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# Reverse Remodeling of the Atria After Treatment of Chronic Stretch in Humans

## Implications for the Atrial Fibrillation Substrate

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**Objectives** The aim of this report was to study the effect of chronic stretch reversal on the electrophysiological characteristics of the atria in humans.

**Background** Atrial stretch is an important determinant for atrial fibrillation. Whether relief of stretch reverses the substrate predisposed to atrial fibrillation is unknown.

**Methods** Twenty-one patients with mitral stenosis undergoing mitral commissurotomy (MC) were studied before and after intervention. Catheters were placed at multiple sites in the right atrium (RA) and sequentially within the left atrium (LA) to determine: effective refractory period (ERP) at 10 sites (600 and 450 ms) and P-wave duration (PWD). Bi-atrial electroanatomic maps determined conduction velocity (CV) and voltage. In 14 patients, RA studies were repeated ≥6 months after MC.

**Results** Immediately after MC, there was significant increase in mitral valve area (2.1 ± 0.2 $cm^2$, $p < 0.0001$) with decrease in LA (23 ± 7 mm Hg to 10 ± 4 mm Hg, $p < 0.0001$) and pulmonary arterial pressures (38 ± 16 mm Hg to 27 ± 12 mm Hg, $p < 0.0001$) and LA volume (75 ± 20 ml to 52 ± 18 ml, $p < 0.0001$). This was associated with reduction in PWD (139 ± 19 ms to 135 ± 20 ms, $p = 0.047$), increase in CV (LA: 1.3 ± 0.3 mm/ms to 1.7 ± 0.2 mm/ms, $p = 0.006$; and RA: 1.0 ± 0.1 mm/ms to 1.3 ± 0.3 mm/ms, $p = 0.002$) and voltage (LA: 1.7 ± 0.6 mV to 2.5 ± 1.0 mV, $p = 0.005$; and RA: 1.8 ± 0.6 mV to 2.2 ± 0.7 mV, $p = 0.09$), and no change in ERP. Late after MC, mitral valve area remained at 2.1 ± 0.3 $cm^2$ ($p = 0.7$) but with further decrease in PWD (113 ± 19 ms, $p = 0.04$) and RA ERP (at 600 ms, $p < 0.0001$), with increase in CV (1.0 ± 0.1 mm/ms to 1.3 ± 0.2 mm/ms, $p = 0.006$) and voltage (1.8 ± 0.7 mV to 2.8 ± 0.6 mV, $p = 0.002$).

**Conclusions** The atrial electrophysiologic and electroanatomic abnormalities that result from chronic stretch due to MS reverses after MC. These observations suggest that the substrate predisposing to atrial arrhythmias might be reversed. (J Am Coll Cardiol 2010;55:1217–26) © 2010 by the American College of Cardiology Foundation

A common feature of many of the conditions predisposed to atrial fibrillation (AF) is chronic atrial "stretch." Atrial size is known to be an important marker for the development of AF (1). Electrical remodeling caused by short-term stretch of the atria due to asynchronous ventricular pacing has been demonstrated to be reversible with restoration of atrioventricular synchrony (2). However, several studies have identified structural change as an important component of chronic conditions predisposed to AF (3–10). Whether reversal of chronic atrial stretch in a clinical condition known to have such structural and electrophysiological abnormalities alters the AF substrate is not known.

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**Abbreviations and Acronyms**

**AF** = atrial fibrillation
**CL** = cycle length(s)
**CS** = coronary sinus
**CV** = conduction velocity
**DP** = double potential(s)
**ECG** = electrocardiogram
**ERP** = effective refractory period
**FS** = fractionated signals
**LA** = left atrium
**LAT** = local activation time
**MC** = mitral commissurotomy
**MS** = mitral stenosis
**MVA** = mitral valve area
**PWD** = P-wave duration
**RA** = right atrium

Severe mitral stenosis (MS) is an established substrate for AF and results in chronically elevated atrial pressures and atrial enlargement (8). Mitral commissurotomy (MC) is now the treatment of choice for patients with severe MS and favorable valve morphology. We aimed to characterize the immediate and late effects of chronic stretch reversal by performing high-density electrophysiological and electroanatomical mapping of the atria before and serially after MC.

## Methods

**Study population.** The study comprised 21 patients with severe MS due to rheumatic heart disease, mitral valve area (MVA) of $<1.5$ cm$^2$ associated with significant symptoms (New York Heart Association functional class $\geq$II), and mitral valve morphology suitable for MC. Other structural heart disease, hypertension, atrial arrhythmias (by history and monitoring for $>48$ h), amiodarone use, or the presence of left atrial thrombus formed exclusion criteria.

All patients gave written informed consent to the study, which was approved by each institutional clinical research and ethics committee. All antiarrhythmic drugs were ceased at least 5 half lives before the study. Echocardiography was performed to determine the atrial volumes with the equation for prolate ellipsoid (10). Patients underwent either electrophysiological or electroanatomical mapping as detailed in the following text.

