Limited Posterior Left Atrial Cryoablation in Patients With Chronic Atrial Fibrillation Undergoing Valvular Heart Surgery

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OBJECTIVES
We sought to evaluate whether a limited surgical cryoablation of the posterior region of the left atrium was safe and effective in the cure of atrial fibrillation (AF) in patients with associated valvular heart disease.

BACKGROUND
Extensive surgical ablation of AF is a complex and risky procedure. The posterior region of the left atrium seems to be important in the initiation and maintenance of AF.

METHODS
In 32 patients with chronic AF who underwent heart valve surgery, linear cryolesions connecting the four pulmonary veins and the posterior mitral annulus were performed. Eighteen patients with AF who underwent valvular surgery but refused cryoablation were considered as the control group.

RESULTS
Sinus rhythm (SR) was restored in 25 (78%) of 32 patients immediately after the operation. The cryoablation procedure required $20 \pm 4$ min. There were no intraoperative and perioperative complications. During the hospital period, one patient died of septicemia. Thirty-one patients reached a minimum of nine months of follow-up. Two deaths occurred, and SR was present in only four (25%) of 16 patients.

CONCLUSIONS
Linear cryoablation with lesions connecting the four pulmonary veins and the mitral annulus is effective in restoration and maintenance of SR in patients with heart valve disease and chronic AF. Limited left atrial cryoablation may represent a valid alternative to the maze procedure, reducing myocardial ischemic time and risk of bleeding. (J Am Coll Cardiol 2000; 36:159–66) © 2000 by the American College of Cardiology

Atrial fibrillation (AF) is the most frequent supraventricular arrhythmia, and its pharmacologic therapy is not always satisfactory. However, it has been shown that a radical cure of AF might be possible. Cox et al. (1–4) were the first investigators who successfully treated AF using the maze procedure, which consisted of an extensive dissection with compartmentalization of both atria. Although effective, this long operation is rather complex and causes severe damage to the atria. Therefore, this procedure is not routinely used to cure AF in patients undergoing cardiovascular surgery.

Recently, a catheter ablation technique mimicking the maze procedure has been proposed. Despite a relatively high success rate, it has a significant risk of complications (5–7). Moreover, catheter ablation of atrial foci localized in the pulmonary veins, which trigger AF, has been shown to be effective (8), but it is still limited to those patients with paroxysmal AF.

The possibility of performing selective ablation has several advantages, such as less atrial damage and, consequently, better preserved atrial mechanical function, shorter procedure time and less risk of related complications.

Previous studies in animals (9,10) and humans (11) have shown that ablation of limited atrial areas may be effective in the cure of AF. Few data available on left atrial mapping showed that the posterior wall seems to be a critical area for the maintenance of AF in patients with valvular heart disease (12). On the basis of these considerations, we decided to evaluate the effectiveness of linear cryoablation confined only to the posterior region of the left atrium between the pulmonary veins and the mitral annulus.

Cryoablation has been successfully used for over two decades in the surgical treatment of cardiac arrhythmias. It has been shown that cryoablation creates more homogeneous lesions and, above all, leaves the atrial endocardium intact (7,13). This may be important, especially in the future endeavors to reproduce such lesions with a transvenous catheter approach, because it could significantly reduce the risk of thromboembolism, which, at present, is the worst complication related to the extensive endocardial damage created by multiple radiofrequency (RF) deliveries.

Therefore, the objective of this study was to evaluate whether a limited surgical cryoablation of the posterior...
region of the left atrium was safe and effective in the cure of chronic AF in patients who also had valvular heart disease.

**METHODS**

**Study group.** The study group included 32 patients with chronic AF undergoing heart valve surgery owing to mitral or aortic valve disease, or both. Written, informed consent was required from all patients before the operation. Table 1 shows the patients’ clinical characteristics in detail. The mean duration of AF was 6.1 ± 5.2 years. In 9% of patients, previous systemic embolization was reported. In the majority of patients, the mitral valve was diseased, only 6% being purely aortic. A cardiac reintervention was performed in 16% of patients.

Eighteen consecutive patients with chronic AF who were matched for age, AF duration and heart valve disease treated with valve surgery, but who refused the cryoablation procedure, were selected and considered as the control group.

**Surgical procedure and cryoablation.** All operations were performed by the same surgeon, under routine cardiopulmonary bypass with double venous cannulation and moderate hypothermia. The left atrium was opened through the usual left paraseptal incision after cold cardioplegic arrest. The left appendage, when present, was externally ligated at this moment. Once inspection of the mitral and/or aortic valves had been completed and the valve was repaired or removed, cryoablation was started.

