Predictive Value of Early Atrial Tachyarrhythmias Recurrence After Circumferential Anatomical Pulmonary Vein Ablation

EMANUELE BERTAGLIA,* GIUSEPPE STABILE,† GAETANO SENATORE,‡ FRANCO ZOPPO,* PIETRO TURCO,§ CLAUDIA AMELLONE,‡ ANTONIO DE SIMONE,† MASSIMO FAZZARI,‡ and PIETRO PASCOTTO*

From the *Dipartimento di Cardiologia, Ospedale Civile di Mirano (VE); †Laboratorio di Elettrofisiologia, Casa di Cura “San Michele” di Maddaloni (CE); ‡Unità Operativa di Cardiologia, Ospedale Civile di Giriè (TO); and §Laboratorio di Elettrofisiologia, Casa di Cura “Villa Maria” di Cotignola (RA), Italy

BERTAGLIA, E., ET AL.: Predictive Value of Early Atrial Tachyarrhythmias Recurrence After Circumferential Anatomical Pulmonary Vein Ablation. Objective: Radiofrequency (RF) ablation at the ostia of the pulmonary veins (PVs) to cure atrial fibrillation (AF) is often followed by early AF recurrence. The aims of this study were to determine the rate of early atrial tachyarrhythmias as recurrence after circumferential anatomical PV ablation; to evaluate whether the early recurrence of atrial tachyarrhythmias correlates with the long-term outcome of ablation; and to identify the predictors of early atrial tachyarrhythmias relapse.

Methods: We studied 143 consecutive patients who underwent circumferential anatomical PV ablation. We defined early atrial tachyarrhythmias relapse as the recurrence of atrial tachyarrhythmias during the first 3 months after RF ablation.

Results: After a mean follow-up of 18.7 ± 7.2 months, 102/143 patients (71%) were deemed responders to ablation. Atrial tachyarrhythmias relapsed during the first 3 months of follow-up in 65/143 (46%) patients. Patients without early atrial tachyarrhythmias relapse had a higher probability of long-term clinical success than patients with early atrial tachyarrhythmias relapse (95% vs 43%, P < 0.0001). However, patients who relapsed within the first month had 45.5% probability of long-term clinical success. On multivariate analysis, the presence of structural heart disease and the lack of a successful anatomical ablation of all targeted PV were significantly and independently correlated with early atrial tachyarrhythmias relapse.

Conclusion: A delayed cure may be expected in almost 50% of patients in whom atrial tachyarrhythmias relapses within the first month after circumferential anatomical PV ablation. The presence of structural heart disease and the lack of a successful anatomical ablation of all targeted PV predict early atrial tachyarrhythmias recurrence. (PACE 2005; 28:366–371)

atrial fibrillation, transcatheter ablation, early relapse

Introduction

Radiofrequency (RF) catheter ablation has recently been proposed as a treatment for drug-refractory paroxysmal and permanent atrial fibrillation (AF).1 Since the discovery of the pivotal role of the ostium of the pulmonary veins (PVs) in initiating and perpetuating AF, two different ablative approaches have been developed to isolate the PV ostium: electrophysiologically guided segmental ablation, and circumferential anatomical ablation.2,3 Both strategies display a high rate of acute success, followed, early on, by the reappearance of premature atrial contractions and AF recurrences, which does not seem to predict a poor long-term outcome. However, few data regarding this issue are to be found in the literature, and all refer to the segmental approach.4,5 It was our impression that the large number of RF energy applications required for circumferential ablation constituted an even greater trigger to early AF relapses than the more selective applications required for segmental ablation.

Aims of this study were: to determine the rate of atrial tachyarrhythmias recurrence within the first 3 months after circumferential anatomical PV ablation; to evaluate whether early atrial tachyarrhythmias relapse correlated with the long-term outcome of circumferential anatomical ablation; and to identify the predictors of early atrial tachyarrhythmias relapse.

Methods

Of 158 consecutive patients who underwent circumferential anatomical PV ablation using the CARTO nonfluoroscopic navigation
system (Biosense Webster) for paroxysmal or persistent AF refractory to ≥2 antiarrhythmic drugs in three different Italian hospitals (Ciriè, Madaloni, Mirano) from March 2001 to March 2003, we considered 143 patients who had not yet undergone a PV ablation procedure. All patients underwent ablation while receiving previous ineffective antiarrhythmic therapy, which was continued for at least 7 months. After this period, the decision to continue or not the antiarrhythmic medications was based not only on AF occurrence, but also on the presence of ectopic beats or heart disease.