**Electrophysiological mapping.** Electrophysiological study was performed in the fasted state with sedation. Electrophysiological evaluation of the right (RA) and left atria (LA) was performed before and immediately after MC. At $\geq$6-month follow-up electrophysiological study was performed in the RA. The following catheters were positioned for the study protocol: 1) 10-pole catheter (2-5-2 mm inter-electrode spacing, Daig Electrophysiology, St. Jude Medical, St. Paul, Minnesota) within the coronary sinus (CS) with the proximal bipole at the CS ostium; 2) 20-pole "crista" catheter with 1-3-1 mm interelectrode spacing (Biosense-Webster, Diamond Bar, California) positioned with the aid of a long sheath along the crista terminalis and standardized such that the second bipole lay at the junction of the superior vena cava with RA as determined by fluoroscopy and intracardiac echocardiography (Acunav, Siemens Medical, Mountain View, California); 3) 20-pole catheter (2-5-2 mm interelectrode spacing, Daig Electrophysiology) placed along the lateral RA; and 4) 10-pole catheter (2-5-2 mm inter-electrode spacing, Biosense-Webster) was positioned within the LA via transseptal puncture. This catheter was stabilized with the use of a long sheath (Preface, Biosense-Webster, or SL0, Daig Electrophysiology) and sequentially positioned as follows at the: 1) LA roof; 2) inferior LA; 3) mid-posterior LA; 4) LA appendage; and 5) high RA septum (8). Digital images were archived to help standardize catheter locations for subsequent studies.

Surface electrocardiograms (ECGs) and bipolar endocardial electrograms were continuously monitored and stored on a computer-based digital amplifier/recorder system for offline analysis (Bard Electrophysiology, Lowell, Massachusetts). Intracardiac electrograms were filtered from 30 to 500 Hz and measured with computer-assisted calipers at a sweep speed of 200 mm/s.

**EFFECTIVE REFRACTORINESS.** Atrial effective refractory period (ERP) was evaluated at cycle lengths (CL) of 600 and 450 ms with an 8-beat drive followed by an extra-stimulus, starting with an extra-stimulus coupling interval of 150 ms increasing in 10-ms increments. The ERP was defined as the longest coupling interval failing to propagate to the atrium. At each site the ERP was measured 3 times during each CL and averaged. If ERP varied by $>10$ ms, an additional 2 measurements were made, and the total number was averaged. The ERP was measured from the following sites: 1) distal-CS; 2) proximal-CS; 3) low lateral RA; 4) high lateral RA; 5) high septal RA; 6) LA appendage; 7) posterior LA; 8) right superior pulmonary vein–LA roof junction; 9) left superior pulmonary vein–LA roof junction; and 10) inferior LA.

**VULNERABILITY FOR AF.** Vulnerability to AF was defined as irregular atrial activity $>30$ s during the study protocol. Atrial fibrillation lasting $>5$ min was considered sustained; when this occurred, no further data were acquired.

**Electroanatomic mapping.** Electroanatomic maps were created of the LA and RA during sinus rhythm with the CARTO mapping system (Biosense-Webster) both before and immediately after MC. At $\geq$6 months after MC, electroanatomic mapping was performed in sinus rhythm only in the RA. Endocardial contact during point acquisition was facilitated by fluoroscopy, the catheter icon on the CARTO system, and intracardiac echocardiography. Points were acquired in the auto-freeze mode, if the stability criteria in space ($\leq$6 mm) and local activation time (LAT; $\leq$5 ms) were met. Mapping was performed with a fill-threshold of 15 mm. Editing of points was performed offline. The LAT was manually annotated to the peak of the largest amplitude deflection on bipolar electrograms. In the presence of double potentials (DP), the LAT was annotated at the largest potential. If the bipolar electrogram displayed equivalent maximum positive and negative deflections, the maximum negative deflection on the simultaneously acquired unipolar electrogram was used to annotate the LAT. Points not conforming to the 12-lead ECG P-wave mor-

phology or <75% of the maximum voltage of the preceding electrogram were excluded.

**VOLTAGE ANALYSIS.** Regional voltage differences were evaluated by segmenting each atrium with previously validated offline software (11). The RA was segmented as the high- and low-lateral RA, high- and low-posterior RA, high- and low-septal RA, and anterior RA. The LA was segmented as posterior LA, LA-roof, anterior LA, septal LA, inferior LA, and lateral LA. For each region and each atrium the mean voltage was determined by averaging the bipolar voltage of the points within the given region.

Regions of low-voltage were defined as contiguous areas of bipolar voltage ≤0.5 mV, whereas electrically silent areas (scar) were defined as the absence of recordable activity or a bipolar voltage amplitude ≤0.05 mV (the noise level of the system) (6).

**CONDUCTION VELOCITY ANALYSIS.** Isochronal activation maps (5-ms intervals) of the atria were created, and regional conduction velocity (CV) was determined in the direction of the wave-front propagation (11). The system determines the CV between 2 points by expressing the distance between the points as a function of the difference in LAT. For the purposes of evaluating regional conduction differences, each atrium was segmented as described in the preceding text.

The proportion of points demonstrating delayed conduction was determined with the following definitions, as previously described (12): 1) fractionated signals (FS)—complex activity of ≥50-ms duration; and 2) DP—potentials separated by an isoelectric interval of ≥50 ms.

The P-wave duration (PWD) was averaged over 10 beats and measured on lead II of the surface ECG.

**Statistical analysis.** Data were assessed for normality with the Shapiro-Wilk test. Normally distributed variables are reported as mean ± SD and analyzed with paired t test. Data that were not normally distributed are reported as median (range) and compared with Wilcoxon signed rank tests. Categorical variables are reported as number and percentage and compared with the McNemar paired chi-square test.