A dual-probe cardiac cryosurgical system (Frigitronics, Cooper Surgical, Shelton, Connecticut) was used. The pressure in the two cylinders containing nitrous oxide (N₂O) was always maintained above 720 psi (pounds per square inch). The temperature fell abruptly to −60°C at the probe tip when gas was delivered and then maintained for 2 min. The two probes were used simultaneously, close to each other, to cut in half the duration and to not leave any gap between applications, as the acute endocardial lesion is not visible. Cryoablation was performed following the path counterclockwise (Fig. 1).

Finally, a mitral or aortic prosthesis was inserted, if required, and the operation continued as usual. At the end of extracorporeal circulation, adrenaline (0.025 gamma/kg

<table>
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<th>Table 1. Clinical Characteristics of Study Group</th>
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<td><strong>Patients With</strong></td>
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<td><strong>Cryoablation</strong> (n = 32)</td>
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<tr>
<td>Gender (M/F)</td>
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<td>AF duration (years)</td>
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<td>LA diameter (mm)</td>
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<td>Underlying valve disease</td>
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<td>Mitral stenosis</td>
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<td>Mitral regurgitation</td>
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<td>Mitral plus aortic</td>
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<td>Previous embolic episodes</td>
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<td>Reoperation</td>
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Data are presented as the number (%) of patients or mean value ± SD.

AF = atrial fibrillation; F = female; LA = left atrium; M = male; NS = not significant; NYHA = New York Heart Association functional class.
body weight per min) was administered to all patients. Intraoperative direct current cardioversion was routinely performed in all patients who had AF. Amiodarone infusion (150-mg loading dose over 10 to 15 min; then 1 mg/min for 6 h; then 0.5 mg/min until oral administration) was started after weaning from bypass, regardless of the heart rate or rhythm.

To assess whether the damage caused by exposure of the atrial endocardium to freezing was transparietal, an atrial biopsy was performed after cryoablation in eight patients at the beginning of our study.

Postoperative management and follow-up. During the hospital period, patients in both the AF/cryoablation and control groups were monitored by continuous electrocardiography. After intravenous infusion, oral amiodarone (600 mg/day for 10 days; then 400 mg/day for 10 days; then 200 mg/day) was administered to all patients, except for one in whom propafenone (300 mg twice a day) was preferred because of previous dysthyroidism. Antiarrhythmic therapy was routinely withdrawn after three months in the absence of AF recurrence. During the hospital stay, an attempt at electrical cardioversion was performed in all patients with AF.

After discharge, the patients were followed up with a clinical examination and electrocardiographic (ECG) and Holter monitoring at 1, 3, 6, 9, 12 and 18 months. In case symptoms recurred between follow-up visits, a clinical examination and ECG and Holter monitoring were performed and an event recorder was applied. Doppler echocardiography, with evaluation of transtricuspid and transmural flow, was performed before discharge and at three and six months after the operation. After three months, oral anticoagulant therapy was discontinued in patients undergoing valvuloplasty who were in sinus rhythm (SR) with the presence of atrial contraction documented by Doppler echocardiography.

Statistical analysis. Continuous variables are expressed as the mean value ± SD. To compare outcomes, survival analysis and the log-rank test were used. Categoric variables were compared by using the chi-square test or the Fisher exact test, when appropriate. Results were considered to be statistically significant at p < 0.05. Statistical analysis was performed using the “Statistics” software (StatSoft Inc., Tulsa, Oklahoma).

RESULTS

Surgical procedure. Operative data are listed in Table 2. The mean aortic clamping time and extracorporeal circulation times were 20 and 21 min, respectively, longer than those times in the control group, reflecting the mean duration of the cryoablation procedure. Among patients with AF/cryoablation, a bioprosthesis was employed in six (19%) and valvuloplasty was performed in another eight (25%).

In the group of patients with AF/cryoablation, SR was restored in 25 patients (78%), either spontaneously or after intraoperative direct current cardioversion, immediately af-
ter the operation, as compared with four patients (22%) in the control group ($p < 0.001$). There were no intraoperative or perioperative complications. Inotropes were used in all patients in the immediate postoperative period both in the AF/cryoablation group and the control group. High doses of intravenous inotropes were used in three patients (9%) with postoperative low cardiac output syndrome in the AF/cryoablation group: one patient was in SR; the second one had AF; and the third one was in junctional rhythm. Also, in two patients in the control group, a high dose of intravenous inotropes were used. Both patients had AF.

Atrial biopsies performed after cryoablation in eight patients revealed morphologic features indicating irreversible injury, such as nuclear and cytoplasmic degenerative lesions with no viable cardiomyocytes. The lesions involved the full thickness of the wall (Fig. 2).

