Prospective Assessment of Late Conduction Recurrence Across Radiofrequency Lesions Producing Electrical Disconnection at the Pulmonary Vein Ostium in Patients With Atrial Fibrillation

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Background—In patients with atrial fibrillation (AF) undergoing radiofrequency (RF) electrical disconnection of multiple pulmonary veins (PVs), the incidence of late conduction recurrences has not been systematically determined.

Methods and Results—Using a prospectively designed, multistep approach, we aimed at assessing the correlation between acute achievement and chronic maintenance of electrical conduction block across RF lesions disconnecting the distal tract of the PV in 43 patients (52.3±8.2 years) with AF. Forty-one left superior (LS), 42 right superior (RS), 25 left inferior (LI), and 9 right inferior (RI) PVs were targeted during 108 EP procedures (2.6±0.5 per patient). Seventeen patients underwent 2 procedures, 23 patients underwent 3 procedures, and 3 patients underwent 4 procedures. During the first attempt, electrical disconnection was achieved in 112 PVs (95.7%). During a next procedure (time interval, 4.6±1.9 months), conduction recurrence was observed in 32 of 39 LSPVs (82.1%), 29 of 40 RSPVs (72.5%), 20 of 24 LIPVs (83.3%), and 7 of 9 RIPV (77.8%). After reablation at gap sites, a later procedure (time interval, 5.1±2.4 months) revealed a second recurrence in 13 of 22 LSPVs (59.1%) and 14 of 19 RSPVs (73.7%).

Conclusions—Conduction recurrence across disconnecting RF lesions can be observed in ~80% of cases 4 months after ablation. After reablation, similar recurrence rates are observed 5 months later. This high rate of late conduction recurrence may contribute significantly to AF recurrence in patients undergoing catheter ablation aiming at disconnection of multiple PVs. (Circulation. 2003;108:1599-1604.)

Key Words: fibrillation | catheter ablation | electrophysiology

After the discovery of one or multiple pulmonary venous foci initiating human atrial fibrillation (AF), different techniques have been proposed to target the source of arrhythmia, including selective ablation of identifiable foci and electrical disconnection of pulmonary veins (PVs) from the adjacent atrium. In particular, electrical disconnection of PVs has developed into a reproducible technique enabling achievement of electrophysiological (EP) success during one procedure in most patients.

Recent studies have shown that the ability to disconnect multiple PVs during one procedure in >90% of targets is associated with clinical success in 22% to 85% of patients during intermediate follow-up. Conduction recurrence across acutely disconnecting lesions has been shown to be present in patients undergoing reablation attempts after recurrence of clinical AF. However, the incidence of this phenomenon and its distribution, depending on the targeted PV, is unknown.

In the present study, we prospectively investigated the correlation between acute achievement and chronic maintenance of conduction block across radiofrequency (RF) lesions deployed at the PV ostium in multiple PVs of patients with paroxysmal or persistent AF.

Methods
This study was based on a multistep catheter ablation protocol introduced at our center in January 2001 for the curative treatment of AF. Ethical approval was obtained for the study protocol. All patients were informed about the experimental nature of the study and gave written informed consent. Patients were included in the study if they met the following criteria: (1) drug-refractory AF; (2) age ≤70 years; (3) left atrium maximal transverse diameter ≤55 mm; (4) left ventricular (LV) ejection fraction >35%; and, (5) no prior cardiac surgery.

Patient Characteristics
Out of 48 consecutive patients meeting the entry criteria, 43 (33 men; 52.3±8.2 years) were recruited by January 2002, of whom 27 had
TABLE 1. Clinical Characteristics of Patients According to Type of AF