Repeated measures analysis of variance was used to compare echocardiographic and hemodynamic data over time. To compare voltage, CV, and atrial refractory period across regions and over time, linear mixed effects models were fitted to the data. In the models, region, time, and the interaction between region and time were fitted as fixed effects. Random effects were fitted in the models to account for the dependence in observations from the same patient. The analyses of the CV and voltage data were stratified by atria, whereas the atrial refractory period analyses were stratified by both atria and CL. Statistical significance was established at $p < 0.05$.

## Results

**Acute reversal of stretch. HEMODYNAMIC AND MECHANICAL CHANGES.** Table 1 summarizes the hemodynamic characteristics of these patients before and after MC. These patients had severe MS with a mitral valve gradient of 16 ± 6 mm Hg and LA enlargement of 75 ± 20 ml. The MC was successful in all patients, resulting in significant increase in MVA ($p < 0.0001$), accompanied by decrease in LA volume ($p < 0.0001$) and reduction of mean LA pressure ($p < 0.0001$).

**ATRIAL REFRACTORINESS.** Figure 1 demonstrates the atrial ERP at each site and at both CL evaluated in the RA and LA. There was no significant change in the atrial ERP in

**Table 1 Echocardiographic and Hemodynamic Characteristics**

| | Baseline (n = 21) | After MC (n = 21) | p Value | Follow-Up (n = 14)* | p Value (ANOVA) |
|---|---|---|---|---|---|
| MVA ($cm^2$) | 0.9 ± 0.2 | 2.0 ± 0.2 | <0.0001 | 2.1 ± 0.3 | <0.0001 |
| LA size (mm) | | | | | |
| Longitudinal | 55.8 ± 8.4 | 53.4 ± 7.4 | 0.3 | 48.9 ± 7.4 | 0.005 |
| Transverse | 49.5 ± 6.5 | 41.1 ± 6.3 | <0.0001 | 40.8 ± 8.7 | 0.0001 |
| Volume (ml) | 75 ± 20 | 52 ± 18 | 0.0001 | 45 ± 23 | 0.0004 |
| RA size (mm) | | | | | |
| Longitudinal | 46.2 ± 5.3 | 48.7 ± 8.5 | 0.08 | 45.1 ± 6.6 | 0.06 |
| Transverse | 26.7 ± 5.7 | 28.8 ± 4.8 | 0.008 | 28.6 ± 6.9 | 0.4 |
| Volume (ml) | 18 ± 10 | 22 ± 11 | 0.004 | 21 ± 12 | 0.4 |
| LV size (mm) | | | | | |
| LVEDD | 40.0 ± 5.9 | 41.2 ± 5.0 | 0.2 | 40.9 ± 4.6 | 0.08 |
| LVESD | 27.3 ± 5.3 | 28.6 ± 8.1 | 0.9 | 26.8 ± 4.2 | 0.6 |
| Pressures (mm Hg) | | | | | |
| LA | 23 ± 7 | 10 ± 4 | <0.0001 | 14 ± 9† | <0.0001 |
| PA | 38 ± 16 | 27 ± 12 | <0.0001 | 23 ± 13 | <0.0001 |

*Pre- and post-mitral commissurotomy (MC) values for the 14 patients followed up at >6 months were not statistically different from the total sample size (n = 21) at the beginning of study; †pulmonary capillary wedge.

ANOVA = analysis of variance; LA = left atrial; LV = left ventricular; LVEDD = left ventricular end-diastolic dimension; LVESD = left ventricular end-systolic dimension; MC = mitral commissurotomy; MVA = mitral valve area; PA = pulmonary arterial; RA = right atrium.

