Internal Cardioversion of Chronic Atrial Fibrillation During Percutaneous Mitral Commissurotomy
Insight Into Reversal of Chronic Stretch–Induced Atrial Remodeling

Katherine Fan, MRCP; Kathy L. Lee, MRCP; Wing-Hing Chow, FRCP; Elaine Chau, MRCP; Chu-Pak Lau, MD, FRCP

Background—Mechanoelectrical feedback caused by atrial dilatation plays an important role in atrial fibrillation (AF). To test the hypothesis that remodeling is reversible by reducing atrial stretch, we investigated electrophysiological changes after a reduction of left atrial (LA) pressure in patients undergoing percutaneous balloon mitral commissurotomy (PBMC).

Methods and Results—In 22 patients with chronic AF who were undergoing PBMC for mitral stenosis, internal cardioversion was successful in 19 patients (86%). Twelve patients with sinus rhythm acted as controls. Mean LA pressure was significantly reduced after PBMC (18.5±5.9 mm Hg versus 10.2±4.1 mm Hg; P<0.001). The effective refractory period (ERP), conduction delay (CD), and the index of heterogeneity (CoV) of the ERP and CD were compared. Changes in LA pressure were only significantly correlated with AF vulnerability (r=0.7; P=0.02) and CoV of CD (r=0.3; P=0.03). There were no significant changes in ERP and CD immediately after PBMC in the AF group. However, the overall CoV of ERP was reduced in the AF group after PBMC. There were homogenous, although not significant, increases in regional ERP in the control group immediately after PBMC. Atrial CD and CoV of CD were significantly reduced after PBMC in the control group; this was most prominent within the regions of the LA.

Conclusions—AF vulnerability and CoV of CD correlated significantly with LA pressure. A homogenous increase in regional ERPs could be demonstrated in the control group after an immediate reduction of atrial stretch, whereas the recovery course of electrical remodeling was prolonged and heterogenous in the AF group. Regional conductions were irreversible in patients with preexisting AF. (Circulation. 2002;105:2746-2752.)

Key Words: arrhythmia ■ cardioversion ■ mitral valve ■ remodeling

Recent studies in humans have improved our understanding of electrophysiological remodeling of the atrial myocardium by the shortening of the effective refractory period (ERP), loss of rate adaptation, increase in ERP dispersion, and regional slowing of conduction after a prolonged period of atrial fibrillation (AF).1,2 Although the electrophysiological effects of atrial pressure or volume overload are still incompletely understood, it is clear that mechanoelectrical feedback caused by atrial dilatation plays an important role in the development of AF. Few studies have assessed the role of mechanoelectrical feedback in atrial tissue on the vulnerability of AF.3–8 However, the majority of these data were obtained from animal models or patients with a normal structural heart who had changes in electrophysiology induced by brief periods of atrial pacing or induced AF. Information in humans on true clinical AF-induced electrical remodeling in the presence of a substrate such as chronic atrial stretch associated with structural heart disease was lacking. Preliminary animal data suggested that the key changes in atrial electrophysiology caused by heart failure seem to involve alterations in conduction properties caused by interstitial fibrosis rather than increasing regional disparity of refractoriness caused by AF remodeling itself.9

It is important to know the relative contribution of electrical and/or structural remodeling to the substrate of AF in sustained atrial stretch and whether this remodeling is reversible. This possibility forms an attractive theoretical basis for interventions to reduce atrial pressure overload in such patients. Alternatively, if atrial remodeling were found to be irreversible in humans, then it would be difficult to support such a strategy in this patient group, at least on the basis of the atrial remodeling hypothesis.

Methods

Patient Selection

From January 2000 to June 2001, 34 patients (11 men and 23 women aged 47±10 years) undergoing percutaneous balloon mitral commissurotomy (PBMC) were enrolled. The protocol was approved by our Research and Ethics Committee. Informed consent was obtained from all patients. Echocardiographic examinations were performed...
to evaluate mitral valve area, gradient, and mitral regurgitation by planimetry and Doppler studies. Left atrial (LA) size was quantified during the diastolic phase by an M-mode study in the parasternal long-axis view. The mitral valve anatomy was scored using the definitions of Wilkins et al.\textsuperscript{10} Exclusion criteria for PBMC were Wilkins scores ≤8, heavily calcified mitral valves, mitral regurgitation greater than grade II, LA thrombus (detected by transesophageal echocardiogram), and significant aortic valve or coronary artery disease. PBMC was performed using the Inoue balloon, as described previously.\textsuperscript{11}