<table>
<thead>
<tr>
<th></th>
<th>Paroxysmal AF (n=27 Patients)</th>
<th>Persistent AF (n=16 Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>51.4±8.9</td>
<td>53.8±6.8</td>
</tr>
<tr>
<td>Male sex</td>
<td>25 (92.6%)</td>
<td>11 (68.8%)</td>
</tr>
<tr>
<td>Patients with history of AF &gt;5 y</td>
<td>9 (33.3%)</td>
<td>8 (50.0%)</td>
</tr>
<tr>
<td>No. of AA drugs</td>
<td>3.6±1.6</td>
<td>4.2±1.7</td>
</tr>
<tr>
<td>Atrial flutter</td>
<td>11 (40.7%)</td>
<td>8 (50.0%)</td>
</tr>
<tr>
<td>Heart disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery</td>
<td>1 (3.7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Valvular</td>
<td>3 (11.1%)</td>
<td>2 (12.5%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (14.8%)</td>
<td>5 (31.3%)</td>
</tr>
<tr>
<td>Left atrium max TD, mm</td>
<td>42.8±5.8</td>
<td>41.8±5.9</td>
</tr>
<tr>
<td>EF</td>
<td>0.60±0.03</td>
<td>0.59±0.04</td>
</tr>
<tr>
<td>Follow-up duration</td>
<td>8.1±6.7</td>
<td>6.2±3.8</td>
</tr>
</tbody>
</table>

EF indicates ejection fraction; max TD, maximal transverse diameter.

paroxysmal AF and 16 had persistent AF. The clinical arrhythmia had been present for a median of 4.5 years (range, 2 to 11 years) and refractory to 3.9±1.6 antiarrhythmic (AA) drugs. Atrial flutter was documented and treated with ablation in 19 patients (44.2%). Five patients (11.6%) had valvular heart disease and 1 (2.3%) had coronary artery disease. Hypertension was documented in 9 (20.9%) patients. The left atrium maximal transverse diameter was 42.2±5.8 mm. The ejection fraction was 59.2±3.6%. Patient characteristics are summarized in Table 1 according to the type of AF.

Description of the Protocol

The study protocol consisted of two to three procedures per patient.

First Procedure

During the first procedure, electrical disconnection of both (ie, lateral and septal) superior PVs and of a middle PV, when present, was aimed for. At the end of the session, patients were discharged under AA drugs and oral anticoagulants.

Second Procedure

A second procedure was planned at least 3 months later, before which AA drugs were discontinued for 15 days. During this procedure, both superior (and middle) PVs were mapped and reablated in case of conduction recurrence. In addition, 10 to 15 RF pulses ("refinement" pulses) were empirically delivered proximal to the site of block, according to a perimetric design around the PV ostium.

At this stage, the protocol was dichotomized, depending on whether or not the patient had been free of symptoms and whether or not AF had been documented between the first and the second procedures: (1) patients without symptoms and AF concluded the protocol and were discharged under AA drugs that were then discontinued about 20 days later; (2) patients with symptoms and/or documented AF after the first procedure underwent electrical disconnection of both (ie, lateral and septal) inferior PVs and the superior vena cava (SVC); also, RF pulses were delivered at the endocardial surface corresponding to the Marshall vein, as identified according to EP criteria; these patients were discharged under AA drugs and oral anticoagulants.

Third Procedure

In candidates for a third procedure, AA drugs were discontinued 15 days in advance. During this procedure, all PVs were mapped and reablated in case of recurrence. In addition, 10 to 15 RF refinement pulses were delivered to each of the inferior PVs.

We anticipated that the possibility of a fourth procedure would be discussed with the patient if symptoms or evidence of recurrent AF were observed at the end of the protocol.

Oral anticoagulants were discontinued 6 months after the end of the protocol in the absence of AF.

Electrophysiological Study

A transesophageal echocardiogram was performed before each procedure. Oral anticoagulants were replaced 3 days before admission by subcutaneous heparin.

For each procedure, 4 multipolar catheters were introduced. Through a left femoral venous approach, a 6F decapolar catheter was advanced to the His bundle region. Through the left subclavian venous approach, a 6F decapolar catheter was advanced to the distal coronary sinus; and, finally, with two SF long sheaths (Daig, St Jude) advanced through the right femoral vein, a 7F 4-mm-tip quadripolar ablation catheter (Bard Electrophysiology) and a 15- or 20-mm-diameter decapolar preformed circular catheter (Lasso, Webster Biosense) were placed transseptally at the ostium of the target PVs for detailed mapping and ablation.