Transesophageal and transthoracic echocardiography was performed before ablation in order to measure the left atrial antero-posterior diameter and the left ventricular ejection fraction, and to exclude the presence of intra-atrial thrombi.

The details of mapping and RF ablation of PV ostia have already been published.\textsuperscript{6,7} Two quadripolar catheters were inserted through the right femoral vein and left subclavian vein and were placed in right ventricular apex and coronary sinus, respectively. Left atrium and PV were explored using a transseptal approach. Real-time 3D left atrium maps were reconstructed using a non-fluoroscopic navigation system (CARTO, Biosense Webster Inc., Diamond Bar, CA, USA), acquiring a minimum of 60 points. External or internal cardioversion was performed before starting 3D mapping. Maps were acquired during pacing from the coronary sinus or, in patients with immediate AF relapse, during AF. The ostium of the PV was identified by fluoroscopic visualization of the catheter tip entering the cardiac silhouette with simultaneous impedance decrease and appearance of atrial potential. RF pulses were delivered using a 3.5-mm (with a temperature setting up to 45°C and a RF energy up to 50 W) cooled-tip catheter (Navistar, Biosense Webster Inc.). RF energy was delivered up to 120 seconds until the local electrogram amplitude was reduced ≥80%. RF ablation sites were tagged by red dots on the reconstructed 3D map. The ablation lines consisted of contiguous focal lesion deployed at a distance ≥5 mm from the ostia of the PVs, creating a circumferential line of conduction block around each PV or around ipsilateral PVs according to the anatomy (Fig. 1A). Remap process was performed in all patients preferentially in sinus rhythm, utilizing the preablation anatomic map for acquisition of new points. A minimum of 5 points per each circumferential line was sampled. The end point of the ablation procedure was low

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**Figure 1.** (A) 3D reconstructed map of left atrium in posteroanterior view. Black dots identify circumferential lines of ablation around the ipsilateral PV. Tubes identify PV: 1 superior PV and 1 inferior PV with a common ostium on the left; 1 superior PV with an early branch and 1 inferior PV on the right. (B) 3D reconstructed map of left atrium in left lateral view. Solid black arrow indicates the ablation line along the isthmus between the mitral annulus and the left inferior PV.
peak-to-peak bipolar potentials (<0.1 mV) inside the lesion, as determined by local electrogram analysis.

Starting from the beginning of 2002, adjunc-tive RF ablation lines were created in the right or left atrium: along the cavo-tricuspid isthmus with electrophysiological assessment of transisthmic block, and along the isthmus between the mitral annulus and the left inferior PV (Fig. 1B) without electrophysiological assessment of transisthmic block.

After RF ablation, cardiac rhythm was continu-ously monitored during the first 36–48 hours. Outpatient visits and 24-hour ECG Holter monitor-ing were scheduled at 1 month, 3 months, and every 3 months thereafter. Patients were also advised to undergo an additional ECG in the event of pal-pitations. Transesophageal echocardiography was usually repeated 3 months after ablation in order to exclude the presence of PV’s stenosis.

We defined early relapse as the occurrence of atrial tachyarrhythmias during the first 3 months after RF ablation. Patients who did not present symptomatic or asymptomatic atrial tachyarrhythmias lasting >30 seconds after the first 3 months of follow-up were classified as responders.

Patients with early relapses who did not convert spontaneously into sinus rhythm during the first 3 months underwent electrical cardioversion.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation (range). Discrete variables are presented as percentages. Univariate comparisons between variables were made by means of Fisher’s exact test or χ² test for categorical variables, and unpaired Student’s t-test for continuous variables. To compare groups, categorical variables were tested using the χ² test. A P value <0.05 was considered statistically significant.

To identify predictors of early atrial tachyarrhythmias relapse, a multivariate analysis with a logistic regression and stepwise backward selection according to Wald was performed using all the variables with a P < 0.10 on the univariate analysis.

Cox proportional hazards multivariate regression analysis was performed to determine the clinical and procedural predictors of responders to PV ablation among patients with early atrial tachyarrhythmias relapse using all the variables with a P < 0.10 on the univariate analysis.

A significant increase in risk was obtained if the 95% confidence interval exceeded 1 and the P value of the Wald test was <0.05.

