Reversal of Atrial Mechanical Dysfunction After Cardioversion of Atrial Fibrillation

Implications for the Mechanisms of Tachycardia-Mediated Atrial Cardiomyopathy

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**Background**—Atrial mechanical “stunning” develops after cardioversion of atrial fibrillation (AF) and is implicated in the genesis of thromboembolic complications. However, the mechanisms responsible for this phenomenon are poorly understood. Whether atrial mechanical dysfunction caused by AF can be reversed by pacing at increased rates or by pharmacological agents is unknown.

**Methods and Results**—Twenty-six patients with AF undergoing cardioversion were dichotomized prospectively on the basis of the duration of arrhythmia as short-duration (1 to 6 months) or long-duration (≥3 years) AF. Left atrial appendage emptying velocities (LAAEVs) and spontaneous echocardiographic contrast (LASEC) were assessed by transesophageal echocardiography during AF, after reversion to sinus rhythm, during atrial pacing at cycle lengths of 750 to 250 ms, after a postpacing pause, and with isoproterenol. In patients with short-duration AF, LAAEV decreased (42.0±2.7 to 18.5±2.0 cm/s; \(P<0.0001\)) and LASEC increased (0.9±0.3 to 2.2±0.3; \(P<0.01\)) with termination of AF; pacing increased LAAEV (48.3±4.1 cm/s; \(P<0.0001\)) and decreased LASEC (1.5±0.3; \(P<0.01\)); and isoproterenol increased LAAEV (73.3±7.8 cm/s; \(P<0.0001\)) and decreased LASEC (0.3±0.2; \(P<0.01\)) and the postspacing pause increased LAAEV (68.3±3.8 cm/s; \(P<0.0001\)). In contrast, patients with long-duration AF demonstrated a significantly attenuated response of atrial mechanical function at each time point. With termination of AF, LAAEV decreased (19.1±2.6 to 8.2±1.0 cm/s; \(P=0.003\)) and LASEC increased (2.0±0.2 to 3.3±0.2; \(P<0.01\)); pacing increased LAAEV (18.4±2.7 cm/s; \(P<0.0001\)) and decreased LASEC (2.3±0.2; \(P<0.01\)); isoproterenol increased LAAEV (26.1±3.9 cm/s; \(P=0.2\) to equivalent atrial rate) and decreased LASEC (1.0±0.3; \(P<0.01\)); and the postspacing pause increased LAAEV (27.2±2.4 cm/s; \(P=0.007\)).

**Conclusions**—Atrial pacing at increased rates and isoproterenol can reverse atrial mechanical stunning associated with short-duration AF. In contrast, long-duration AF is associated with an attenuated response to these maneuvers. These findings suggest a functional contractile apparatus in the mechanically remodeled atrium caused by AF; however, with longer durations of AF, additional factors may determine atrial mechanical function. (Circulation. 2003;108:1976-1984.)

**Key Words:** arrhythmia ■ atrium ■ cardioversion ■ echocardiography ■ remodeling

Atrial fibrillation (AF) is associated with progressive atrial mechanical remodeling, which is implicated in the development of thromboembolic stroke.\(^1\)\(^2\) Cardioversion of AF results in further deterioration in atrial mechanical function, called atrial mechanical “stunning,” a process considered pivotal in the heightened thromboembolic risk after cardioversion.\(^3\)

Why atrial mechanical function deteriorates on termination of rapid atrial rates is not understood. An inotropic effect of rate (positive force-frequency relationship) has been demonstrated in isolated ventricular muscle fiber preparations, with reversal of this relationship in ventricular muscle fibers isolated from patients with heart failure.\(^4\) In isolated atrial myocardial fibers from patients with chronic AF, Schotten et al\(^5\) have demonstrated reversal of atrial myocardial fiber dysfunction with isoproterenol and calcium, suggesting that at the myocardial fiber level, atrial mechanical remodeling is functional. We have previously extended these observations to the whole atrium in a clinical study of patients with atrial mechanical stunning after the cardioversion of chronic atrial flutter by radiofrequency ablation.\(^6\) After the development of atrial mechanical stunning in these patients, atrial mechanical dysfunction could be reversed acutely with increased stimulation rates, calcium, and isoproterenol, demonstrating a positive force-frequency relationship.\(^6\)

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However, chronic AF is likely to be associated with structural remodeling and fibrosis that would be expected to contribute to atrial mechanical dysfunction.\textsuperscript{7,8} Whether atrial mechanical dysfunction because of AF can be reversed is unknown.