**Early postoperative period.** Table 2 shows in detail the early postoperative data in patients with AF/cryoablation and in control subjects. The mean hospital stay was 7 ± 4 days (range 5 to 22) in patients with AF/cryoablation. There was no significant statistical difference in the hospital stay between patients with AF/cryoablation and control subjects. The number of direct current cardioversions performed was higher in the control group.

In the AF/cryoablation group, one patient (3%) had another operation within one week due to periprosthetic leakage. There was one in-hospital death (3%) because of septicemia occurring three weeks after the operation. This patient was in SR. In one patient (3%) with AF, a permanent pacemaker (VVI) was implanted because of symptomatic bradycardia.

Twenty-three (74%) of 31 patients with AF who underwent cryoablation were in SR at the time of hospital discharge.

In the control group, one patient died from heart failure the day after the operation. Among the remaining
17 patients, only two (12%) were in SR at the time of discharge, despite attempts at electrical cardioversion.

**Follow-up.** In the cryoablation group at three-month follow-up, 27 (87%) of 31 patients were in SR. Among these patients, 21 (68%) were treated with cryoablation only.

Four patients (13%) had a few episodes of paroxysmal AF during the first three months, but they maintained SR during the remaining follow-up period. All four patients received antiarrhythmic drugs: two received amiodarone and two received propafenone.

Two patients (6%) were in SR with episodes of paroxysmal atrial tachycardia. Both patients underwent an electrophysiologic study with a nonfluoroscopic mapping system (CARTO, Biosense-Webster). In one patient, the mapping revealed a pattern of radial activation modified by intervening scar tissue, resembling a pattern of perimitrail reentry. A single application of RF energy at the site of earliest activation was effective in eliminating the tachycardia, suggesting a focal mechanism. In the second patient, the atrial mapping did not determine the tachycardia mechanism. Neither entrainment nor RF energy application between the right inferior pulmonary vein and the mitral annulus, where a gap was present, further clarified the nature of the atrial tachycardia. The patient underwent electrical cardioversion with restoration of normal SR, and sotalol therapy (80 mg twice a day) was initiated. No further episodes of atrial tachycardia or AF were detected in both patients.

All patients reached a minimum of nine months of follow-up, during which two deaths occurred. One patient with chronic AF died of heart failure four months after the operation, and the other one in SR died of intracerebral hemorrhage after seven months of follow-up. The patient was not taking anticoagulant agents because of a bioprosthesis.

Of the remaining 29 patients, 26 were in SR at nine months. Of these patients, 20 (69%) were in SR and had cryoablation alone; 21 (73%) had cryoablation and RF ablation; and 26 (90%) had cryoablation and RF ablation and took antiarrhythmic drugs (Fig. 3).

This trend was maintained at 12 months, at which time 18 (90%) of 20 patients remained in SR with cryoablation, RF ablation and antiarrhythmic drugs.

After the cryoablation procedure, 12 patients, including the aforementioned two patients with episodes of atrial tachycardia, underwent an electrophysiologic study, which did not show fibrillation in any part of the left atrium.

Table 3 shows the characteristics of cardiac rhythm in patients with AF/cryoablation at discharge and 1, 3, 6, 9 and 12 months.

In the control group at three-month follow-up, one death occurred from heart failure. In the remaining 16 patients, four (25%) were in SR: two who took an antiarrhythmic drug and two who did not. Two patients were discharged in SR that was maintained during follow-up. In two patients, electrical cardioversion was successful one month after the operation and no more episodes of AF were detected. The remaining 12 patients (75%) had chronic AF. This trend was consistent at 6, 9 and 12 months of follow-up (Fig. 3).

The difference in outcome between the two groups was statistically significant during follow-up (p < 0.0001) (Fig. 4).

When comparing patients in SR with those with AF after cryoablation, no statistically significant difference was seen regarding the patients’ age, right and left atrial size, type of surgical procedure and duration of extracorporeal circulation and aortic clamping time. The difference in duration of AF was not statistically significant, but it was longer than 10 years in three of four patients who still had chronic AF at the end of follow-up (188, 144 and 132 months, respectively).

Among patients with AF who underwent cryoablation, one in SR had another operation for mitral valvuloplasty failure one month later; interestingly, during the second operation, no evidence of the cryoablation lesions was present on gross inspection of the endocardium. Another patient required implantation of a dual-chamber permanent pacemaker because of symptomatic sinus bradycardia four months after the initial procedure.