Patients were divided into 2 groups: those with clinically documented AF who underwent internal cardioversion and those with sinus rhythm (SR) at baseline who acted as a control group. In the AF group, failure of conversion to SR with internal cardioversion was excluded in the final analysis because determination of ERP and conduction delay (CD) could not be performed in the presence of AF. Patients successfully cardioverted from AF were started on 150 mg of propafenone 3 times daily and 120 mg of verapamil once daily while continuing with oral anticoagulation therapy. The combination of class Ic agents with calcium antagonists were chosen because of their relatively shorter half-lives, such that profound drug-induced electrophysiological changes could be minimized at the 3-month follow-up study after stopping the medications shortly beforehand. Recurrence of AF before the 3-month follow-up study was excluded in final paired analysis.

**Internal Cardioversion Protocol**

All patients in the AF group received anticoagulation therapy with oral warfarin that had an international normalized ratio between 2 and 2.5 for at least 3 months; note that low-intensity anticoagulation is preferred in Chinese patients because of the substantially higher risks of bleeding complications with warfarin.\textsuperscript{12} Intravenous midazolam was used for conscious sedation. A system of a balloon-guided single catheter and an external defibrillation device (ALERT System, EPMed Systems) was used for internal cardioversion.\textsuperscript{13} It consists of a 7.5F balloon catheter with 2 high-energy electrode arrays. The distal array is positioned in the left pulmonary artery, and the proximal array is placed in the right atrium. The system senses an endocardial ventricular signal coming from a small electrode in the ventricle referenced to the pulmonary artery electrode. Synchronized biphasic shocks of 50% tilt were used starting at 1 J, followed by a 3-J step-up protocol until termination of AF or a maximum of 15 J was reached.

**Electrophysiology Study**

All antiarrhythmic medications were discontinued for at least 5 half-lives before the procedure. A 20-pole electrode catheter was positioned around the tricuspid annulus. A 10-pole electrode catheter was positioned in the coronary sinus (CS), with the proximal electrode pair placed at the CS ostium. Two other intracardiac electrodes were positioned in the His bundle region and the right ventricular apex.

Sinus node function was evaluated by determining the corrected sinus node recovery time (SNRT) after right atrial pacing at 500 ms for 60 seconds. The SNRT was defined as the interval between the last paced atrial response and the first spontaneous sinus response. The corrected SNRT (CSNRT) was assessed by subtracting the mean spontaneous sinus cycle length before the beginning of atrial pacing. Careful comparison of the escape depolarization at different atrial recording sites at the termination of pacing was performed to ensure that the atrial response originated from the sinus node.

Atrial ERP was evaluated at 5 different sites, the high right atrium (HRA), low right atrium (LRA), right atrial anterior septum, proximal CS, and distal CS, at cycle lengths of 500 ms and 300 ms. ERPs were determined using an 8-beat (S\textsubscript{1}) drive train and an incremental technique starting with an S\textsubscript{1} coupling interval of 150 ms that was increased by 5 ms until atrial depolarization. The atrial ERP was defined as the longest S\textsubscript{S} interval failing to evoke an atrial depolarization. A\textsubscript{1} and A\textsubscript{2} were the atrial electrograms resulting from S\textsubscript{1} and S\textsubscript{2}, respectively. Bipolar recording sites for measuring CD included HRA, mid right atrium, LRA, high right atrial septum, right atrial anterior septum, proximal CS, mid-CS, and distal CS. Local CD at all recording sites in response to premature extrastimuli from the 4 different atrial pacing sites (HRA, LRA, proximal CS, and distal CS) at a cycle length of 500 ms was evaluated. Local CD was calculated as the time interval between A\textsubscript{1} and A\textsubscript{2} after subtracting the corresponding S\textsubscript{1} S\textsubscript{2} interval (A\textsubscript{1} A\textsubscript{2} corresponds to S\textsubscript{1} S\textsubscript{2}). The overall ERP and CD for each patient were calculated from the average of each regional value. An index of heterogeneity was obtained by calculating the coefficient of variation (CoV = SD/mean×100%). The vulnerability to AF induction in each patient was quantified by the number of inductions of AF by a single extrastimulus at cycle lengths of 500 ms and 300 ms at all 5 sites (maximum of 10 inductions). If induced AF lasted for >15 minutes, internal cardioversion was performed to restore SR.