In this prospective clinical study, we used transesophageal echocardiography to determine the effect of atrial stimulation rates and isoproterenol on the mechanical performance of the atria in humans with atrial mechanical stunning after the cardioversion of AF. We studied patients with AF either for 1 to 6 months or persisting for \(\geq 3\) years to evaluate the contribution of the chronicity of the arrhythmia to the atrial mechanical response to these maneuvers.

Methods

Study Population

The study comprised 26 patients with AF undergoing elective cardioversion or cardioversion at the time of electrophysiological study. AF was defined by its characteristic surface ECG appearance and was confirmed at the time of cardioversion by the presence of an irregular intracardiac electrogram pattern. The duration of AF was defined from the time of initial ECG diagnosis to the time of cardioversion. All patients had at least 2 electrocardiograms in this interval demonstrating AF with no documentation of sinus rhythm (SR). Patients were dichotomized on the basis of the duration of AF, defined as (1) short-duration AF (n=11): 1 to 6 months, and (2) long-duration AF (n=15): \(\geq 3\) years.

All patients gave written informed consent to the study, which was approved by the Clinical Research Ethics Committee of the Royal Melbourne Hospital.

Patient Preparation

All antiarrhythmic drugs with the exception of amiodarone (n=7) were ceased \(\geq 5\) half-lives before study. In all cases, the study was performed under general anesthesia to facilitate the performance of continuous transesophageal echocardiography without patient discomfort. A standardized general anesthetic with endotracheal intubation and mechanical ventilation was administered with propofol, with documentation of return to baseline of the coronary sinus catheter. LAAEV and LASEC grades were assessed during (1) AF before cardioversion, (2) SR immediately after cardioversion of AF, and (3) atrial pacing cycle lengths of 750, 700, 600, 500, 400, 300, and 250 ms.

To control for potential drift in atrial mechanical function, LAAEV was also determined at the completion of the pacing protocol and compared with baseline. During the pacing protocol, measurements of LAAEV were performed 10 seconds after the commencement of pacing at each rate and in SR at least 30 seconds after the cessation of pacing to avoid recording transitional velocities.

Postpacing Pause

The effect of the postpacing pause on LAAEV was determined after pacing at 250 ms for a 2-minute period. The LAAEV of the first postpacing pause beat in each patient was determined and compared with LAAEV in SR.

Pharmacological Intervention

In 11 patients in each group, the effect of isoproterenol on atrial mechanical function was determined at the completion of the pacing protocol in SR. Isoproterenol was commenced at a rate of 2 \(\mu\)g/min for 10 minutes and titrated (maximum of 4 \(\mu\)g/min) to achieve a sinus cycle length of 750 to 700 ms. LAAEV was recorded during isoproterenol infusion at atrial cycle lengths of 750 ms and with concurrent atrial pacing at 700, 600, 500, 400, 300, and 250 ms. LAAEV was assessed at an atrial cycle length of 600 ms.

In the initial 6 patients with long-duration AF, the effect of isoproterenol was also measured during AF before cardioversion. Isoproterenol was commenced at a rate of 2 \(\mu\)g/min for 10 minutes and titrated (maximum of 4 \(\mu\)g/min) to achieve a maximum ventricular cycle length of 750 to 700 ms. LAAEV and LASEC were determined before and after isoproterenol infusion. In these patients, cardioversion was performed \(\geq 30\) minutes after the cessation of isoproterenol, with documentation of return to baseline of the LAAEV.

