Reentrant and Focal Activations During Atrial Fibrillation in Patients With Atrial Septal Defect

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Background. Adult patients with atrial septal defect (ASD) frequently experience atrial fibrillation (AF). The incidence of AF can be more than 10% if it is not corrected by the time the patient is 40 years old [1, 2]. AF can develop even after the ASD is corrected after the patient is 40 years old [3, 4]. The association with AF impairs quality of life, increases the risk of thromboembolisms, and can affect survival [1, 2]. Surgical procedures for AF concomitant with ASD closure should improve the symptoms, quality of life, and long-term survival postoperatively [5, 6].

The optimal lesion set of the surgical procedure for AF in adult patients with ASD remains controversial because the underlying mechanism of AF has not been determined. The volume load of the right-sided heart and pulmonary veins (PVs) caused by a left-to-right shunt through an ASD may change the electrophysiology of the right atrium (RA) and PVs. Elevated pulmonary arterial pressure and aging have been shown to be risk factors for the development of AF in ASD patients [3]. The association of mitral and tricuspid valve regurgitation with left atrial (LA) dilatation has also been shown to increase the incidence of AF [4]. However, little is known about the electrophysiologic abnormalities causing AF in adult ASD patients. To the best of our knowledge, there has been no direct study of atrial activation during AF in this subset of patients. We performed an intraoperative mapping study to examine atrial activation during AF in adult ASD patients with AF.

Patients and Methods

Ten adult patients undergoing surgical procedures for ASD and AF participated in an intraoperative mapping study. The study was approved by the institutional review board, and written informed consent was received from each patient before the operation. There were 7 men and 3 women, whose average age was 54 ± 11 years. Eight patients had a secundum defect and 2 a primum defect. There were 4 patients with paroxysmal atrial fibrillation and 6 with long-standing persistent atrial fibrillation. A modified biatrial Maze procedure was performed in 6 patients and pulmonary vein isolation with no other left atrial lesions in 4.

Results. The reentrant or focal activations driving atrial fibrillation were confined within the right atrium in all patients with paroxysmal atrial fibrillation, whereas multiple focal activations arising from the pulmonary veins or posterior left atrium and reentrant activations in the left atrium were observed in 5 of 6 patients with long-standing persistent atrial fibrillation. In 9 patients, sinus rhythm was restored postoperatively and 8 of those patients have been free of any atrial fibrillation during a follow-up period of 94 ± 45 months.

Conclusions. The pattern of the atrial activation during atrial fibrillation correlated with the type of atrial fibrillation and varied from a simple right atrial reentry to complex reentrant and focal activations in the left atrium.

patient with paroxysmal AF and 3 with long-standing persistent AF were associated with more than moderate regurgitation of the mitral and tricuspid valves.

The patients were followed up by cardiologists or general physicians postoperatively. The average follow-up period was 94 ± 45 months. Their medical records were reviewed to determine the postoperative cardiac rhythm and any morbidities or mortalities. The cardiac rhythm was examined by an electrocardiogram and 24-hour Holter monitoring.

Intraoperative Mapping

Intraoperative mapping was performed before the patient underwent cannulation for cardiopulmonary bypass. A 256-channel dynamic mapping system and custom-made mapping electrode patches were used for data acquisition and analysis as described previously [7]. Data processing was performed on Silicon Graphics graphic workstations (Indigo2 and O2, Silicon Graphics Inc, Mountain View, CA). In all, 253 unipolar or bipolar electrodes were distributed over three silicone sheets: the right atrial free wall, the left atrial free wall including the posterior left atrium between the PVs, and the anterior atrium behind the great arteries, with interelectrode distances of 5 to 7 mm. The electrograms were recorded from 253 atrial sites over the entire atrial epicardial surface during AF. In the patients with paroxysmal AF, burst pacing at a cycle length of 100 ms was applied on the right atrial appendage with a handheld electrode to induce AF. After continuance of AF for more than 5 minutes was confirmed, the atrial electrograms were recorded. All the recorded signals were stored on a hard disk drive for offline data analysis.