Results

Clinical Characteristics

We analyzed the follow-up of 143 patients (66% male) with paroxysmal (45%) or persistent (55%) drug-refractory AF. The mean age was 61.4 ± 8.1 years (35–78). Their arrhythmic history lasted 5.0 ± 4.0 years (0.5–20), and they had tried a mean of 3.2 ± 0.8 antiarrhythmic drugs (2–5).

A structural heart disease was present in 89/143 patients (62%): hypertension was the most frequent disease (present in 73 patients), followed by ischemic heart disease (14 patients). The mean antero-posterior left atrial diameter was 47.4 ± 5.2 mm (36–63), and the mean left ventricular ejection fraction was 57.7 ± 8.4% (25–77). Only 6 patients (6%) presented an impaired systolic function (left ventricular ejection fraction lower than 40%).

Mapping and Ablation Procedure

The mean number of separate PV ostia mapped per patient was 4.0 ± 0.5 (2–6), while the mean number of separate PV ostia encircled per patient was 3.8 ± 0.7 (2–6). The mean procedure duration was 199.7 ± 73.1 minutes (63–530), and the mean fluoroscopic exposure 26.2 ± 10.8 minutes (10–67). The mean duration of RF applications per patient was 55.5 ± 17.4 minutes (23–116), and the mean duration of RF applications per each isolated PV ostium was 15.2 ± 6.1 minutes (5–45).

Documentation of successful anatomical ablation of all the targeted PV was obtained in 125/143 (87%) patients. Ablation of the right isthmus was performed in 118/143 (83%) patients, while ablation of the left isthmus was performed in 96/143 (68%) patients.

Major complications were observed in 6/143 patients (4.2%): cardiac tamponade in 2; transient paralysis of the right phrenic nerve in 1; transient ischemic attack in 1; AV block in 1; and pseudoaneurysm of the right femoral artery in 1.

Clinical Outcome

After a mean follow-up of 18.7 ± 7.2 months (9–36), 102/143 (71%) patients were deemed responders. Among these, 64/102 (62%) were still on a previous ineffective antiarrhythmic drugs: 40/102 (39%) on amiodarone, and 24/102 (23%) on 1C class drugs.

Early Atrial Tachyarrhythmias Relapse

Atrial tachyarrhythmias relapsed during the first 48 hours in 32/143 (22%) patients, between the first 48 hours and the first month in 28/143 (20%) patients, and during the second and third month in 5/143 (3%) patients. In total, 65/143 (46%) patients had atrial tachyarrhythmias during the first 3 months of follow-up (AF in 62 and
left atrial flutter in 3). Sinus rhythm had to be restored by means of electrical cardioversion in 20/65 (31%) patients who experienced atrial tachyarrhythmias during the first 3 months. Left atrial flutter disappeared spontaneously after the first 3 months in 2 patients, while it persisted also after the first 3 months in the other patient, and was successfully ablated. However, for the aim of the study this patient was considered nonresponder to AF ablation.

Predictors of Early Atrial Tachyarrhythmias Relapse

Results of univariate analysis are presented in Table I. Early atrial tachyarrhythmias relapse resulted more frequent in patients with structural heart disease (73.8% vs 50.0%, P = 0.004), and less frequent in patients in whom all targeted PVs were successfully ablated (80.0% vs 93.6%, P < 0.02).

On multivariate analysis, the presence of structural heart disease (HR 2.322, 95% confidence intervals 1.091–4.941, P < 0.03) proved significantly and independently correlated with early atrial tachyarrhythmias relapse, while successful anatomical ablation of all targeted PV (HR 0.310, 95% confidence intervals 0.101–0.950, P = 0.04) inversely correlated with early atrial tachyarrhythmias relapse.

Predictive Value of Time Course of Early Atrial Tachyarrhythmias Relapses

Patients without early atrial tachyarrhythmias relapse had a higher probability of long-term clinical success than patients with early atrial tachyarrhythmias relapse (95% vs 43%, P < 0.0001) (Table II). Among patients without early atrial tachyarrhythmias relapse, late AF recurrence occurred only in four cases (3 on antiarrhythmic drugs, 1 after the discontinuation of antiarrhythmic drug).

In order to ascertain whether the time course of early atrial tachyarrhythmias relapses could influence the clinical outcome of RF ablation, we compared three groups of patients: those with atrial tachyarrhythmias relapses during the first 48 hours, those with atrial tachyarrhythmias relapses between the first 48 hours and the first month, and those with atrial tachyarrhythmias relapses between the second and the third month.