Doppler echocardiography revealed the presence of right and left atrial contractility in 24 (92%) of the 26 patients in SR.

**DISCUSSION**

**Major findings.** There were three major findings from this study: 1) The creation of a few linear cryolesions in the posterior region of the left atrium in patients with chronic AF undergoing heart valve surgery is effective in restoration
and maintenance of SR, allowing for the recovery of atrial function in the majority of the patients. 2) Our procedure has proved to be feasible and requires only a little extra time to the heart valve surgery time (~20 min). 3) The atrial linear lesions created by cryoablation during cardiac surgery have shown to be safe.

**Electrophysiologic background.** It is generally accepted that the electrophysiologic substrate responsible for the maintenance of AF is the presence of multiple, simultaneous reentrant waves circulating through the atrial tissue (14,15). The surgical maze procedure divides the atrial myocardium into multiple, small segments, thus reducing the mass of tissue electrically activated and impeding the multiple wavelets of reentry to be sustained. However, several recent reports (9,11,16,17) have shown that different patterns of electrical activity in various atrial regions are present during AF, with the simultaneous presence of regions with relatively regular activation and other areas with completely disorganized atrial activity. These studies suggested that the fibrillatory process is far from random and seems to be significantly influenced by anatomic and electrophysiologic factors. Therefore, although the atria, as a whole, participate in the process of AF, not all the atrial regions contribute equally to the perpetuation of fibrillation. This hypothesis also seems to be corroborated by the success of selective ablation of critical areas reported in some cases (9,11). Morillo et al. (9) showed that in dogs, the shortest FF intervals during AF were recorded in the left posterior wall. Cryoablation limited to this zone was effective in terminating and preventing reinduction of the arrhythmia in 82% of cases. Sueda et al. (12) showed that in patients with chronic AF and mitral valve disease, the areas with the shortest FF intervals were at the base of the left atrial appendage and the posterior wall lateral to the left pulmonary veins. Furthermore, they demonstrated that the surgical isolation of these areas restored SR in most patients. The importance of the left atrium in the maintenance of AF is also confirmed by reports on percutaneous catheter ablation of AF (5,6,8), showing a higher success rate when linear lesions were applied within the left atrium. However, the safety of a procedure that includes extensive ablation of the left atrium has not been sufficiently demonstrated, and severe complications, such as cardiac tamponade or thromboembolism, have been reported (5–7). This risk of severe complications encourages us to limit the ablation areas as much as possible. Identifying localized atrial regions responsible for the initiation and maintenance of AF would be crucial for a safe and effective ablation procedure.

Recently, Haissaguerre et al. (8) showed that in patients with idiopathic AF, the pulmonary veins represent important areas in triggering and maintaining AF, and RF ablation limited to these areas was successful in a high percentage of cases.

In our study, using cryoenergy, we performed linear lesions connecting the four pulmonary veins and the inferior pulmonary veins to the posterior mitral annulus with the purpose of isolating this area. Cryoablation limited to this zone was effective in terminating and preventing reinduction of the arrhythmia in 82% of cases. Sueda et al. (12) showed that in patients with chronic AF and mitral valve disease, the areas with the shortest FF intervals were at the base of the left atrial appendage and the posterior wall lateral to the left pulmonary veins. Furthermore, they demonstrated that the surgical isolation of these areas restored SR in most patients. The importance of the left atrium in the maintenance of AF is also confirmed by reports on percutaneous catheter ablation of AF (5,6,8), showing a higher success rate when linear lesions were applied within the left atrium. However, the safety of a procedure that includes extensive ablation of the left atrium has not been sufficiently demonstrated, and severe complications, such as cardiac tamponade or thromboembolism, have been reported (5–7). This risk of severe complications encourages us to limit the ablation areas as much as possible. Identifying localized atrial regions responsible for the initiation and maintenance of AF would be crucial for a safe and effective ablation procedure.

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In our study, using cryoenergy, we performed linear lesions connecting the four pulmonary veins and the inferior pulmonary veins to the posterior mitral annulus with the purpose of isolating this area. Our results confirmed the critical role of the posterior region of the left atrium. It is still not possible to establish whether the restoration of SR depends on the modification of the substrate of AF by the linear lesions or whether it is due to the isolation or elimination of potential focal triggers within the pulmonary veins, or a combination of both mechanisms.

In contrast, we should consider that the creation of linear lesions, especially incomplete ones, may represent a substrate for the occurrence of new intra-atrial tachycardias whose mechanism is difficult to establish.