Selective pulmonary venography allowed identification of PV ostia and assessment of the anatomy and the diameter before and after ablation. RF pulses of 60-second duration were delivered at sites of earliest circumferential activation, using preset values of 50°C limit temperature and 15-W limit power. At sites where changes in the PV activation sequence were observed and at reconnecting sites, the pulse duration was extended to 120 seconds and power increased to a limit of 30 W. Disconnection from the adjacent left atrial potential was indicated by elimination or disso- ciation of all PV potentials distal to the ablation site.5,6 With the Lasso catheter positioned distal to the ablation site, we referred to the A-PV interval as to the time interval between the onset of the earliest atrial (A) and the earliest (earliest A-PV) PV potential recorded by any of the 10 catheter electrode pairs.

Local PV electrograms at ablation sites were evaluated 30 minutes after electrical disconnection, and reablation was performed if conduction recurred.

Ablation of the vein of Marshall was attempted by means of 5 to 10 RF pulses (limit preset temperature, 55°C; limit power, 50 W) applied at endocardial sites on the assumed course of the ligament of Marshall and highlighted by the presence of local potentials dissociated from the A potential during pacing from the coronary sinus.7 Electrical disconnection of the SVC was attempted by means of RF pulses at sites of earliest A-SVC potentials recorded by the Lasso catheter positioned inside the SVC, distal to the ablation site.7,8 Bipolar electrograms (bandpass, 0.01 to 500.00 Hz) were recorded on a multichannel polygraph (LabSystem Duo, Bard Electrophysiology). Bipolar stimulation (cycle length, 600 to 800 ms) was performed at twice diastolic threshold with a pulse width of 2 ms. RF energy was applied with a StocKert (Cordis Webster) generator delivering a 500- to 550-kHz sine wave output.

Deep sedation was achieved by means of intravenous pentanest, midazolam, and propofol. After the double transseptal puncture, intravenous heparin was administered at the dose of 0.5 mg/kg, followed by a repeat bolus to ensure an antithrombin coagulation time (ACT) constantly above 240 seconds.

The next day, a control transthoracic echocardiogram was performed and oral anticoagulants were reinitiated. Patients were discharged 48 hours after the procedure.

Clinical Follow-Up

The clinical follow-up was initiated at the end of the protocol. Evidence for AF was evaluated by means of a 24-hour Holter monitoring performed at months 1, 2, and 3 and by outpatient evaluation at months 1 and 3. After completion of the protocol, a 24-hour Holter monitor and an outpatient evaluation or transtelephonic interview were scheduled at months 1, 3, 6, and 12 and every 6 months thereafter. In addition, patients were invited to contact our center in case of symptom recurrence.
**Statistics**

Descriptive analysis was performed with the use of mean±SD for continuous variables and percentage values for noncontinuous variables. Mean changes in A-PV intervals were compared by means of the Student’s t test for dependent samples (α=0.05). Noncontinuous variables were compared by means of the χ² Fisher’s exact test (α=0.05). Cumulative event rates were calculated by means of the Kaplan-Meier method, with the time to the first event as the outcome variable.

**Electrophysiological Data**

One hundred seventeen PVs were targeted for electrical disconnection during 108 sessions (2.6±0.5 per patient). In detail, 17 patients underwent 2 sessions (time interval from former session, 4.3±1.8 months), 20 patients underwent 3 sessions (5.1±2.4 months), and 3 patients underwent 4 sessions (5.7±1.2 months). Session duration and fluoroscopy time were 194±65 minutes and 29±13 minutes, respectively.

During the first ablation attempt, electrical disconnection was obtained in 39 (95.1%) of 41 left superior (LS) PVs, 40 (95.2%) of 42 right superior (RS) PVs, 24 (96.0%) of 25 left inferior (LI) LIPVs, and 9 (100%) of 9 right inferior (RI) PVs with 24.1±11.7, 23.7±14.4, 6.2±9.8, and 2.0±7.2 minutes of RF delivery, respectively (Table 2). RF pulses were delivered 3.2±1.1 mm inside the PV ostium. Recurrence of conduction within 30 minutes from disconnection was observed in 4 LSPVs (10.3%), 2 RSPVs (5.0%), 1 LIPV (4.2%), and 0 RIPV (0%). One patient (2.3%) had interpulmonary connections between the LSPV and the LIPV. Two patients (4.6%) had spontaneous episodes of AF and underwent disconnection of the culprit PV only (LSPV in 1 and RSPV in 1). A middle septal PV with a separate ostium was found in 4 patients (9.3%) and was disconnected with 2.2±0.7 minutes of RF delivery in all cases. In 17 patients, access to the RIPV was not possible because of adverse anatomy; in these patients, 3.5±1.9 minutes of RF delivery were applied empirically at the PV ostium.