**Statistical Analysis**

All data are presented as mean±SD. Student’s t test was used to compare all paired data in the same group. The differences between groups were analyzed with 2-factor ANOVA with Bonferroni adjustments for multiple comparisons. The association of LA pressures with other measured parameters was assessed by the Spearman correlation test. Statistical significance was established at P<0.05.

**Results**

PBMC was successfully performed in all patients, with a significant reduction in the transmural gradient without an elevation of mean left ventricular end-diastolic pressures.
Mean LA pressure was significantly reduced after PBMC (from 18.5±6.5 mm Hg at baseline to 10.2±4.1 mm Hg after PBMC; *P*<0.001). Mean right atrial pressure, however, did not change significantly (from 10.2±2.6 mm Hg to 8.3±4.2 mm Hg; *P*>0.1). Mean LA dimensions were reduced after PBMC, with no significant changes by the 3-month follow-up study (from 5.6±0.7 cm at baseline to 4.9±0.6 cm after PBMC; *P*>0.0001). Of the 22 patients with chronic AF, 19 (86%) were successfully cardioverted to SR, and AF recurred in 6 of these 19 patients (5.3%) at follow-up (mean duration of SR was 4.4±0.6 weeks; Figure 1). Therefore, 13 patients in the AF group were included in the final analysis. The electrophysiological evaluation was completed successfully in all 12 patients in the control group.

**Termination and Induction of AF**

The AF group was further divided into 2 subgroups according to the timing of successful cardioversion: 7 patients (group I) had successful internal cardioversion before PBMC and 12 patients (group II) failed before PBMC but had successful restoration of SR after the procedure. Three other patients demonstrated a total absence of sinus node activity, despite successful termination of AF with internal cardioversion followed by reinitiation of AF; they were excluded from final analysis. There were no significant differences in the mean energy required for successful internal cardioversion (defined as atrial defibrillation threshold) between groups I and II (9.9±3.5 J versus 10.3±7.7 J in group I versus group II; *P*>0.1). AF vulnerability was substantially higher in the AF group (79% of 19 episodes of AF induced), and repeated internal cardioversion was required in 42% of the induced episodes of AF. Correlation analysis found a significant association between AF vulnerability and LA pressure (r=0.7; *P*=0.02) but not atrial defibrillation thresholds (r=0.12; *P*=0.45; Figure 2).

**Changes in Electrophysiological Properties**

**Sinus Node Function**

At baseline before PBMC, the CSNRT obtained from the AF group (group I) was significantly prolonged when compared with the control group (360.2±122 ms versus 165.3±50 ms for AF versus SR; *P*=0.01). Mean right atrial pressure, however, did not change significantly (from 10.2±2.6 mm Hg to 8.3±4.2 mm Hg; *P*>0.1). Mean LA dimensions were reduced after PBMC, with no significant changes by the 3-month follow-up study (from 5.6±0.7 cm at baseline to 4.9±0.6 cm after PBMC; *P*>0.0001). Of the 22 patients with chronic AF, 19 (86%) were successfully cardioverted to SR, and AF recurred in 6 of these 19 patients (5.3%) at follow-up (mean duration of SR was 4.4±0.6 weeks; Figure 1). Therefore, 13 patients in the AF group were included in the final analysis. The electrophysiological evaluation was completed successfully in all 12 patients in the control group.

**AF Group**

The temporal changes in overall atrial ERP are shown in Figure 3A. In group I, there were no significant changes in the overall atrial ERP before and immediately after PBMC at both drive cycle lengths of 500 ms and 300 ms. However, overall ERP increased significantly at 3 months after conversion to SR. Furthermore, overall ERP determined at 300 ms was shorter than that at 500 ms, suggesting that the rate-adaptation of ERP was preserved both at restoration of SR and at follow-up. Regional ERPs at baseline were not significantly different between the 5 regions measured. There were, however, heterogeneous changes in regional atrial ERP immediately after PBMC at both drive cycle lengths, with a significant increase at the right atrial anterior septum and distal CS regions but a reduction in the LRA region (Figures 3C and 3D). This resulted in a significant reduction of spatial ERP (CoV-ERP) after PBMC (Figure 3B).

