Can Common-Type Atrial Flutter Be a Sign of an Arrhythmogenic Substrate in Paroxysmal Atrial Fibrillation?

Clinical and Ablative Consequences in Patients With Coexistent Paroxysmal Atrial Fibrillation/Atrial Flutter

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Background—The coexistence of atrial fibrillation (AF) and atrial flutter (AFL) is well recognized. AF precedes the onset of AFL in almost all instances. We evaluated the effect of 2 ablation strategies in patients with paroxysmal AF (PAF) and AFL.

Methods and Results—Ninety-eight patients with PAF/AFL were prospectively recruited to undergo pulmonary vein cryoisolation (PVI). Those with at least 1 episode of sustained common-type AFL were assigned to cavotricuspid isthmus cryoablation followed by a 6-week monitoring period and a subsequent PVI (n=36; group I). Patients with PAF only underwent PVI (n=62; group II). The study included 76 men with a mean age of 50±10 years. Most patients (76 [78%]) had no structural heart disease. When the 2 groups were compared, residual AF after a blanking period of 3 months after PVI occurred in 24 patients (67%) in group I versus 7 (11%) in group II (P<0.05).

Conclusions—In patients with PAF and no documented common-type AFL, PVI alone prevented the occurrence of AF in 82%, whereas in patients with AFL/PAF, cavotricuspid isthmus cryoablation and PVI were used successfully to treat sustained common-type AFL but appeared to be insufficient to prevent recurrences of AF. In this population, AFL can be a sign that non–pulmonary vein triggers are the culprit behind AF or that sufficient electrical remodeling has already occurred in both atria, and thus a strategy that includes substrate modification may be required. (Circulation. 2007;116:2786-2792.)

Key Words: atrial fibrillation ■ atrial flutter ■ electrophysiology ■ pulmonary veins ■ catheter ablation

It is known that for the macroreentry circuit of common-type atrial flutter (AFL) to occur, a line of block between the venae cavae needs to be present along with other fixed anatomic lateral boundaries (the crista terminalis and the tricuspid annulus).1–3 The former is almost always functional and usually develops during an initial period of transient atrial fibrillation (AF; Figure 1).4 Actually, Waldo suggests that in most instances, without preceding AF, there will be no classic AFL.5 Percutaneous ablative techniques for the treatment of AF can be performed with high success rates.6–10 Because of the likely role of AF as the initiator of AFL, we were interested in the best ablation approach for patients with paroxysmal atrial fibrillation (PAF) and AFL. Two cryoablation protocols in patients with PAF/AFL were evaluated prospectively in the present study with regard to the outcome of those arrhythmias.
period (group I; PAF/AFL). This group consisted of 36 patients. In patients in whom only PAF was documented (no history of sustained common-type AFL), only PVI was performed (group II). This group included 62 patients. A consent form, approved by the local ethics committee, was signed by all participants of the study.

Before PVI, all individuals were treated with oral anticoagulants to a therapeutic international normalized ratio of 2 to 3 for at least 3 weeks and up to 3 months after ablation. A transesophageal echocardiogram was performed during the procedure to exclude left atrial thrombus and to aid in the transseptal puncture. Antiarrhythmic drugs (AADs) were not discontinued before PVI.

Electrophysiological Study and Ablation

All patients were studied in the fasting state without sedation. Those presenting in AF while in the catheterization room were converted to sinus rhythm by internal or external cardioversion.

Group I underwent CTI cryoablation first. The following protocol was used: intravenous heparin was given as a 100-IU/kg bolus dose after the venous sheaths were inserted; via the femoral route, a decapolar catheter was positioned in the distal coronary sinus (for evaluation of left atrial activation), a duodecapolar catheter (2-mm interelectrode spacing, Halo catheter, Biosense Webster, Baldwin Park, Calif) was placed to map the right atrial lateral wall, and a quadripolar catheter was inserted in the His bundle region. An additional deflectable 10.5F cryoablation catheter (CryoCor Inc, San Diego, Calif) with a 6.5-mm-tip electrode was inserted into the right atrium through a 12F, 65-cm-long sheath (DAIG, St Jude Medical or Cook Inc), and a linear lesion was created by use of a point-by-point technique with gradual pullback of the cryocatheter in a ventricular atrial fashion. The first application was delivered at the ventricular insertion of the CTI. Each cryoapplication lasted 3 minutes with a constant target temperature of −90°C. After bidirectional isthmus conduction block was achieved, short-term success was defined if it persisted for 30 minutes after the last application without and with isoproterenol infusion (1 to 3 μg/min). Oral anticoagulation therapy was continued for all patients, and patients returned 6 weeks later for their PVI. During this period, daily TTMs were provided to assess arrhythmia burden compared with the preablation TTM data.