During the second ablation attempt, a first conduction recurrence across the disconnecting lesion was observed in 32 (82.1%) of 39 LSPVs, 29 (72.5%) of 40 RSPVs, 20 (83.3%) of 24 LIPVs, and 7 (73.8%) of 9 RIPVs (Table 2). Table 3 shows the changes in the shortest and the longest A-PV intervals recorded at baseline between the first and the second procedure and between the second and the third procedures, according to the different targeted PVs. Larger increments of shortest A-PV (69.7±30.7 versus 60.6±22.1, P<0.05) and longest A-PV intervals (107.7±36.7 versus 92.5±27.3, P<0.05) were found in 14 patients who became asymptomatic as compared with 21 patients who remained symptomatic. No conduction recurrences were observed in any of the targeted PVs within 30 minutes from disconnection. The correlation between the presence or absence of conduction recurrence across the isolating lesion in LSPVs and/or RSPVs and the clinical outcome between the first and the second sessions is reported in Table 4.

At sites of conduction gap, reablation was successfully performed in all PVs with 12.5±12.3, 10.5±11.64, 2.9±5.6, and 0.4±1.2 minutes of RF delivery, respectively.

During the third ablation attempt, a second conduction recurrence across the isolating lesion was observed in 13 (59.1%) of 22 LSPVs and 14 (73.7%) of 19 RSPVs; 10 patients with conduction recurrences across the disconnecting line did not undergo a third procedure because they were asymptomatic and free of documented AF after the first procedure. No conduction recurrences were observed in any of the targeted PVs within 30 minutes from disconnection. The correlation between the presence or absence of conduction recurrence across the isolating lesion in LSPVs and/or RSPVs and the clinical outcome between the first and the second sessions is reported in Table 4.

In 3 patients, a fourth session was proposed because of the persistence of symptoms at the end of the protocol. Recurrence in 1 or more targeted PVs was found in all cases and was reablated with 5.4±1.7 minutes of RF delivery.

### Table 2. Relation Between Acute Disconnection and Late Recurrence Across Ostial Pulmonary Venous RF Lesions Observed in Targeted PVs During Different Procedures of Study Protocol

<table>
<thead>
<tr>
<th>Target Vein</th>
<th>Disconnection During First Ablation Attempt</th>
<th>Conduction Recurrence During Subsequent Ablation Attempts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First Procedure (Patients=43)</td>
<td>Second Procedure (Patients=43)</td>
</tr>
<tr>
<td>LSPV</td>
<td>39/41*† (95.1%)</td>
<td>...</td>
</tr>
<tr>
<td>RSPV</td>
<td>40/42† (95.2%)</td>
<td>...</td>
</tr>
<tr>
<td>LIPV</td>
<td>...</td>
<td>24/25* (96.0%)</td>
</tr>
<tr>
<td>RIPV</td>
<td>...</td>
<td>9/9§ (100%)</td>
</tr>
</tbody>
</table>

*One patient excluded because of presence of a common orifice in PVs.
†One patient excluded because of RF ablation delivered only at one other (culprit) PV.
‡Ten patients with a first conduction recurrence across the disconnecting line did not undergo a third procedure because they were asymptomatic and free of documented AF after the first procedure.
§Access to PV not possible in the remaining 17 patients.
Clinical Data After Conclusion of the Protocol

During a follow-up of 9.1 ± 7.0 months, of which 8.0 ± 5.9 were free of AA drugs, 41 (95.3%) of 43 patients did not have any subjective or objective evidence of AF recurrence (Figure 2). In two patients with paroxysmal AF, a single AF episode terminated early after intake of oral flecainide was reported after 8 and 11 months of follow-up; AA drug therapy and oral anticoagulation were reinitiated and associated with no later clinical recurrences. In another patient, AAs were readministered because of repeat symptomatic atrial premature beats.

Complications

One patient had hemothorax from the subclavian puncture requiring drainage. In the other 2 patients, local surgery was required to repair a right femoral pseudoaneurysm and a left femoral arteriovenous fistula, respectively. A 20% to 30% narrowing of one PV was observed in 8 (18.6%) patients by selective pulmonary venography 4 to 9 months after the ablation procedure; these patients were asymptomatic.