Data Analysis

A 4,000-ms duration of data was analyzed to characterize the activation pattern in each patient in the offline data analysis. Local activation times were determined as the maximum negative derivative of the unipolar electrogram and the maximum absolute amplitude of the bipolar electrogram. Computer-picked activation times were verified manually. The activation maps were displayed in a dynamic mode as a movie with three-dimensionally constructed atrial models on a computer to analyze multiple wave fronts that merged with each other, diverged, and disappeared.

Reentry was defined as reactivation of a site by a wave front that continued from the preceding activation of the site. Focal activation was defined as early activation without any late activation from a previous cycle adjacent to the early activation site. When an atrium was activated by a wave front that originated from the other atrium, the activation pattern was considered to be passive.

Surgical Procedure

Closure of the secundum ASD was performed with or without the use of a pericardial patch, and closure of the primum ASD was performed with a patch. Four patients also underwent annuloplasty of the mitral and tricuspid annulus. Various surgical procedures were performed for AF because it was uncertain whether the LA incisions were necessary to prevent the recurrence of AF. A modified Maze procedure, consisting of a bilateral PV isolation and biatrial incisions, was performed in 6 patients. In the remaining 4 patients, PV isolation with or without an RA lesion (2 patients each) was performed. No LA incisions were made in those 4 patients. PV isolation was performed in all 10 patients. The type of AF, duration of AF, or diameter of the LA did not affect the selection of the lesion set for the AF procedure. In the patients with a primum ASD, the posterior limbus of the interatrial septum was not ablated to preserve the posterior intermodal tract [8]. Cryothermia was used in 4 patients who underwent operations before 1998, whereas a bipolar radiofrequency ablation device (AtriCure Isolator Surgical Ablation System, AtriCure Inc, West Chester, OH) was used in the remaining patients.

Continuous values are expressed as the mean ± 1 SD. Student’s t test was used to compare the continuous data between the two groups when appropriate. A \( \chi^2 \) test was used to analyze the nonparametric data.

Results

Findings of Intraoperative Mapping

The patterns of atrial activation during AF varied from a simple RA reentry to complex reentrant and focal activations in the LA. The complexity of the pattern of atrial activation correlated with the type of AF. In the patients with paroxysmal AF, the reentrant and focal activations driving the AF were confined within the RA, whereas combined reentrant and focal activations were observed in the right and left atria in the patients with long-standing persistent AF.

In 3 of 4 patients with paroxysmal AF, the pattern of the atrial activation indicated a common type of RA flutter. Because this was an epicardial mapping study and the electrograms of the interatrial septum were not recorded, the entire circuit of the tachycardia was not recorded, and conclusive diagnosis of RA flutter was not possible. However, in 2 patients, the activation appeared at the superior septum between the RA and the LA, then the activation propagated down the lateral RA, and the RA...
activation converged at the inferior RA, suggesting the counterclockwise activation pattern of common RA flutter. In another patient, the activation pattern of the lateral RA was in the totally reversed direction, suggesting the clockwise activation pattern of reversed common RA flutter (Fig 1). The cycle lengths were irregular and varied beat by beat in these 3 patients with RA flutter. The average cycle lengths of atrial flutter ranged from 236 to 396 ms. The LA was passively activated by the wave front that traversed from the RA through Bachmann’s bundle or other interatrial conduction pathways. The conduction from the RA to the LA was delayed or blocked beat by beat, resulted in irregular and complex activation of the LA.

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Clinical Outcomes
No complications were related to the intraoperative mapping. No operative or long-term deaths occurred during the follow-up period of 130 ± 45 months. No thromboembolic complications occurred in any patients during the follow-up period. None of the patients received a permanent pacemaker. One patient underwent implantation with a defibrillator for prevention of sudden death because of ventricular tachyarrhythmia associated with cardiac sarcoidosis 5 months after the operation.

Nine patients converted to sinus rhythm postoperatively. One patient with a primum ASD and long-standing persistent AF with an extremely complex pattern of atrial activation, as described earlier, remained in AF immediately after the operation extending through the follow-up period. Another patient with a secundum ASD and long-standing persistent AF had a recurrence of AF 7 years postoperatively. The other 8 patients have been free of AF during the follow-up period.