Statistical Analysis

All variables are reported as mean±SEM. Sequential data measurements were analyzed by repeated-measures ANOVA, followed by the Newman-Keuls test for multiple comparisons. Comparison between groups was performed with either Student’s t test or the Wilcoxon rank-sum test. Statistical significance was established at a value of \(P<0.05\). The study was designed prospectively, requiring 11 patients in each group to demonstrate a 10.0±8.3-cm/s increase in peak LAAEV achieved through pacing with 80% power.\textsuperscript{9}

Results

There was a clear difference in the duration of AF between the 2 groups: 3.2±0.5 versus 57.7±8.7 months (\(P<0.0001\)). There were no significant differences between the groups in baseline characteristics; the groups were matched for age,
atrial size, ventricular size and function, and use of amiodarone. Eight patients with long-duration AF and 5 with short-duration AF had structural heart disease (P=NS).

**Atrial Mechanical Function on Termination of AF**

In all cases, cardioversion to SR was achieved. In patients with short-duration AF, LAAEV decreased from 42.0±2.7 to 18.5±2.0 cm/s (56% decrease) after cardioversion to SR (P<0.0001; Figure 1). In patients with long-duration AF, LAAEV decreased from 19.1±2.6 to 8.2±1.0 cm/s (57% decrease) with cardioversion to SR (P=0.003). Neither group showed a change in the baseline LAAEV or sinus cycle length during the pacing protocol.

No patient had atrial thrombus before cardioversion. In patients with short-duration AF, LASEC increased from 0.9±0.3 to 2.2±0.3 (144% increase) after cardioversion (P<0.01; Figure 2). In patients with long-duration AF, LASEC increased from 2.0±0.2 to 3.3±0.2 (65% increase) after cardioversion (P<0.01). No patient developed a thrombus after reversion to SR.

LAAEV was significantly lower in patients with long-duration than short-duration AF, both during AF (P=0.0001) and after cardioversion to SR (P=0.0006; Figure 1). There was no significant difference in the sinus cycle length between the 2 groups of patients (P=NS). LASEC was significantly greater in patients with long-duration than short-duration AF, both during AF (P<0.01) and after cardioversion to SR (P<0.01; Figure 2).

No relationship was observed between LAAEV and the method or energy used for cardioversion.

**Effect of Pacing Rate on Atrial Mechanical Function**

An increase in the atrial rate of stimulation achieved through pacing resulted in a significant increase in LAAEV in the stunned left atrium. In patients cardioverted from short-duration AF, LAAEV improved from 18.5±2.0 to a peak of 48.3±4.1 cm/s (161% increase) at an atrial cycle length of 500 ms (P<0.0001; Figures 3 and 4). In patients cardioverted from long-duration AF, LAAEV improved from 8.2±1.0 to a peak of 18.4±2.7 cm/s (124% increase) at an atrial cycle length of 600 ms (P<0.0001; Figures 5 and 6).
In patients cardioverted from short-duration AF, there was a significant decrease in LASEC with pacing from 2.3±0.4 to 1.5±0.3 (35% decrease; P<0.01; Figure 2). In patients cardioverted from long-duration AF, there was a significant decrease in LASEC with pacing from 3.3±0.2 to 2.3±0.2 (30% decrease; P<0.01; Figure 2).

LAAEv was significantly lower in patients cardioverted from long-duration than those cardioverted from short-duration AF at all atrial cycle lengths (P<0.0001). LASEC grade with pacing was significantly greater in patients cardioverted from long-duration than short-duration AF (P<0.01).

Effect of Isoproterenol on Atrial Mechanical Function During AF
The administration of isoproterenol during AF resulted in significant improvement of atrial mechanical function. LAAEv increased from 15.3±2.6 to 32.5±4.3 cm/s (P=0.002; Figure 7), and LASEC decreased from 3.0±0.4 to 0.8±0.3 (P=0.02; Figure 7), with complete elimination of LASEC in 2 patients.