**SR Group**

The overall atrial ERP was significantly increased immediately after PBMC (Figure 3A). The regional ERPs increased homogenously after PBMC, especially those measured at
CL500 ms (Figure 3C and 3D), with no significant differences in CoV-ERP before and after PBMC (Figure 3B).

**AF Versus SR Group**

The overall atrial ERPs were significantly shorter in patients who were converted from chronic AF than those who were in SR at baseline and after PBMC. Significant differences in regional ERP in the AF group existed only in certain regions when compared with the SR group. Before PBMC, a significantly shorter ERP existed in the regions of the right atrial anterior septum, proximal CS, and distal CS in the AF group compared with controls (Figures 3C and 3D). The CoV-ERP was also significantly increased in the AF group when compared with SR groups before PBMC (16±2% versus 9±3% for AF versus SR; *P*<0.01; Figure 3B). With an immediate reduction of LA pressure, site-dependent differences in ERP changes could be demonstrated between the AF and SR groups in the regions of the LRA, right atrial anterior septum, and proximal CS. At the 3-month follow-up study, regional ERPs and CoV-ERP in the AF group increased significantly to values comparable to the SR group after PBMC. No significant correlation could be demonstrated between LA pressures and regional ERPs (*r*<0.08, *P*>0.6) or CoV-ERP (*r*<0.05, *P*>0.8) in either group.

**Regional Atrial CD**

There were no significant differences in global atrial CD and CoV-CD at 4 different atrial pacing sites at baseline, after PBMC, and during follow-up study in the AF group. In the SR group, the global atrial CD and CoV-CD induced by different atrial pacing sites were significantly reduced after PBMC (Figure 4). From individual regional pacing analysis, only HRA and LRA pacing resulted in significant interatrial CD (from right to left atrium) at baseline in both groups (Figures 5A and 5B). After PBMC, significant improvement in LA regional conduction properties occurred only in SR groups with HRA, LRA, and distal CS pacing (Figure 5). No significant regional changes occurred in the AF group after PBMC and at the 3-month follow-up study. Using logistic regression analysis, only CoV-CD, but not CD, correlated significantly with changes in LA pressures (Figure 6).

**Discussion**

**Major Findings**

This study systematically assessed the effect of a reduction of chronic LA stretch on the electrophysiological changes in patients with rheumatic mitral stenosis undergoing PBMC. The findings were as follows. (1) With a reduction of LA pressure in the SR group (without preexisting AF), there was a rapid restitution and homogenous increase of regional atrial ERPs. In addition, there were improved conduction properties, predominantly within the LA region. (2) An inhomogeneous distribution of regional ERPs occurred in the AF group when compared with controls. The heterogeneity index of ERP improved significantly after LA stretch reduction. Atrial conduction properties, however, were not reversible in patients with preexisting AF. (3) Only AF vulnerability and CoV-CD showed a significant correlation with changes in LA pressures.
Electromechanical Feedback Effect of Atrial Stretch

To our knowledge, this study is the first to determine the relative role of chronic atrial stretch and prolonged high atrial rate on the process of electrophysiological remodeling by assessing the electrophysiological properties of the dilated atrium in chronic mitral valvular disease with and without AF. Atrial stretch secondary to pressure and volume overload has long been considered a primary stimulus of AF-induced remodeling. Studies from animal models of acute atrial dilatation produced a shortening of atrial ERP that led to increased vulnerability to AF.3,4 In humans, conflicting reports showed that atrial ERP lengthened with increased pressure and atrial size,6 remained unchanged,7 or shortened with an increased propensity to develop AF.8 More importantly, all these studies essentially looked at the effect of acute atrial stretch, and little information is available on the long-term effects of chronic dilatation on atrial electrophysiology. In a study by Le Grand et al,14 monophasic action potential durations were markedly shortened in dilated human atrial trabeculae. Because almost 75% of these patients with dilated right atria were not fibrillating, the authors concluded that the observed action potential shortening could not result from AF. In fact, these changes could favor the occurrence of

Figure 4. The temporal changes in CD (A) and CoV-CD (B) for HRA pacing (○), LRA pacing (●), proximal coronary sinus (PCS) pacing (▲), and distal coronary sinus (DCS) pacing (△). *P<0.01 compared with baseline.