**Comparison with previous studies.** Over the last decade, several reports have presented different surgical techniques
to cure AF (1–4,12,18,19–21). The corridor operation was the first one to show that operation may control AF (19). It consists of isolating a strip of atrial tissue (corridor) that harbors the sinus node and the atrioventricular node. It was observed that the left atrium remained in AF, pointing to the importance of the left atrium in the genesis of AF. Graffigna et al. (21) have reported that 71% of patients with mitral valve disease returned to SR after left atrial isolation. With these surgical approaches the problem is the persistence of AF in the left atrium or part of it leaving the hemodynamic and thromboembolic problems unresolved. The maze procedure was shown to be effective in eliminating AF and restoring atrial contractility in the majority of patients (1–4). In a long-term follow-up study, the maze procedure had a success rate of 93% for restoration of SR, without use of antiarrhythmic drugs, in a population mostly characterized by idiopathic AF (3). Kosakai et al. (20) reported that the maze procedure was effective in maintaining SR also in patients with organic heart disease, even if ~30% of patients did not present with left atrial contraction during follow-up. However, the maze procedure is time-consuming and requires an intricate pattern of atrial incisions, extensive suturing, relevant blood loss and a prolonged cardiopulmonary bypass.

With the aim of minimizing blood loss and reducing the cardiopulmonary bypass time, Chen et al. (22) have simulated the classic maze operation in 12 patients undergoing mitral valve surgery by using the combination of RF catheter ablation and cryoablation instead of extensive atrial surgical incisions. They reported that at the end of six-month follow-up, SR was restored in 60% of patients, but only 30% of patients showed left atrial contractility. Recently, Sueda et al. (12,18) developed a surgical procedure mainly involving the posterior wall of the left atrium for treatment of chronic AF associated with mitral valve disease. They reported a disappearance of AF at six months after the operation in 78% of patients, with recovery of left atrial contractility in 61% of patients.

In our study, we chose to limit the part of the left atrium involved in the procedure as much as possible to reduce the time of the operation and to preserve normal atrial contractility, and we used only cryoenergy to perform the linear lesions. During follow-up, we observed restoration of SR in 90% of the patients. In 69% of patients, cryoablation alone was sufficient to maintain normal SR; one patient also required RF ablation of atrial tachycardia; and five patients also had pharmacologic therapy. The early success of the cryoablation procedure is predictive of long-term efficacy. The proarrhythmic effect related to the cryoablation scar, although present, appears to be minimal, and in some cases can be resolved with RF ablation. We have not found variables predictive of failure, but we noticed that in patients who still had chronic AF after the cryoablation procedure, a long AF duration (>10 years) was evident in three of four patients. Most important, the majority of the patients (92%) in SR showed restored right and left atrial contractility. Furthermore, the procedure required only 20 min, and the aortic cross-clamp time and cardiopulmonary bypass times were very short in comparison with those in previous studies (1,4,18,20,22). This significant reduction of myocardial ischemic time may allow us to perform this procedure routinely in patients with AF undergoing heart valve surgery.

Potential advantages of cryoablation. The risk of thromboembolic complications in patients undergoing multiple linear lesions in the left atrium using RF energy is high (5,7). We chose to deploy cryotherapy as an alternative energy source to create linear lesions for two reasons. First, cryoablation has the advantage of leaving the endocardium intact (7,13,23), thus reducing the thromboembolic risk, as demonstrated by most of the data on surgical cryoablation (7,24,25) as well as by experimental studies (13,23,26,27). Second, the lesion created by cryoablation has been demonstrated to be transmural and well circumscribed. The chronic scar is made of dense fibrotic tissue without viable cardiomyocytes, with no tendency to rupture or dilate, because cryoablation induces necrosis of myocardial tissue but spares the collagenous fiber (13,25–27), as confirmed by our histologic data. In contrast, the lesions produced with RF energy are less circumscribed and nonhomogeneous, with clear evidence of viable cardiomyocytes, and, most important, this energy causes endocardial disruption with a consequent potential risk of a thromboembolic event (13).

Clinical implications. The study shows that cryoablation, creating linear lesions connecting the four pulmonary veins and the inferior pulmonary veins to the mitral annulus in patients with chronic AF and valvular heart disease, is effective. Moreover, the procedure is simpler and faster, with less atrial damage, than the maze operation.

These data are important if we consider that elimination of AF and maintenance of atrial contractility provide hemodynamic benefit, especially in patients with associated heart disease; moreover, the use of anticoagulant therapy may be avoided in those patients who undergo valvuloplasty or a bioprosthesis operation.

Furthermore, these data may also be used for the reproduction of the same type of lesions using percutaneous catheter ablation in patients with chronic AF with or without associated heart disease, avoiding the need of open heart surgery and related complications.

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