Effect of Isoproterenol on Atrial Mechanical Function After Cardioversion
In patients cardioverted from short-duration AF, isoproterenol resulted in a significant increase in LAAEv, from 18.5±2.0 to a peak of 73.3±7.8 cm/s (296% increase) at an atrial cycle length of 500 ms (P<0.0001; Figure 3). Compared with the equivalent atrial cycle length achieved by pacing alone, isoproterenol used in patients cardioverted from short-duration AF resulted in a significantly greater improvement in LAAEv at each atrial cycle length (P<0.05 at a cycle length of 750 ms and P<0.01 at all other cycle lengths; Figure 3).

In patients cardioverted from long-duration AF, isoproterenol resulted in a significant increase in LAAEv from 8.2±1.0 to a peak of 26.1±3.9 cm/s (218% increase) at an atrial cycle length of 600 ms (P<0.0001; Figure 5). However, compared with the equivalent atrial cycle lengths achieved through pacing alone, isoproterenol was not associated with a significant increase in LAAEv in patients with long-duration AF.

In patients cardioverted from short-duration AF, isoproterenol was associated with a decrease in LASEC from 2.3±0.4
to $0.3 \pm 0.2$ (87% decrease; $P<0.01$; Figure 2). In patients cardioverted from long-duration AF, there was a significant decrease in LASEC with isoproterenol from $3.3 \pm 0.2$ to $1.0 \pm 0.3$ (70% decrease; $P<0.01$; Figure 2).

LAAEV was significantly lower in patients cardioverted from long-duration than those cardioverted from short-duration AF at all atrial cycle lengths with isoproterenol ($P<0.0001$). LASEC was significantly greater in patients cardioverted from long-duration than those cardioverted from short-duration AF with isoproterenol ($P<0.05$).

Effect of the Postpacing Pause on Atrial Mechanical Function

LAAEV for the first sinus beat after the postpacing pause increased significantly compared with that at baseline immediately after cardioversion. LAAEV increased from $18.5 \pm 2.0$ to $68.3 \pm 3.8$ cm/s (269% increase; $P<0.0001$) in patients cardioverted from short-duration AF (Figure 8A) and from $8.2 \pm 1.0$ to $27.2 \pm 2.4$ cm/s (232% increase; $P=0.007$) in patients cardioverted from long-duration AF (Figure 8B). The LAAEV observed with the first postpacing pause beat was significantly greater than that observed during AF in patients cardioverted from short-duration ($P=0.0001$) and those cardioverted from long-duration AF ($P=0.006$). The LAAEV of the first postpacing beat was significantly greater in patients cardioverted from short-duration than those cardioverted from long-duration AF ($P<0.0001$). The increase in the LAAEV observed with the first postpacing pause beat gradually diminished over the ensuing 5 to 10 beats to that of the mechanically stunned atrium in both groups (Figure 8).

Discussion

New Findings

This study presents new information regarding atrial mechanical function in the remodeled atrium caused by AF. First, the present study demonstrates a positive force-frequency relationship in the stunned, mechanically remodeled atrium caused by AF of short duration ($3.2 \pm 0.5$ months) in humans. We have demonstrated that pacing the atrium at rates higher than SR results in an improvement in atrial mechanical function and reversal of mechanical stunning. In addition,
pharmacological modulation of this force-frequency relationship has been demonstrated. Isoproterenol led to a marked increase in LAAEV and a significant reduction in LASEC. Second, in patients with AF of short duration, despite marked impairment of atrial mechanical function after cardioversion to SR, immediate and significant improvement in mechanical function could also be demonstrated by the effect of the first postpacing pause beat, providing further evidence for the presence of an intact contractile apparatus. Third, in contrast to the observations in patients with short-duration AF, patients with AF of long duration (57.7 ± 8.7 months) demonstrated significantly greater impairment of atrial mechanical function both during AF and after the development of atrial mechanical stunning in SR. These patients demonstrated a significantly attenuated response to an increase in the atrial rate and the postpacing pause and a lack of response to isoproterenol over the effect seen with rate alone.