The PVI cryoablation protocol has been described previously. Briefly, during the procedure (but after the transseptal punctures), intravenous heparin was given as a 100-IU/kg bolus dose, followed by boluses of 5000 IU every 1.5 hours if needed to maintain an activated clotting time ≥300 seconds. A decapolar catheter was positioned in the distal coronary sinus and a quadripolar catheter in the His bundle region via the femoral route. Double transseptal catheterization was performed under fluoroscopic and transesophageal guidance.

Left atrial angiography (to visualize the pulmonary vein [PV] ostia) was performed after adenosine administration. A deflectable, circumferential decapolar mapping catheter (LASSO, Biosense-Webster) was advanced into the left atrium and positioned at the ostium of each PV. A deflectable 10.5F cryoablation catheter (CryoCor Inc) with a 6.5-mm-tip electrode was inserted into the left atrium through a 12F, 65-cm-long sheath (DAIG, St Jude Medical or Cook Inc).

Segmental isolation of PVs, guided by the recording of their potentials with the LASSO catheter, was performed with the CryoCor cryoablation system as described previously. Efforts were made to identify the arrhythmogenic PV (culprit PV) by use of adenosine (24 to 40 mg) or isoproterenol (1 to 5 μg). If the culprit PVs were not identified, all veins with potentials recorded at their ostium were targeted for ablation. Isolation of the PV was performed during sinus rhythm or coronary sinus pacing by the delivery of cryoablation at ostial sites that had the earliest bipolar potential.

At each effective target site, defined by the abolishment of a PV potential or a change in the PV potential activation sequence during cryothermal application, 3 minutes of cryoablation was delivered. If no changes in the electrogram were observed after 20 seconds despite a catheter tip temperature of −90°C, the application was stopped, and the catheter was repositioned. The early procedural end point was complete electrical isolation of PVs based on abolition of all ostial PV potentials or complete entrance conduction block into the PV.
Postablation Management

Every patient was monitored in the hospital for 24 hours, and oral anticoagulation therapy was started the day of the ablation. The same AADs were continued for at least 3 months after the procedure. After 3 months, the need for long-term anticoagulation was assessed by the number of recurrences of AFL/PAF and the presence of risk factors for thromboembolic events.

All patients had a Holter recording at hospital discharge and during each clinic visit (1, 3, 6, 9, and 12 months) or earlier if they had symptoms. They were also instructed to keep a diary of events associated with their TTMs. A blanking period of 3 months (starting after the PVI procedure) was used before recurrences were assessed.

We adopted the following definitions according to the latest American College of Cardiology/American Heart Association/European Society of Cardiology guidelines for the management of patients with AF:15 (1) PAF was defined as self-terminating episodes of AF that lasted >30 seconds and up to 7 days (usually <24 hours); (2) common-type AFL was defined as organized atrial rhythm with a rate typically between 250 and 350 bpm in which the macroreentry circuit was dependent on the CTI in either a counterclockwise or clockwise fashion.

Statistical Analysis

Continuous variables are presented as mean±SD where appropriate. In cases of a non-normal distribution, medians and quartiles are given. Categorical variables are expressed as numbers and percentages of patients.

Statistical analysis was performed with the Student t test for unpaired data. The χ² test was used to compare categorical variables. The McNemar test was applied to evaluate the differences in medication use from preablation to post-PVI. A Kaplan–Meier analysis was used to estimate the probability of freedom from recurrent PAF. These curves were constructed for both groups with and without PAF recurrences and compared between them with the Wilcoxon and log-rank tests. All values were considered significant at P<0.05.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

Results

The study cohort consisted of 98 patients considered for segmental PVI after being appropriately screened by both the referring cardiologist and our group. Review of Holter recordings, TTMs, failure of AADs, functional capacity, type of AF, and imaging studies were the main criteria used to recruit patients. In patients with a prior history of coronary artery disease, myocardial perfusion studies were performed to exclude active ischemia.