Comment
Mechanisms of AF Associated with an ASD
This intraoperative mapping study demonstrated that the pattern of the atrial activation varied between patients with paroxysmal AF and those with long-standing persistent AF. In the patients with paroxysmal AF, no reentrant or focal activation was observed in the LA or PVs, and the LA was passively activated by the activation traversed from the RA through Bachmann’s bundle.

In 5 of 6 patients with long-standing persistent AF, combined focal and reentrant activations were observed. In 1 patient, a stable focal activation arising from the posterior LA coexisted with an unstable macroreentrant activation in the RA (Fig 2). In another patient, stable reentrant activation around the LA appendage and focal activation arising from the posterior LA were observed (Fig 3). The number of LA foci was one or two per patient (Fig 4). In the patients with combined reentrant and focal activations or in those with multiple foci, the different cycle lengths of each activation resulted in irregular and complex patterns of atrial activation. The LA foci were distributed around the right and left PVs and posterior LA. The RA was passively activated by the wave front that traversed from the LA through Bachmann’s bundle or other interatrial conduction pathways. The conduction from the LA to the RA was delayed or blocked beat by beat and resulted in irregular and complex activation of the RA. The atrial activation in another patient with long-standing persistent AF was extremely complex, and no specific pattern of activation was determined. This patient had a primum ASD with severe mitral and tricuspid valve regurgitation with extremely dilated right and left atria.

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Fig 1. Right atrium (RA) macroreentrant activation. The atrial epicardium was mapped for AF induced by burst pacing from the RA appendage in a 43-year-old man with a secundum atrial septal defect and paroxysmal AF for 3 years. Maps A, B, and C represent activation of lateral RA during time intervals A, B, and C indicated in ECG, respectively. Isochrones are demonstrated by color codes as indicated in lower panel. Repetitive activation appeared in lower RA between IVC and RV and propagated upward. The pattern of activation was unstable, and AF terminated spontaneously. (AF = atrial fibrillation; ECG = electrocardiogram; IVC = inferior vena cava; RPVs = right pulmonary veins; RV = right ventricle; SR = sinus rhythm; SVC = superior vena cava.)
are extremely important for determining the optimal lesion set in the surgical treatment of AF.

**Mechanism of Paroxysmal AF**

The RA flutter presented with a clockwise or counterclockwise macroreentrant activation around the tricuspid valve annulus. The activation wave front needs to take a time long enough to travel around the tricuspid valve annulus to allow the atrial myocardium at each point around the annulus to recover from the refractoriness so as to complete the macroreentrant activation. Therefore, the requirements for RA flutter are a dilated tricuspid valve annulus. The activation wave front needs to take a time long enough to travel around the tricuspid valve annulus to allow the atrial myocardium at each point around the annulus to recover from the refractoriness so as to complete the macroreentrant activation. Therefore, the requirements for RA flutter are a dilated tricuspid valve annulus.
valve annulus for the extension of the conduction path, slow conduction, prolonged refractory period, or a combination of these. The left-to-right shunt through an ASD increases the blood flow passing through the tricuspid valve, resulting in dilatation of the tricuspid annulus and the RA chamber. An echocardiographic study of the patients with ASD demonstrated that the right ventricular dimension, as an index of the tricuspid valve annulus, was significantly increased in 97% of the patients [9]. The volume load of the RA may affect the electrophysiology of the atrial myocardium, such as a conduction disturbance or prolongation of the refractoriness. Canine experimental studies have demonstrated that chronic atrial enlargement increases the susceptibility to atrial arrhythmias associated with a prolonged refractory period and interstitial fibrosis that interferes with local conduction [10, 11]. An electrophysiologic study of patients with ASD has suggested that the RA stretch resulting from the volume load causes electrical remodeling with modest increases in the effective refractory period of the RA, a conduction delay at the crista terminalis, and sinus node dysfunction [12]. All these mechanical and electrophysiologic abnormalities may provide the substrate and conditions for RA flutter in the patients with ASD.