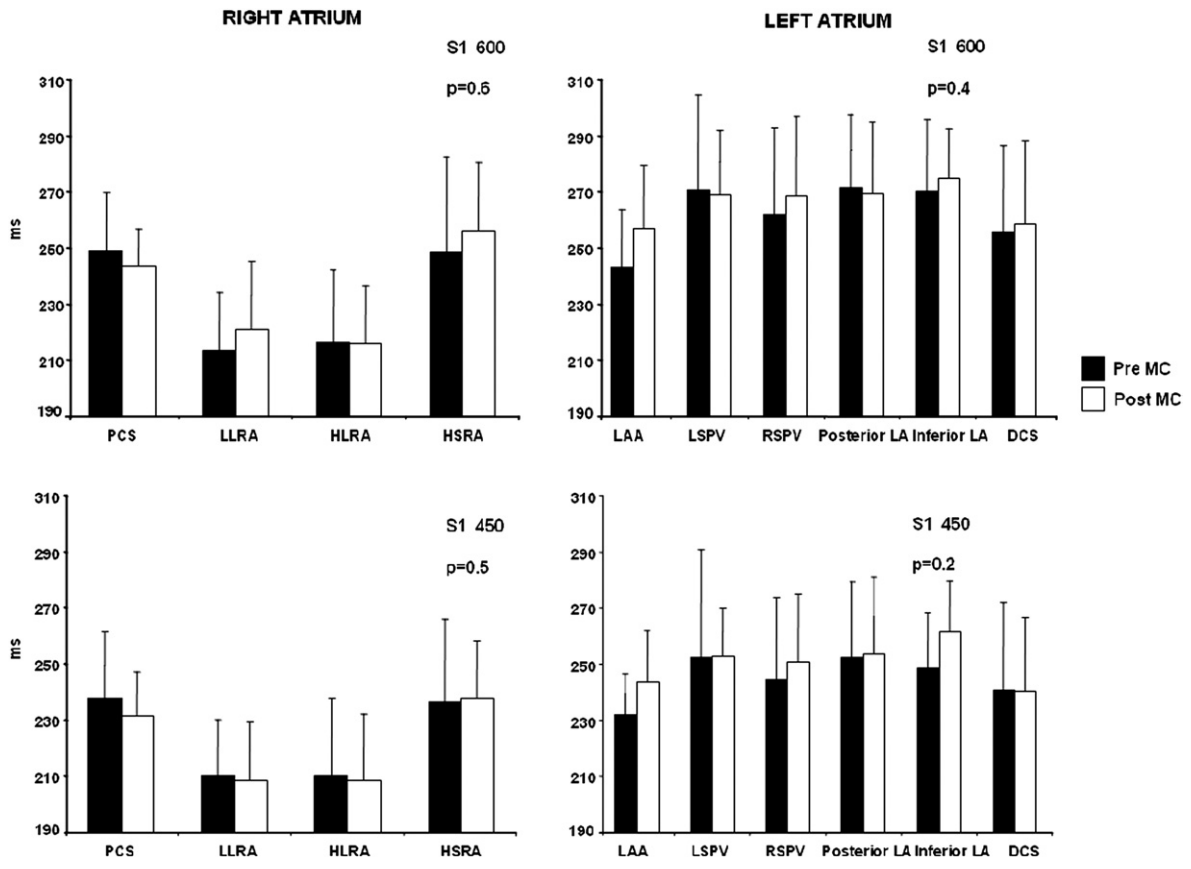


**Figure 1** **Effective Refractory Period Acutely After Stretch Reversal**

Effective refractory period at cycle lengths of 600 and 450 ms before and after mitral commissurotomy (MC). The group main effect p value is shown for each cycle length. DCS = distal coronary sinus; HL = high lateral; HP = high posterior; LA = left atrium; LAA = left atrial appendage; LL = low lateral; LS = left superior; PCS = proximal coronary sinus; PV = pulmonary vein; RA = right atrium.

the LA (600 ms, p = 0.4; 450 ms, p = 0.2) or RA (600 ms, p = 0.6; 450 ms, p = 0.5) immediately after MC.

**BIPOLAR VOLTAGE.** There was a significant reduction in LA volume (129 ± 40 ml to 111 ± 40 ml, p = 0.03) with no change in RA volume (71 ± 22 ml to 78 ± 21 ml, p = 0.2). The bipolar voltage of the LA increased immediately after MC (1.7 ± 0.6 mV to 2.5 ± 1.0 mV, p = 0.005). The increase in voltage was a global phenomenon without specific regional preference (group × region p = 0.9; Fig. 2). Although an increase in voltage was also observed within the RA, this did not reach statistical significance (1.8 ± 0.6 mV to 2.2 ± 0.7 mV, p = 0.09). There was no change in areas of electrical silence immediately after MC in the 7 patients who had demonstrated areas of electrical silence.

**CONDUCTION VELOCITY.** The CV in both atria improved after MC: in the LA from 1.3 ± 0.3 mm/ms to 1.7 ± 0.2 mm/ms (p = 0.006), and in the RA from 1.0 ± 0.1 mm/ms to 1.3 ± 0.3 mm/ms (p = 0.002). The improvement was not specific to a particular region within the atria (group × region p = 0.4 and p = 0.3, for the left and right atria, respectively) (Fig. 3).

The PWD decreased immediately after MC from 139.5 ± 19.5 ms to 135.5 ± 19.9 ms (p = 0.047).

The number of points demonstrating FS or DP did not change; in the LA, 29 ± 11% versus 29 ± 12% (p = 0.9), and in the RA, 45 ± 24% versus 37 ± 17% (p = 0.1). These points were distributed throughout the atria with clustering along the crista terminalis in the RA and anterior wall, pulmonary vein region, and roof in the LA.

**VULNERABILITY FOR AF.** Sustained AF was observed in 7 of 21 patients before MC, whereas it was present in only 4 of 21 after the procedure (p = 0.08).

**Late effects of stretch reversal.** There were 14 patients who consented to follow-up study (mean 6.6 ± 0.9 months).

**HEMODYNAMIC AND MECHANICAL CHANGES.** The MVA remained unchanged (p = 0.7 vs. post-MC) with a further decrease in LA volume (p = 0.07 vs. post-MC) and RA volume (p = 0.2 vs. post-MC) (Table 1). The