The characteristics of the patients are shown in Table 1. The total number of patients was 98, with a mean age of 50±10 years (range 21 to 69 years). The majority of patients (n=76; 78%) had no structural heart disease. Of the 22 patients with structural heart disease, 6 had a history of coronary artery disease, and 16 had a history of arterial hypertension, all well-controlled at the time of ablation.

As previously mentioned, patients in group I first underwent CTI cryoaulation and then, 6 weeks later, PVI. During this period, daily TTMs were compared with those before CTI cryoaulation, and the average number of AF episodes per patient (1±1 registered daily AF episode) did not change. The long-term outcome of this group was as follows: most AFL recurrences occurred in the first 6 months, which confirmed our prior data,17 and 5 patients underwent a second successful CTI cryoaulation. Two of those AFL patients continued to have symptomatic AF episodes; therefore, a second PVI was performed. On the other hand, 24 patients had recurrences of PAF. In the majority of these (17 patients), the arrhythmia was well-controlled with an AAD. Six patients underwent a second successful PVI, and the remaining patient opted to undergo the Maze operation (Figure 2).

With regard to the long-term outcome of group II, 7 patients had PAF recurrences. All of these patients underwent a second PVI. Five patients were asymptomatic after the second procedure and did not require AADs. The remaining 2 patients were given an AAD. Interestingly, 5 of the 62 patients developed new-onset common-type AFL (along with sporadic PAF episodes) as the predominant arrhythmia, each of whom underwent a successful CTI ablation. Despite the CTI ablation procedure, all 5 patients continued to experience PAF. Their PAF was controlled with a repeat PVI (2 patients).
or an AAD (1 patient), and 2 patients had asymptomatic PAF and were not given an AAD (Figure 3). No differences existed in procedural characteristics with regard to PVI between group I (procedure time 337 minutes and fluoroscopy time 90 minutes) and group II (procedure time 331 minutes and fluoroscopy time 88 minutes; \( P = \text{NS} \)).

No significant differences were found when we compared the characteristics of the 2 groups (Table 1). The only 2 factors that reached statistical significance were residual PAF after PVI (24 [67%] versus 7 [11%] patients from groups I and II, respectively; \( P < 0.05 \)) and the number of patients who required an AAD after the 3-month blanking period after PVI (17 patients [47%] from group I and 5 [8%] from group II; \( P < 0.05 \); Table 2).

The results of patients who underwent PVI taken as a whole are as follows: 67 patients (68%) were free of arrhythmia after the index procedure, and 13 (13%) were free of arrhythmia after a second PVI, which yielded an overall freedom from PAF (and AAD) of 82%. Seventeen patients (17%) had significant improvement with AAD and refused a second procedure.

The percentage of freedom from PAF in both groups is shown in Figure 4. After a mean follow-up of 26±17 months, no complications related to the procedure occurred, and no evidence existed of atypical (including left-sided) AFL.

**Discussion**

**Main Findings**

To the best of our knowledge, this is the first study analyzing a population with coexistent PAF/AFL, treated with 2 different strategies, to demonstrate that a previous history of AFL is a bad sign with regard to AF recurrences after catheter ablation. Additionally, the present study demonstrated that a prophylactic ablation of the CTI should not be included in the treatment of patients with PAF and no documented common-type AFL. Therefore, a careful screening of the index arrhythmia(s) (eg, PAF only or PAF/AIDS) will enable the correct ablation strategy to be chosen and an optimal long-term outcome to be attained. The success rate in group II (PAF only) was 89%, whereas in group I (PAF/AIDS), it was only 33%.

Those numbers were acquired by means of a follow-up in which daily TTM and the common methods used to assess recurrences (patient’s symptoms with Holter and 12-lead ECG monitoring being used only during clinic visits) were utilized. Although TTM represent only a fraction of the day, they still can be used to estimate the incidence of asymptomatic episodes; however, it is known that patients’ symptoms after AF ablation do not correspond to their actual arrhythmia burden (as demonstrated by Hindricks and colleagues18), and continuous rhythm registration would be the ideal method for estimation of the success of the ablative procedure.

