction after isoproterenol infusion. Recordings obtained during CS pacing in sinus rhythm. First 2 paced beats (430-ms interval) are last beats of basic 10-beat drive. Note single wave front of RA activation, implying retrograde isthmus conduction block. Two extrastimuli are delivered at 300 and 210 ms. Second extrastimulus initiated a sustained counterclockwise AFL (cycle length, 290 ms), indicating resumption of anterograde isthmus conduction.}\]
tion. These findings imply an improvement in velocity of impulse conduction and an increase in the safety factor for impulse propagation in the incompletely ablated isthmus. In canine myocardial tissue, isoproterenol has been shown to improve conduction velocity in case of nonuniform anisotropy.21 Thus, isoproterenol can unmask apparent BIC block by improving conduction velocity in the incompletely ablated isthmus.

After a mean follow-up of 7.3 ± 7.6 months (range, 2 to 31 months), 2 (4.5%) of 44 patients had a recurrence of AFL at 3 and 7 months after ablation, respectively. At the last follow-up, 29 patients were receiving AADs for AF recurrences. After demonstration of noninducibility of AFL and BIC block, an AFL recurrence rate of 6% to 9% is reported, with the majority of recurrences occurring within the initial 6 months after ablation.23 The low AFL recurrence rate in the present study provides evidence that demonstration of noninducibility of AFL and BIC block under isoproterenol infusion may be a better end point after RF ablation of AFL. However, the recurrence of AFL in 2 patients despite documentation of BIC block under isoproterenol indicates a small risk of reversal of BIC block over time.

Study Limitations

Our explanation of profound conduction slowing in the nonuniformly anisotropic RA isthmus after RF ablation as the cause of an apparent BIC block should be proven by detailed mapping of the RA isthmus with recordings from a closely spaced multipolar catheter22 or by the nonfluoroscopy CARTO system.23 Before isoproterenol is used, pacing close to the line of block may be attempted as another method to detect persistent slow conduction in the incompletely ablated isthmus. However, despite these efforts to validate BIC block, conduction may still persist through deeper (epicardial) fibers surviving below the ablated endocardial region. Currently, this may not be demonstrable, because methods to “check” conduction in this dimension (ie, depth) with an adequate resolution do not exist for use in a clinical setting. During the procedure, a resumption of isthmus conduction may occur due to an improvement in conduction velocity purely as a function of time rather than isoproterenol. The time course of recovery has been reported to be within 30 minutes and sometimes 1 hour after the last RF application.24,25 In the present study, isoproterenol was used soon after demonstration of an apparent BIC block, and hence this question cannot be adequately addressed. However, the resumption of BIC 23 ± 11 minutes after the last RF application suggests that use of isoproterenol immediately may provide a means to more rapidly end the study.

Conclusions

Partial linear RF ablation could possibly aggravate preexisting nonuniformly anisotropic conduction in the RA isthmus, resulting in profound slowing of conduction and apparent BIC block. Isoproterenol can unmask apparent BIC block by improving conduction in the incompletely ablated isthmus. This provides an opportunity, importantly during the same procedure, to assess an early reversal of BIC block and completeness of isthmus ablation. The low (4.5%) recurrence incidence of AFL reported in the present study suggests that noninducibility and BIC block under isoproterenol infusion may be a better end point of successful AFL ablation.

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References


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