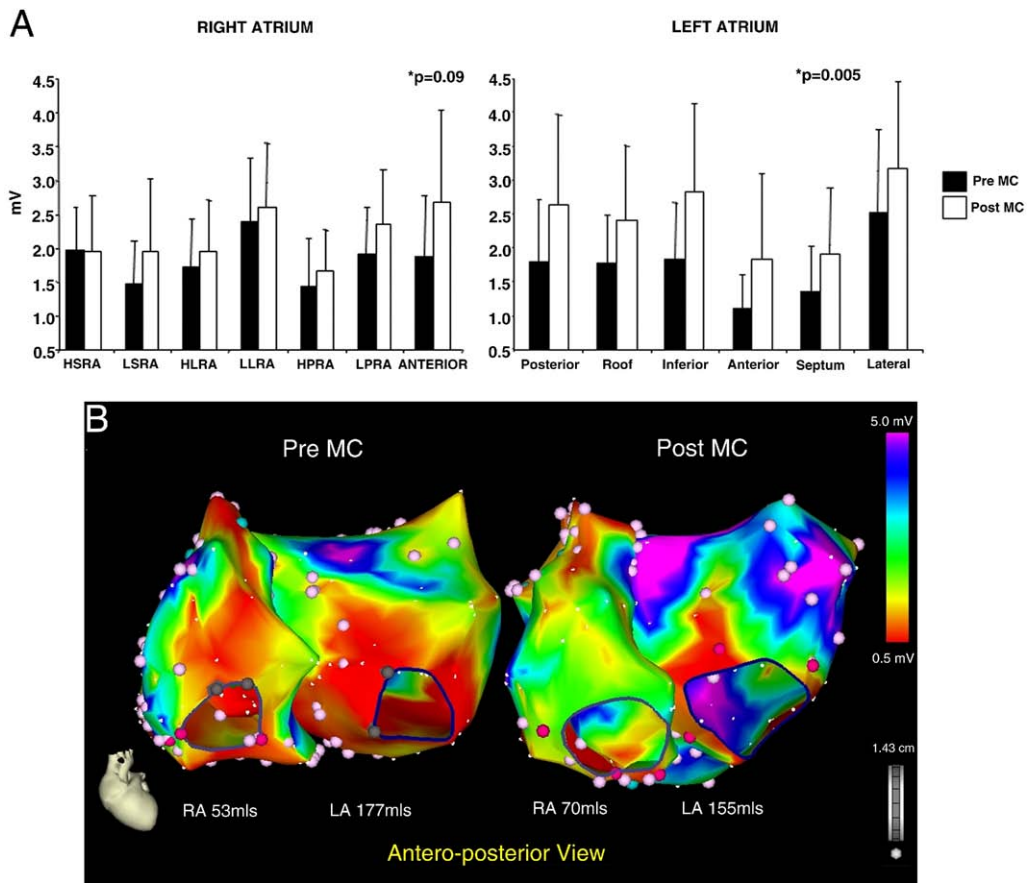


**Figure 2** **Regional Bipolar Voltage Acutely After Stretch Reversal**

**(A)** Regional differences in bipolar voltage before and after MC. **(B)** Voltage map of the LA and RA before and immediately after MC. *Mixed effects group main effect p value is shown for RA and LA. Abbreviations as in Figure 1.

pulmonary wedge was 14 ± 9 mm Hg, and pulmonary arterial pressures (28 ± 14 mm Hg to 23 ± 13 mm Hg, p = 0.9 vs. post-MC) were similar to the values immediately after MC.

**ATRIAL REFRACTORINESS.** At long-term follow up, the atrial ERP was significantly shortened compared with the baseline (600 ms, $p < 0.0001$; 450 ms, $p = 0.0001$). Figure 4 demonstrates the change in ERP over time at the various sites.

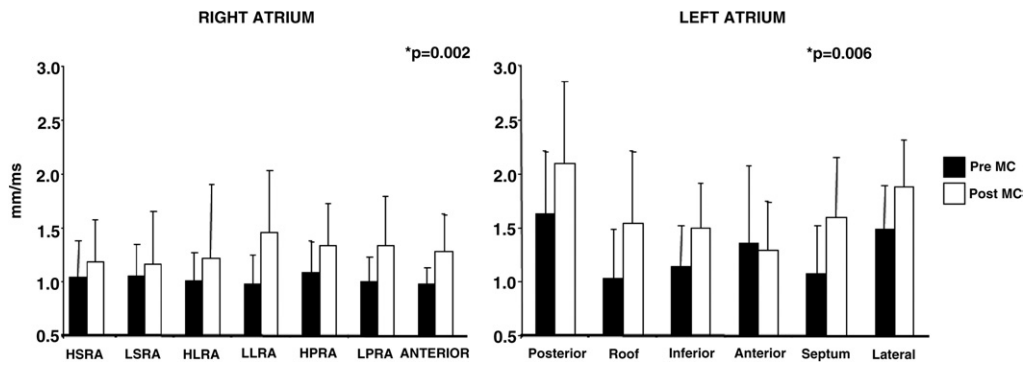


**Figure 3** **Regional Conduction Velocity Acutely After Stretch Reversal**

Regional differences in conduction velocity before and after MC. *Mixed effects group main effect p value is shown for RA and LA. Abbreviations as in Figure 1.