In the patients with paroxysmal AF, induced atrial tachyarrhythmias were mapped in this mapping study. The pattern of the atrial activation of spontaneously occurring paroxysmal AF can differ from that of induced AF. The RA flutter could have degenerated into a different pattern of activation beyond the time of data acquisition.

**Mechanism of Long-Standing Persistent AF**

Reentrant or focal activations were observed in the LA in all patients, except for 1 patient in whom no specific pattern of activation was determined, with long-standing persistent AF with and without mitral valve regurgitation. We previously showed that focal activations arising from the PVs or LA and fibrillatory conduction to the RA are the mechanisms of AF in patients with mitral valve stenosis or regurgitation [7]. In the present study, 3 of 6 patients with long-standing persistent AF had moderate to severe mitral valve regurgitation that required mitral annuloplasty. The volume or pressure load to the LA might have provoked rapid activation in the PVs or LA sites or affected the atrial electrophysiologic characteristics in the patients with mitral valve regurgitation. Interestingly, the focal activations in the PVs or LA were observed even in patients without mitral valve regurgitation. The LA was moderately dilated in the 3 patients with an LA diameter that ranged from 41 to 45 mm (average, 43 ± 2 mm), but there was no significant mitral valve regurgitation. The increased pulmonary blood flow for a long time by a left-to-right shunt through an ASD might have resulted in dilatation of the PVs and LA. Roberts-Thomson and colleagues [13] demonstrated, in ASD patients without mitral valve regurgitation, that chronic LA stretch caused by an enlarged RA results in mechanical and electrophysiologic remodeling of the LA: dilatation, prolonged refractory periods, regional conduction slowing, a reduced atrial voltage, and others. These abnormalities suggest a loss of myocardium and scar formation in the LA, and they may be associated with the sustenance of AF.

The LA foci were distributed around the right and left PVs and posterior LA in the present mapping study. The characteristic distribution of the LA foci may be explained by the dilatation of the PVs and LA caused by the left-to-right shunt through an ASD. In the present study, the electrode patches covered only the atrial epicardium, and the electrograms from the infero-septal and atrial epicardium close to the atroventricular groove might not have been fully recorded. Focal activations arising from these atrial sites could have been obscured.

The difference in the mechanism of AF between paroxysmal and long-standing persistent AF may be explained by the time difference until the hemodynamic abnormalities cause significant electrophysiologic abnormalities, a patient’s age, and others. Actually, the patients with long-standing persistent AF were older than those with paroxysmal AF in the present study. Age-related...
fibrosis or other changes in the LA, not specific to ASD, might have occurred and participated in the development of reentrant and focal activations in the PVs or LA.

**Clinical Implications**

A variety of surgical procedures have been applied in patients with ASD and AF [6, 14–16]; however, the optimal procedure for AF has not been determined. Theodoro and colleagues [14] first performed a right-sided Maze procedure without any incisions on the LA in 18 patients with congenital heart diseases, including 1 isolated ASD patient. Later, Kobayashi and colleagues [15] compared the modified Maze procedure with biatrial incisions to the right-sided Maze procedure in 26 patients with isolated ASD. All 3 patients who underwent the right-sided Maze procedure returned to AF postoperatively, whereas 96% of the patients who underwent the biatrial Maze procedure remained in sinus rhythm. Stulak and colleagues [6] performed a right-sided Maze procedure in 99 patients with congenital heart disease, including 8 isolated ASD patients, and concluded that the right-sided Maze procedure is advantageous over the biatrial Maze procedure because of the shorter operating time, fewer suture lines, and avoidance of a postoperative noncontractile LA with the risk of subsequent systemic embolization. More recently, Im and colleagues [17] stated that the postoperative freedom from AF after the biatrial Maze procedure was significantly better than that after the right-sided Maze procedure (69% vs 45% 5 years postoperatively) during a median follow-up period of 49 months after operation for ASD and AF. The preoperative presence of significant tricuspid valve regurgitation was demonstrated as a risk factor for postoperative AF recurrence by multivariate analysis.