Discussion

The results of this study demonstrate that late conduction recurrence across acutely disconnecting RF lesions delivered at the ostia of multiple PVs is a common finding in patients undergoing catheter ablation of AF. About 5 months after the first attempt, we found that 79% of ablated PV ostia showed some degree of conduction recurrence. Five months after a new disconnection during a second ablation attempt, conduction reoccurred again in 66% of superior PVs, and a third recurrence in the superior PVs was documented in 3 patients still symptomatic at the end of the protocol who accepted a fourth catheter procedure.

Together with alternative techniques for PV ablation,11 the strategy of disconnecting PVs at proximal sites has proven appropriate; however, its effectiveness has failed to match the expectations based on a PV electrical disconnection rate >95%.4,6,7,9 Investigators have outlined a potential correlation between clinical failure and conduction recurrence across RF disconnecting lesions, and repeat ablations have proved effective in increasing clinical success.4 Still, arrhythmia recurrence has been documented in 20% to 40% of patients despite multiple attempts, and we lack predictors of failure.3,4,6,7,9 The data from the present study show that conduction recurrence across RF disconnecting lesions within one or multiple PVs is not only associated with AF recurrence after a single ablation procedure but also with new AF recurrences after subsequent ablation procedures.

An interesting observation from this study is that clinical success after the first procedure was observed in 32% of patients despite the presence of late conduction recurrence.
across the disconnecting line of one or both superior PVs (Table 4); in particular, 11 (79%) such patients had conduction recurrences in both superior PVs. This finding suggests that clinical efficacy of catheter approaches aiming at PV electrical disconnection can also be achieved, at least for some time, despite conduction recurrence. Causes accounting for this effect may include occasional ablation of the culprit arrhythmogenic focus and severe impairment of conductive PV tissue crucial for arrhythmia generation and/or perpetuation. The latter speculation is supported by the observation that larger increments of shortest and longest A-PV intervals were found in patients who became asymptomatic as compared with patients who remained symptomatic between the first and the second procedure.

The overall success rate in the present series is very encouraging, and, if confirmed in larger populations with similar or even more complex anatomic characteristics, may contribute to improve our understanding about the pathophysiology of human AF and the current success rate of ablation techniques.

**Study Limitations**
A systematic approach based on 2.6 procedures per patient should be regarded as investigational and offers poor applicability to common clinical practice. In our experience, such an approach was not associated with an increased risk of complications, and the patient compliance to the protocol was 100%. Also, the information collected by using the present approach may help to develop improved techniques to minimize the number of procedures required for a successful outcome.
Because the amount of maximal energy delivered in accordance with the present protocol was lower than that used by other investigators, we cannot exclude that the incidence of conduction recurrence in this study is overestimated. However, achievement of the limited preset temperature was obtained in most instances despite 10 to 15 W of applied energy, and conduction block was obtained in 95% of targeted PVs. In addition, at all sites showing activation changes or electrical disconnection, the maximum power was increased to 30 W, with the aim to minimize the gap between the temperature recorded at the thermocouple and that at the target tissue.

In the present study, a clinical outcome free of symptoms was regarded as indicative of clinical efficacy. In addition, a 24-hour Holter monitoring free of AF was used to corroborate the clinical observation with regard to possible asymptomatic episodes. Because we could not continuously monitor the ECG, it is not possible to exclude that asymptomatic AF may have recurred in some patients.

Finally, the present study does not allow us to draw conclusions about the relation between electrical disconnection of the targeted PVs and clinical outcome. In fact, empiric ablation of Marshall veins and disconnection of SVC in subsets of patients as well as refinement lesions may have contributed in variable and not measurable degree to the clinical effect.

Conclusions

Using a prospectively designed, multistep approach, late conduction recurrence across disconnecting RF lesions was found in \( \approx 80\% \) of the targeted PVs. Reablation at gap sites did not prevent a second recurrence in \( \approx 65\% \) of superior PVs. The high rate of late recurrence may contribute significantly to clinical recurrence in patients with AF undergoing catheter ablation aiming at electrical disconnection of multiple PVs.

References

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