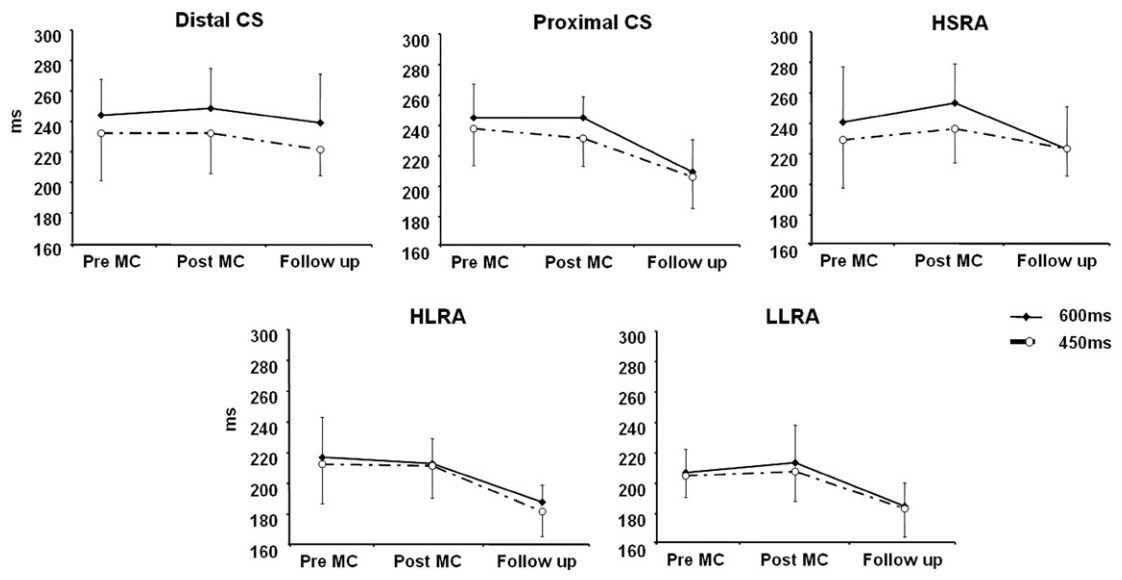


**Figure 4** Effective Refractory Period Late After Stretch Reversal

Effective refractory period at cycle lengths of 600 and 450 ms before and immediately after MC and ≥6-month follow-up. Mixed effects group main effect p value for 600 ms, $p < 0.0001$, and for 450 ms, $p = 0.0001$. Abbreviations as in Figure 1.

The reduction in refractoriness was not specific to any region within the RA (group × region $p = 0.7$ and $p = 0.8$ at 600 and 450 ms, respectively).

**BIPOLAR VOLTAGE.** At follow-up study there was a significant increase in the bipolar voltage in the RA from 1.8 ± 0.7 mV to 2.8 ± 0.6 mV ($p = 0.0002$), involving all regions

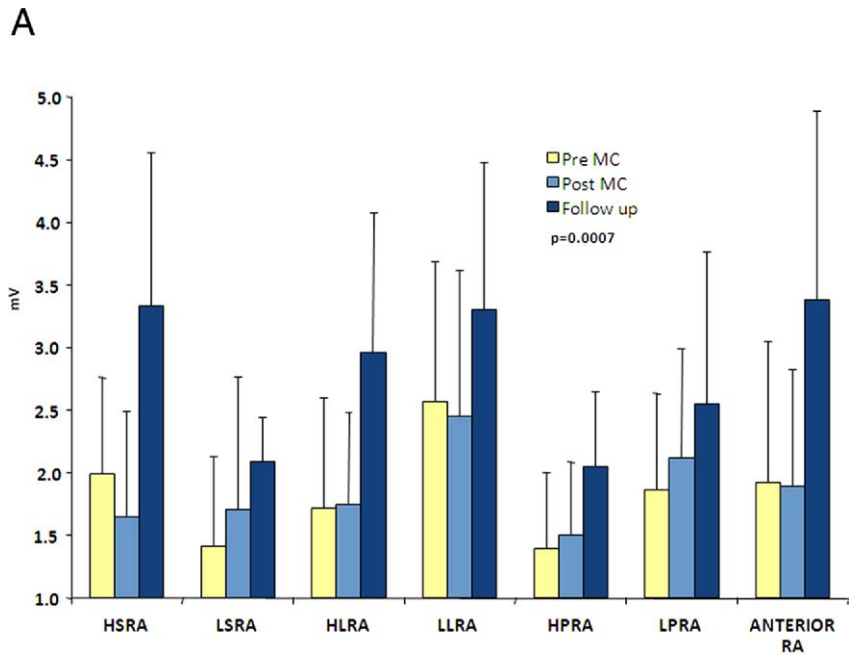


**Figure 5** Regional Bipolar Voltage Late After Stretch Reversal

**(A)** Regional voltage in the RA before and immediately after MC and ≥6-month follow-up.
Linear mixed effects model p value for the comparison of the 3 time points is shown. *Continued on next page.*