Patients who relapsed during the first 48 hours, and patients who relapsed between the first 48 hours and the first month had a higher probability of long-term clinical success than patients who relapsed during the second or third month (45.5% vs 42.9% vs 20.0%, respectively).

Table I.

Predictors of Early Atrial Tachyarrhythmias Relapses: Results of Univariate Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Early Relapse</th>
<th>Early Relapse</th>
<th>P</th>
<th>Variable</th>
<th>No Early Relapse</th>
<th>Early Relapse</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>67.9</td>
<td>63.1</td>
<td>0.54</td>
<td>Duration of RF/PV (minutes)</td>
<td>15.4 ± 5.4</td>
<td>15.4 ± 6.7</td>
<td>0.73</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.8 ± 8.9</td>
<td>62.0 ± 6.8</td>
<td>0.38</td>
<td>Ablated PV (n)</td>
<td>3.8 ± 0.7</td>
<td>3.9 ± 0.7</td>
<td>0.65</td>
</tr>
<tr>
<td>History of AF (years)</td>
<td>4.7 ± 3.8</td>
<td>5.4 ± 4.2</td>
<td>0.35</td>
<td>PV anatomical ablation (%)</td>
<td>93.6</td>
<td>80.0</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>SHD (%)</td>
<td>50.0</td>
<td>73.8</td>
<td>0.004</td>
<td>RA isthmus ablation (%)</td>
<td>83.3</td>
<td>82.8</td>
<td>0.93</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>57.6 ± 7.5</td>
<td>58.0 ± 9.4</td>
<td>0.76</td>
<td>LA isthmus ablation (%)</td>
<td>73.1</td>
<td>60.9</td>
<td>0.12</td>
</tr>
<tr>
<td>Left atrial size (mm)</td>
<td>46.7 ± 5.4</td>
<td>48.3 ± 4.9</td>
<td>0.06</td>
<td>Amiodarone during early</td>
<td>62.8</td>
<td>54.5</td>
<td>0.41</td>
</tr>
<tr>
<td>follow-up (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal AF (%)</td>
<td>53.8</td>
<td>56.9</td>
<td>0.71</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; LA = left atrial; LVEF = left ventricular ejection fraction; PVs = pulmonary veins; RA = right atrial; RF = radiofrequency; SHD = structural heart disease. Data are presented as mean ± SD if not otherwise specified.

Table II.

Relationship Between Long-Term Outcome of PV Ablation and Occurrence of Early Atrial Tachyarrhythmias Relapse

<table>
<thead>
<tr>
<th>Patients to PV Ablation</th>
<th>Responders</th>
<th>Nonresponders</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with early relapse</td>
<td>28</td>
<td>37</td>
<td>65</td>
</tr>
<tr>
<td>Patients without early relapse</td>
<td>74</td>
<td>4</td>
<td>78</td>
</tr>
<tr>
<td>Total</td>
<td>102</td>
<td>41</td>
<td>143</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation.
P < 0.005). Accordingly, patients who were in atrial tachyarrhythmias at the 1-month follow-up examination were significantly more responsive than patients who were still in atrial tachyarrhythmias at the 3-month examination (41.0% vs 14.0%, P < 0.005). In addition, considering only patients who relapsed within the first month, only 3 of 29 (10%) of those who continued to present atrial tachyarrhythmias during the second and third month resulted responders to ablation.

At univariate and multivariate analysis no clinical and procedural variables identified responders to PV ablation among patients with early atrial tachyarrhythmias relapse.

Discussion

Main Findings

This study demonstrated that the rate of early atrial tachyarrhythmias relapse is very high (46%) after circumferential anatomical PV ablation. Patients who did not relapse within the first 3 months had a very good (95%) long-term clinical outcome. Nevertheless, almost half of the patients with atrial tachyarrhythmias relapses within the first month had a good long-term clinical outcome despite these early atrial tachyarrhythmias relapses. The presence of structural heart disease and the lack of successful anatomical ablation of all targeted PV identified patients with early atrial tachyarrhythmias relapses.