Although these findings confirm the existence of a functional contractile apparatus in the mechanically remodeled atrium caused by AF, it suggests that there may be additional factors that determine atrial mechanical function with longer durations of AF.

Figure 7. Effect of isoproterenol during AF on LAAEV and LASEC.
Atrial Mechanical Function During AF and After Cardioversion

An inotropic effect of increasing frequency of stimulation has been described in normal ventricular myocardial fibers and has been called the “Bowditch-Treppe effect.” This phenomenon achieves a peak inotropic effect, with further increases in frequency resulting in a plateau or decrease in the force of contraction. Intracellular calcium homeostasis, in particular the sarcoplasmic storage and release of calcium, is implicated in frequency-dependent force generation. The decreased diastolic interval available for calcium storage with increasing frequencies is implicated in the negative effect observed after peak contraction. Although these mechanisms have been well studied in ventricular mechanical dysfunction caused by heart failure, much less information is available on the mechanisms leading to atrial mechanical dysfunction caused by atrial arrhythmias. The importance of heart rate to atrial mechanical function has been suggested in some clinical studies. An observational report of LAAEV in patients with normal ventricular function without atrial arrhythmias found a positive relationship with heart rate. Furthermore, after the cardioversion of AF, worsening LASEC grade was accompanied by a variable degree of bradycardia, impairment of atrial contraction, or both.

In isolated atrial myocardial fibers from patients with chronic AF, Schotten et al demonstrated significant reversal of myocardial fiber contractility with isoproterenol and calcium. Further evidence for the functional nature of the atrial mechanical dysfunction during AF is also available from small clinical studies. Kamlesh et al demonstrated a modest improvement in LAAEV in patients in AF and an improvement in LASEC in 2 of 5 with the use of dobutamine. Stefanadis et al demonstrated similar findings determining left atrial pump function using left atrial pressure-area relations during AF with the use of dobutamine. We have previously demonstrated, after the cardioversion of chronic atrial flutter in humans, significant improvement and reversal of atrial mechanical stunning with increasing atrial pacing rates, isoproterenol, and calcium.

In the present study, in patients with AF, there was a significant increase in LAAEV and reduction in LASEC during AF with the use of isoproterenol. These findings are similar to previous observations with the use of dobutamine during AF. After the cardioversion of chronic AF of short duration, there was an increase in LAAEV and a reduction in LASEC. The present study suggests that the atrial mechanical dysfunction during AF is reversible with drug therapy and may be related to the increased heart rate and increased atrial electrical activity.
duration (≤6 months), the mechanically stunned atrium demonstrates a positive force-frequency relationship with a stepwise increase in LAAEV with increasing atrial rates and significant reduction in LASEC. Furthermore, there is significant postpause potentiation of LAAEV. Isoproterenol results in further improvement in atrial mechanical function, with almost complete resolution of LASEC. These findings are similar to that observed after the cardioversion of chronic atrial flutter.

**Atrial Mechanical Function in Short- Versus Long-Duration AF**

Patients with long-duration AF (≥3 years) demonstrated strikingly different physiology than those with short-duration AF. In these patients, atrial mechanical function during AF was significantly more impaired, and after cardioversion a greater degree of atrial mechanical dysfunction was demonstrated. There was an attenuated response to an increase in the atrial rate after cardioversion. Although these patients demonstrated improvement in LAAEV over that seen in stunned left atrium in SR, the absolute improvement was significantly less than in patients with short-duration AF. Furthermore, the postpacing pause potentiation of atrial mechanical function was markedly attenuated, and no significant response to isoproterenol over the effect seen with atrial rate could be demonstrated.