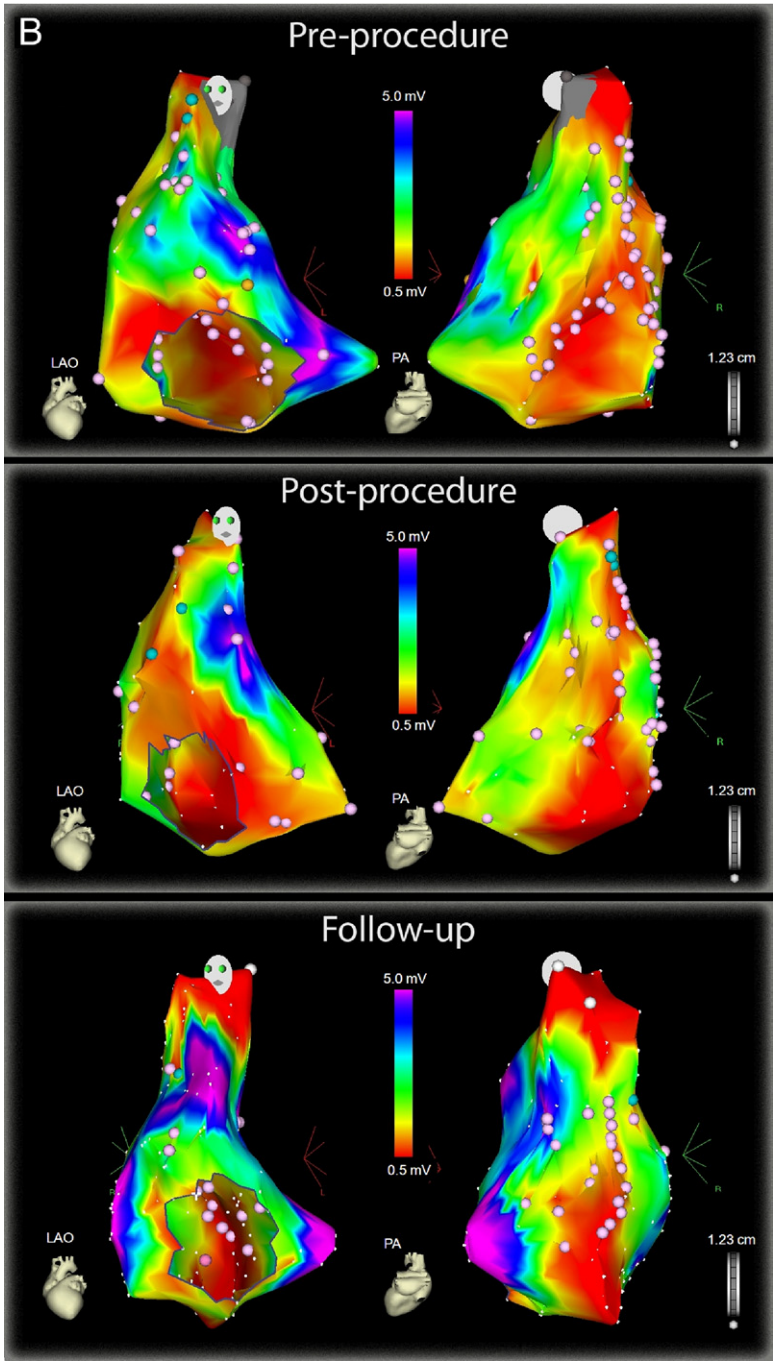


**Figure 5** Continued

**(B)** Voltage maps of the RA before (pre), immediately after (post), and ≥6 months (follow-up). LAO = left anterior oblique; PA = posteroanterior; other abbreviations as in Figure 1.

in the atria without being specific to a particular region (group × region p = 0.4) (Fig. 5).

**CONDUCTION VELOCITY.** The CV in RA improved from 1.0 ± 0.1 mm/ms to 1.3 ± 0.2 mm/ms (p = 0.006) (Fig. 6) associated with reduction in number of points demonstrating FS/DP from 45.4 ± 24.0% to 11.8 ± 6.5% (p = 0.002). The improvement in CV was not significantly greater in one region compared with the other (group × region p = 0.3).

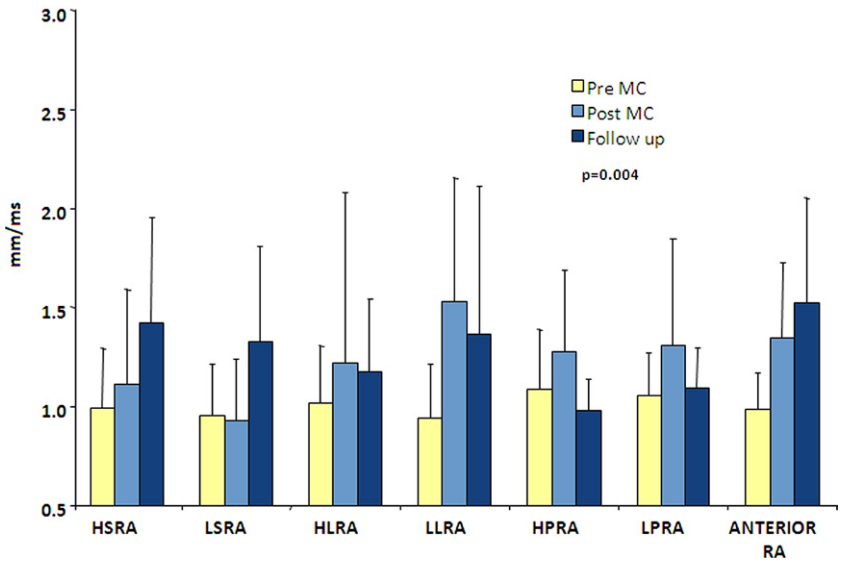


**Figure 6** Regional Conduction Velocity Late After Stretch Reversal

Regional conduction velocity in the RA before and immediately after MC and at ≥6-months follow-up. Linear mixed effects model p value for the comparison of the 3 time points is shown. Abbreviations as in Figures 1 and 4.

The PWD reduced further from 136.9 ± 22 ms immediately after MC to 113.2 ± 19.1 ms (p = 0.04).

VULNERABILITY FOR AF. Of the 14 patients undergoing repeat study, 5 patients had sustained AF before MC, and only 1 had AF at long-term follow-up (p = 0.1).

## Discussion

**Major findings.** This study presents new information on the reversal of atrial remodeling after therapy directed at the cause of the chronic stretch.

Acutely after reversal of chronic stretch, there was marked reduction in LA pressure and volume associated with improvement in bipolar voltage with increased CV in both atria and reduction in PWD. In contrast, atrial refractoriness remained unaltered. This resulted in a trend for reduced vulnerability for AF.

Late after reversal of chronic stretch, there was progressive improvement in bipolar voltage with increased CV and reduction in fractionated electrograms. In addition, there was a further dramatic reduction in PWD and a decrease in atrial refractoriness. Perhaps as a result of this reversal of atrial abnormalities that occurred due to stretch, fewer patients were observed to develop AF.