On the basis of the findings in the present mapping study, the right-sided Maze procedure may not be effective in patients with ASD and long-standing persistent AF. PV isolation or a box lesion is required to isolate the focal activations arising from PV and the posterior LA in those patients. Patients with paroxysmal AF may be treated with a right-sided Maze procedure to prevent any RA reentrant activation without performance of PV isolation. However, AF can develop even after the ASD is corrected in patients after the age of 40 years [3, 4], and whether the mechanical and electrophysiologic remodeling of the LA can be reversed after the closure of the ASD is not certain. Further study is required to determine whether PV isolation is also required in patients with paroxysmal AF. Bilateral PV isolation and LA ablation can be easily and safely performed with the aid of a radiofrequency ablation device in the current era [18]. Therefore, the biatrial Maze procedure is recommended for patients with any type of AF associated with ASD.

**Limitations**

The number of patients was limited in this intraoperative mapping study. Data from many patients with precise clinical characteristics may provide more predictive information on AF associated with ASD. The atrial electrograms were recorded during general anesthesia for a short time. In patients with paroxysmal AF, the atria were mapped during electrically induced AF. The atrial activations can differ during a longer recording time and without general anesthesia, and AF can spontaneously occur in patients with paroxysmal AF.

**Conclusions**

The pattern of atrial activation during AF varied from simple RA reentrant activation to complex reentrant and focal activations in the LA. The reentrant and focal activations driving the AF were confined to within the RA in all patients with paroxysmal AF, whereas multiple focal activations arising from the PVs or the posterior LA and reentrant activations in the LA were observed in the majority of patients with long-standing persistent AF.

**References**

INVITED COMMENTARY

Nitta and coworkers are to be commended for a highly insightful article investigating the pathophysiology of atrial fibrillation (AF) [1]. Earlier experience with concomitant ablation in patients with atrial septal defect (ASD) or other congenital conditions with right-sided overload seemed to indicate that a right-sided Maze operation could actually fix the problem in most cases. Interestingly, in patients with ASD this seems to be the case only with paroxysmal AF. Although not unexpected, this is an important finding. Recent trials have shown better rhythm outcomes at late follow-up in patients with ASD who had biatrial ablation rather than a right-sided Maze operation, but these series are quite small and the studies are retrospective.

Furthermore, it is hard to envision that solid evidence will arise from randomized trials in the near future. This is why a study of the intrinsic electrophysiology of AF, albeit in a small series of patients, plays an important role in confirming the importance of addressing the left atrium in patients with ASD with AF.

According to the findings of Nitta and colleagues [1], the optimal surgical ablation procedure should actually be based on direct intraoperative electrophysiologic assessment in each patient. Improved technology predictably will make electrophysiologic assessment quicker and more simple, but this advance is not likely to occur in the near future. Thus, when sophisticated mapping systems are not available in the operating theater, it seems wise to extend surgical ablation to both atria in patients with ASD and especially when dealing with persistent AF.

Of course, a right-sided Maze operation is an appealing option for concomitant ablation because it is simpler and can be performed on a beating heart. Results from registries and surveys indicate that surgeons tend to favor a minimalist approach when dealing with concomitant AF ablation. Only a few years ago, a brilliant analysis of the Society of Thoracic Surgeons national cardiac database, published by Gammie and colleagues, showed that more than half of such patients did not receive any ablation at the time of open operation even though ablation added only 9 minutes of operative time [2].

However, when dealing with persistent AF, a full Maze procedure apparently should be performed at the time of ASD closure. Whenever the specific clinical situation dictates an ablation procedure simpler than the Cox-Maze procedure, a right-sided Cox-Maze operation combined with pulmonary vein isolation or with isolation of the posterior left atrium seems a plausible second choice according to the data of Nitta and colleagues.

Finally, because of growing numbers of patients undergoing percutaneous ASD closure, surgeons are starting to see such patients for epicardial ablation of AF. In fact, transcatheter ablation cannot be performed in these patients because the closure device makes transseptal puncture unfeasible. Because we now know that left atrial ablation is mandatory, AF surgery will become increasingly necessary also in this context.

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