No previous study has examined the effects of stimulation rates and β-adrenergic stimulation on atrial mechanical function after cardioversion of AF of 2 distinct durations. Manning et al.13 studied atrial mechanical function in patients with 0.3 to 36 weeks of AF and found that atrial mechanical function was greater immediately, at 24 hours, and at 1 week after cardioversion in patients with brief (≤2 weeks) compared with prolonged (>6 weeks) AF. However, the effect of longer durations of AF on atrial mechanical function is poorly characterized. Atrial myocardial fibers isolated from patients having mitral valve surgery with AF of ≥3 months have been shown to possess a functional contractile apparatus.5 In the present study, although patients with long-duration AF demonstrated a percentage improvement in atrial mechanical function similar to that of patients with short-duration AF, the absolute improvement in atrial mechanical function was markedly reduced.

**Implications for the Mechanisms of Atrial Mechanical Remodeling and Stunning**

Two previous studies have suggested a functional mechanism for atrial mechanical remodeling and stunning, with demonstrable reversibility of atrial mechanical dysfunction that is caused by chronic AF and atrial flutter.5,6 Findings from these studies suggest a central role of calcium in atrial mechanical dysfunction associated with atrial arrhythmias with maneuvers increasing intracellular calcium observed to reverse atrial mechanical dysfunction. Others have reported altered cellular calcium handling16 and intracellular calcium overload associated with atrial arrhythmias,17 perhaps implicating a supranormal intracellular calcium level for the observed effects. However, evidence suggests that homeostatic mechanisms act to reduce the accumulating intracellular calcium by a decrease of the L-type calcium current.5,18 Schotten et al.19 showed an upregulation of the sodium-calcium exchanger, which removes calcium from the cell. These findings suggest that the contractile apparatus is intact in atrial arrhythmias and that the cell adapts to rapid atrial arrhythmias by decreasing the inward calcium channels and increasing the extrusion of calcium from the cell. We speculate that atrial mechanical dysfunction associated with atrial arrhythmias relates to relative or actual intracellular calcium depletion.

Although a functional and reversible mechanism is present with short durations of AF and may persist at the myocardial fiber level even with AF of longer durations,2 the findings of the present study appear to implicate other factors in the mechanical dysfunction of the intact atrium associated with longer durations of AF. One potential mechanism for the observed atrial mechanical dysfunction in response to atrial arrhythmias is that of structural abnormalities, with the disruption of the contractile apparatus itself. Structural remodeling and fibrosis of the atrium in response to atrial arrhythmias have been demonstrated in the experimental and clinical settings.5,8 This process of atrial structural remodeling follows a progressive course commensurate with the duration of the atrial arrhythmia. It might be expected that patients with long-duration AF would have a significantly greater degree of atrial structural remodeling. We posit that such structural abnormalities within the atrium may account for the attenuated response to pacing and isoproterenol observed in the present study in patients with long-duration AF.

**Clinical Implications**

Atrial mechanical remodeling and stunning have been implicated as important pathogenetic factors for cardioembolic stroke associated with AF. The demonstration that heart rate may be important for atrial mechanical function after cardioversion to SR may have implications for the choice of antiarrhythmic drugs used. In addition, transient pacing at higher rates may play a role after cardioversion of AF to reduce thromboembolic complications, especially in patients immediately post–device implantation who are unable to be anticoagulated.

**Limitations**

The duration of AF in this study was determined by ECG documentation and as such may have underestimated the actual AF duration in both groups. Although we have demonstrated the reversal of atrial mechanical stunning by increased pacing rates and pharmacological modulation with isoproterenol, these maneuvers were performed immediately after cardioversion. Whether the improvement in atrial mechanical function could be sustained with continued stimulation and the effects of pacing and isoproterenol on the time course of recovery of atrial mechanical function are important issues that have not been addressed in this study.

**Conclusions**

Left atrial mechanical stunning after the cardioversion of AF of short duration can be modulated by heart rate and reversed by isoproterenol, suggesting the presence of a functional
contractile apparatus. However, with longer durations of AF, there is more substantial atrial mechanical dysfunction and an attenuated response to increased stimulation rates and isoproterenol. These findings may have important implications for the management of patients with AF of various durations.

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