These findings suggest that the substrate predisposing to atrial arrhythmias due to chronic atrial stretch might be reversible with treatments directed at the stretch stimulus. Importantly, it demonstrates marked improvement in the structural and conduction abnormalities that are considered important elements of the AF substrate.

**Stretch and AF.** Studies have implicated stretch and the resultant mechano-electrical feed back in the increased propensity for AF (13). Experimental models have consistently shown that the most prominent abnormality observed with chronic atrial stretch was an increase in fibrosis associated with a reduction in CV, which confers an increased vulnerability to AF (3–5). Indeed, this increased propensity for AF in these models of heart failure, mitral regurgitation, or hypertension occurred despite an increase in the atrial refractoriness. Similarly, clinical conditions associated with chronic stretch—due to atrial septal defect or heart failure—that predispose to the development of AF have also demonstrated conduction abnormalities with prolongation of the atrial refractoriness and yet with greater propensity for AF (6,9,10). These populations demonstrated significant atrial enlargement and regions of low voltage associated with conduction abnormalities characterized by prolongation of the PWD, conduction time, and greater number and duration of DP.

Taken together, these studies have underscored the importance of structural changes and resultant conduction abnormalities rather than the changes in refractoriness in the substrate for AF in conditions that cause chronic atrial stretch.

**Reversal of stretch.** A few studies have evaluated the effect of reversing stretch. Sparks et al. (2) studied the reversal of electrical remodeling with correction of atrial stretch induced by 3 months of asynchronous ventricular pacing. Eighteen patients were paced in VVI mode, and 12 patients were paced in DDD mode for 3 months. Atrial ERP, corrected sinus node recovery time, and PWD increased significantly at the end of 3 months associated with dilation of atria in the group assigned to VVI pacing. Interestingly, all of the aforementioned measured electrophysiological changes reversed on establishing

atrioventricular synchrony with dual-chamber pacing. Although the aforementioned study demonstrated reversal after 3 weeks of stretch, Morton et al. (10) observed persistence of conduction abnormality along the crista terminalis at repeat electrophysiological studies after closure of the atrial septal defect, suggesting that changes in conduction would not reverse by treating the underlying condition. However, this study was limited by the late evaluation of only 4 of 12 patients.

In patients with MS and AF, Fan et al. (14) described the electrophysiological changes in the RA after MC. Repeat study at 3 months after MC demonstrated an increase in the atrial ERP to become comparable to the sinus rhythm group. Soylu et al. (15) also reported similar observations in 25 patients in sinus rhythm, after MC. They measured ERP at 3 RA sites, but conduction was evaluated by surrogate markers. Immediately after MC, they demonstrated an increase in atrial ERP with improvement in the intra-atrial and inter-atrial conduction time. Neither of these latter studies presented any data on electroanatomic evaluation, which provides information on CV and voltage, both important elements of the AF substrate.

The current study extends these observations by demonstrating in a population in sinus rhythm, without the potentially confounding effects of reverse-remodeling due to termination of AF, reversal of the changes due to chronic atrial stretch. Importantly, it demonstrates marked reversal of the structural and conduction abnormalities with the consequence of reduced fractionation and AF. These data suggest that the substrate predisposing to AF can be reversed by treating the underlying condition.

**Mechanisms of atrial reverse remodeling.** This study has demonstrated marked improvement in the structural changes associated with chronic atrial stretch by therapy directed at the stretch stimulus. It is feasible, at least in the acute setting, that this observation might be consequent to reduction in atrial volume in the presence of constant atrial mass. Thus, the increase in voltage and improvement in conduction might in part be attributable to a mechanical diminution of the atrial size or a reduction in the pressures within the chamber.

There is emerging data to suggest that therapy directed at structural change might reduce the incidence of AF. The renin-angiotensin system promotes cardiac fibrosis. Not surprisingly, both animal models and multicenter trials have demonstrated reduced incidence of AF with angiotensin-converting enzyme inhibitors (16,17).

At the molecular level, stretch activated ion channels have been identified as playing a crucial role in mechano-electrical feedback, which promotes AF (18,19). However, these have been demonstrated to be reversible; perhaps one of the mechanisms for the observed reverse-remodeling (20). Furthermore, connexins are known to be important determinants of conduction and might be altered in models of AF (21). In the present study we observed an acute and then progressive increase in the CV. This might relate to reverse-remodeling of connexins. The absence of change in the number of complex signals immediately after stretch reversal but improvement at follow-up suggests that some elements of the reverse-remodeling occurs over a longer time course. Although it is uncertain whether this coincides with the time-course of reverse-remodeling of connexins, it is likely that some of this improvement is due to such remodeling.

**Clinical implications.** Structural remodeling and the associated conduction abnormalities are increasingly recognized as important precursors for the substrate predisposing to AF. Thus, reversal of these changes could potentially have important implications for the prevention of AF. The present study demonstrates such marked reversal by treatment directed at reversing chronic atrial stretch. It lends weight to a strategy of treatment of the predisposing condition to modify the AF substrate to prevent arrhythmogenesis.

**Study limitations.** Although this study has demonstrated marked reversal of the AF substrate, it was only possible to evaluate the late findings in the RA. Whether similar reverse remodeling would be observed in the LA was not evaluated (but suggested by the findings in immediate reversal). Finally, it is well-recognized that the development of clinical AF is complex and depends not only on substrate but also on other factors such as triggers and initiators. The effect of reversal of stretch on these other factors was not addressed by this study.

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**Key Words:** atrial fibrillation ■ rheumatic mitral stenosis ■ reverse remodeling ■ substrate.