**Is Common-Type AFL a Sign of an Arrhythmogenic Substrate in PAF?**

Current advances in percutaneous ablative therapy for the treatment of AF have helped us understand more completely the importance of triggers and substrate in the pathophysiology of this arrhythmia. Segmental PV isolation, performed in a selected group of patients, has better success rates than use of AADs.19,20

The association of AF and AFL is known, and for the macroreentry circuit of CTI-dependent AFL to occur, an intercaval line of block (in addition to the other anatomic barriers, the crista terminalis and the tricuspid annulus) is required.1–4 Waldo et al’ advocate that a functional line of block between the venae cavea during AF is critical for the pathogenesis of classic AFL. If this functional component of
the AFL circuit does not develop, AF will either persist or spontaneously convert back to sinus rhythm. In those patients in whom AF does not appear to precede the onset of AFL, a very high degree of block or even complete block between the venae cavae may already be present. If we extrapolate those findings to the present study population, one could say that patients from group I had a more critical substrate (intercaval functional line of block) for the development of sustained common-type AFL than did patients from group II.

Another important observation is that although ablation of the CTI permanently interrupted AFL in 86% of patients, residual AF was still present in 67%. That could be the result of non-PV sites acting as triggers (most of which were found in the right atrium) or conditions (eg, right atrial dilatation, electrical remodeling, and fibrosis) that may act as substrate together being responsible for the initiation and maintenance of AF in group I.

The ability to develop the intercaval functional line of block (essential in common-type AFL) could represent a stage in which electrical remodeling of atrial tissue (both right and left) is already important. In such a situation, elimination of the triggers in the PVs alone would not be enough to prevent AF. Any other premature beat could be sufficient to initiate AF, which thereafter perpetuates in the remodeled substrate. Electrical remodeling is known to occur before mechanical remodeling in AF. The latter could be present in those patients from the relatively healthy population in the present study (minimal or no structural heart disease, normal left atrial size, and PAF) who had the worst outcomes. AFL would then be a sign of right-sided triggers and/or advanced electrical remodeling (of both atria) in patients with PAF who also have a history of common-type sustained AFL. In this population, it is tempting to speculate that in addition to PVI, a careful and systematic analysis of the right atrium (eg, measurements of dimensions, search for triggers, and electrogram analysis) is warranted. If no right atrial (or other non-PV foci in the left atrium) arrhythmogenic sources are identified, a percutaneous left atrial ablative approach that aims at substrate modification could potentially lead to better results.

The fact that patients from group II in the present study had only episodes of PAF indicates that no functional line of block was present (or if present, that it was a much shorter line of block). This could represent the absence of a substrate responsible for common-type AFL. Isolation of the PVs (triggers) provided freedom from AF in 89% of those patients during follow-up. These results might indicate that in those patients, prophylactic CTI is not necessary and therefore should not be included as an additional ablative step.

Can the Successful Elimination of AF Prevent the Development of AFL?

Wazni et al evaluated the effect of PVI/left atrial junction radiofrequency ablation in patients with AF/AFL. They showed that after a blanking period of 8 weeks, PVI/left atrial junction ablation alone (without concomitant CTI ablation) decreased the occurrence of not only AF but also AFL. Even though the present study was not designed to evaluate this specific issue, some of our findings are consistent with their results. During an observational period of 2 years, only 5 of 62 patients in the present study (all of whom had associated AF) developed new-onset common-type AFL. This reinforces the theory that AF is needed for the initiation of AFL and that elimination of the initiating arrhythmia (AF) prevents the appearance of common-type AFL. Further investigation of this concept is needed.

Class IC Drugs Versus Ablation for AF/AFL

Before the introduction of PV isolation as a treatment strategy for AF, class IC drugs were reported to be effective in...
converting AF to AFL, which could then be treated by CTI ablation. The proposed mechanism was the rate-dependent prolongation of the atrial refractory period by class IC agents, with an increase in the wavelength, thus facilitating the conversion of AF (multiple smaller reentry circuits) to AFL (a single macroreentrant loop). AADs could also have electrophysiological effects in the intercaval region, creating the needed line of block for common-type AFL. Also, in those studies, a great number of patients had improvement only in their symptoms (while still having bouts of AF), with a rate of conversion to sinus rhythm much lower than that achieved by present-day percutaneous ablation. The inefficacy of AADs in AF was also confirmed in the AFFIRM trial (Atrial Fibrillation Follow-up Investigation of Rhythm Management), with some suggestions of increased mortality. Therefore, ablation of AF appears to be a better solution than the use of AADs to convert AF into AFL.