Early Atrial Tachyarrhythmias Relapse After Circumferential Ablation

In the early years of PV ablation, it was usual to repeat the procedure if AF recurred during the first few days. The possibility of a delayed cure of AF after PV ablation has only recently been supported. Oral et al. reported a 35% rate of atrial tachyarrhythmias recurrence within 2 weeks after segmental isolation of 3 to 4 PV in 110 consecutive patients mainly affected by drug-refractory paroxysmal AF. The rate of long-term clinical success in patients without early atrial tachyarrhythmias recurrences was obviously significantly higher than in those with early atrial tachyarrhythmias relapses (85% vs 31%). Nevertheless, approximately 30% of patients with early atrial tachyarrhythmias recurrences had no further symptomatic atrial tachyarrhythmias, without antiarrhythmic drug treatment, during a mean follow-up of about 7 months. In the paper by O'Donnell et al., atrial tachyarrhythmias relapsed within 3 months of segmental ablation in 26 out of 50 (52%) patients with drug-refractory paroxysmal or persistent AF; however, a delayed cure of AF was observed in 10 of these 26 (39%) patients after a follow-up of 9 months.

Our results demonstrated that the incidence of early atrial tachyarrhythmias relapses was as high after circumferential anatomical PV ablation as after segmental ablation. In accordance with the approach adopted by O’Donnell et al., we prolonged the period in which atrial tachyarrhythmias recurrences were defined as early to 3 months, as we had the impression that a good long-term clinical outcome might also be achieved in several patients who continued to present AF during the first 3 months after ablation. However, not only did almost all (93%) early atrial tachyarrhythmias relapses occur during the first month, but also a delayed cure was observed in only 10% of those patients who relapsed during the first month and who continued to present atrial tachyarrhythmias during the second and third month.

Predictors of Early Atrial Tachyarrhythmias Relapse

Among several clinical and procedural variables, only the presence of structural heart disease and the lack of successful anatomical ablation of all targeted PV identified patients with early atrial tachyarrhythmias relapses.

According to O’Donnell et al., the absence of structural and electrical abnormalities of the left atrium distinguished patients with an acute cure from those with a delayed cure. It is reasonable that an anatomically remodeled atrium requires more time after ablation to reverse its vulnerability to AF triggers, and is more susceptible to early AF relapses.

Our finding of a correlation between the lack of successful anatomical ablation of all targeted PV and the early recurrence of AF might shed light on the significance of early AF relapse after PV ablation. Early AF relapses after PV ablation used to be regarded as the expression of an acute stimulatory effect of RF energy or a delayed therapeutic effect of RF ablation. The correlation between the absence of successful PV ablation and early AF relapse seems to favor the hypothesis of a delayed effect of RF energy. It could be that, even in the PV that were not acutely ablated, a slow process of scarring led to a delayed cure. It has recently been reported in a canine model that a significant proliferative and inflammatory component of PV ablation reached its peak after 42 days, and then decreased over 120 days. In another animal study, complete replacement of necrotic muscle with collagen was observed only 4 weeks after RF PV ablation.

Another point against the hypothesis of a stimulatory effect of RF applications is that we should expect a higher rate of early atrial tachyarrhythmias relapse after extensive circumferential anatomical PV ablation than those already
reported after segmental PV isolation.\textsuperscript{4,5} Indeed, circumferential anatomical PV ablation required a mean of 15.2 minutes RF application per isolated PV ostium, while segmental PV isolation required only 6.4 minutes.\textsuperscript{4} However, despite a great amount of RF application, the rate of atrial tachyarrhythmias relapse was similar: 35\% 2 weeks after segmental PV isolation and 43\% 1 month after circumferential anatomical PV ablation.

**Study Limitations**

Our findings and conclusions should be interpreted in the light of a retrospective analysis of the data.

Atrial tachyarrhythmias recurrences were quantified on the basis of patients’ symptoms, serial ECGs, and Holter monitoring. Trans-telephonic monitoring was available only in a subgroup of patients and was limited to the first months after ablation. Therefore, many asymptomatic AF episodes may have gone undetected.

Most of our patients remained on antiarrhythmic drugs during the follow-up: this could have favorably affected the good long-term outcome of circumferential anatomical PV ablation.

**Clinical Implications**

According to our findings, it seems reasonable, in the event of early atrial tachyarrhythmias recurrences after circumferential anatomical PV ablation, to wait for at least one month before repeating the procedure, as a delayed cure may be expected in almost 50\% of these patients. Patients who continue to present AF after the first month have a very low (10\%) probability of a delayed cure.

**References**

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