Figure 5. Comparison of regional changes in CD with HRA pacing (A), LRA pacing (B), distal coronary sinus (DCS) pacing (C), and proximal coronary sinus (PCS) pacing (D) at baseline, after PBMC, and at 3-month follow-up. MRA indicates mid-lateral right atrium; RAS, right anterior septum; and MCS, mid-coronary sinus *P<0.05 compared with MRA during HRA and LRA pacing; †P<0.05 compared with baseline data of corresponding groups.
AF and may represent conditions predisposing to the development of AF. Our findings suggested a potential reversibility of the electrophysiological features of chronic atrial dilatation after mechanical reduction of LA stretch.

Reversibility of Electrophysiological and Structural Remodeling
In accordance with other studies, atrial ERPs were significantly shorter in our patients converted from chronic AF compared with those in the SR group. Furthermore, the time course of atrial ERP recovery was much slower, with significant regional heterogeneity, in the AF group when compared with the SR group after the reduction of LA stretch. Lee et al15 demonstrated in a canine model of AF induced by chronic rapid pacing of either right or left atria that there was a recovery of ERP shortening and maladaptation with decreased AF vulnerability after 8 weeks of chronic pacing. Pandozi et al1 demonstrated that ERP was significantly shorter in the right atrial lateral wall than in the atrial roof and septum in patients converted from chronic AF and had lengthened on repeat evaluation after 4 weeks of SR. Previous studies have shown different shapes and durations of atrial action potentials at different atrial sites.16 An increase in ERP heterogeneity favors the development of regions of functional block and facilitates the development of AF.17 These nonuniform regional differences could be exaggerated with increased wall stress during elevated intra-atrial pressure by increasing the spatial dispersion of atrial refractoriness.18 We have shown that significant regional differences in atrial electrical remodeling existed and that this pattern changes after an immediate reduction of LA pressures. However, the index of heterogeneity for ERP was reduced up to 3 months after PBMC in those with chronic AF, with a decreased vulnerability to AF.

Conduction Delay
Conditions favoring the development of sustained AF extend beyond a simple measurement of atrial refractoriness. Various factors, such as intra-atrial conduction, that are important in the development of a substrate for AF have also been observed in the setting of atrial stretch. Furthermore, rheumatic inflammatory activity causes changes in the LA myocardium other than valvular structures; these frequently include focal calcification and thickening.19 As a result, chronic atrial stretch and scarring leads to atrial dilatation and conduction slowing and, hence, a tendency toward a shorter atrial wavelength of reentry. A general depression in conduction velocity, a preferential slowing of premature beats, and an increased spatial heterogeneity of CD are all considered pro-fibrillatory and create a substrate for persistent AF. Previous studies have shown that AF alone is associated with abnormally depressed intra-atrial conduction but, unlike atrial ERP, this did not recover during follow-up lasting up to 4 days.20–22 In animal models, a depression of atrial conduction occurring after long-term rapid atrial pacing could be related to structural abnormalities, including changes of connexin43 expression documented by light and electron microscopy.23,24 We have demonstrated that significant intra-atrial slowing of conduction already existed in the LA at baseline in the SR group, with improved conduction properties after a reduction of LA stretch. However, patients with preexisting AF did not show an improvement in conduction properties after reducing LA pressure, thus supporting the notion that chronic AF and/or the structurally remodeled atrium induced further permanent delay in atrial conduction.

Limitations
Pharmacological autonomic blockade was not administered during the procedure. We were fully aware of the influence of neurogenic factors on the heterogeneity of electrophysiological properties. However, we tried to avoid potential hypotensive agents during the invasive procedure of PBMC. CS recordings cannot be used to judge the entire activation in LA. Catheters deployed into the LA should disclose a better LA activation pattern, but they may impose technical difficulties while performing PBMC. Although the 2 groups of patients were comparable in age, LA sizes, and pressures, we could not exclude differences in structural remodeling. However, the temporal changes in ERP and CD in the AF group provide new insight into chronic atrial stretch and the rate effects on the atrial remodeling process.

Implications of the Study
We have shown that a reduction of chronic atrial stretch in mitral stenosis resulted in a favorable reversal of remodeling. Earlier timing of interventions in relieving mitral stenosis and elevated LA pressure may even delay or abort the initiation of AF. These electrophysiological changes provide insights into mechanisms for AF secondary to atrial stretch in other conditions such as congestive heart failure.

References
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