**Study Limitations**
The daily TTM recordings only a fraction of each day and did not represent a 24-hour period; episodes of asymptomatic arrhythmias could have been missed. In addition, the classification of AFL versus AF during follow-up event recordings and 24-hour Holter recordings was not done blindly, which could potentially be a source of bias. Even though the diagnosis of CTI-dependent flutter cannot be made with certainty from the event recorder or Holter tracings, we confirmed the diagnosis in all 10 patients with AFL after PVI by endocardial recordings during the subsequent electrophysiological study in which CTI ablation was performed.

Assessment of atrial anatomy was done with transthoracic echocardiography, which has known limitations for accurate evaluation of the right-sided structures. MRI could give a more precise estimation of right atrial morphology. Furthermore, some patients were taking AADs to control AF during the postablation period. We cannot rule out that AADs were the cause of the transformation of AF into AFL; however, the type of AADs and the percentage of patients taking them in the preablation period were comparable in both groups (Table 2). Thus, this possibility would be pertinent only to the AFLs observed in the postablation period (10 patients). Additionally, the nonrandomized nature of the study may account for a confounding factor.

**Conclusions**
We demonstrated that in patients with PAF and no documented common-type AFL, PVI alone prevents the recurrence of AF in 82%. Therefore, preventive CTI ablation should not be included in the strategy for treatment of PAF. Furthermore, in patients with coexisting PAF/AFL, CTI ablation and PVI were used successfully to treat sustained common-type AFL but appeared insufficient to prevent recurrences of AF. In this population, AFL can be a sign that non-PV triggers (including triggers in the right atrium) are the culprit behind AF or that sufficient electrical remodeling has occurred in both atria, and an ablative strategy that includes substrate modification is already required. Future work is needed to determine whether the combination of PAF/AFL could be a marker of early progression to persistent or permanent AF.

**Disclosures**
Drs Rodriguez and Timmermans have received research grants from CryoCor. Dr Wellens is a member of the Advisory Board of CryoCor. The remaining authors report no conflicts.

**References**

The relation between the common type of atrial flutter (AFL) and atrial fibrillation (AF) was described long ago. Patients with AFL have a tendency to develop AF. On the other hand, AF is often the event that triggers the macroreentry circuit properties (eg, ectopic impulse formation and electrogram analysis) is required for an effective AF ablation, which would be a sign that non–pulmonary vein triggers are the culprit behind AF, and an electrophysiological evaluation of right atrial endocardial structures as barriers to conduction during human type I atrial flutter: activation and entrainment mapping guided by intracardiac echocardiography. Circulation. 1995;92:1839–1848.

The present study prospectively evaluated the best catheter ablation strategy in patients having both paroxysmal AF and AFL. Further evaluation of these mechanisms and their proper treatment is required.

CLINICAL PERSPECTIVE

The relation between the common type of atrial flutter (AFL) and atrial fibrillation (AF) was described long ago. Patients with AFL have a tendency to develop AF. On the other hand, AF is often the event that triggers the macroreentry circuit of AFL. The present study prospectively evaluated the best catheter ablation strategy in patients having both paroxysmal AF and AFL or paroxysmal AF only with regard to outcome. If at least 1 episode of sustained AFL was documented, patients underwent cavotricuspid isthmus cryoablation, followed by pulmonary vein isolation after a 6-week monitoring period (group I). In patients in whom only paroxysmal AF was documented (no history of sustained common-type AFL), only pulmonary vein isolation was performed (group II). During a follow-up of 26±17 months, we found that pulmonary vein isolation only was highly successful in patients from group II (82% success rate), whereas in group I, the combination of cavotricuspid isthmus cryoablation and pulmonary vein isolation successfully treated AFL but was frequently insufficient to prevent recurrences of AF (recurrence rate of 67%). The latter finding suggests the following: (1) AFL can be a sign that non–pulmonary vein triggers are the culprit behind AF, and an electrophysiological evaluation of right atrial properties is required for an effective AF ablation, which would also involve the right atrium; and (2) sufficient electrical remodeling has already occurred in both atria, and thus, a strategy that includes biatrial substrate modification may be necessary for successful percutaneous ablative treatment of patients having both AF and AFL. Further evaluation of these mechanisms and their proper treatment is required.

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