Reversal of Atrial Mechanical Stunning After Cardioversion of Atrial Arrhythmias

Implications for the Mechanisms of Tachycardia-Mediated Atrial Cardiomyopathy

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Background—Atrial mechanical stunning develops on termination of chronic atrial arrhythmias and is implicated in the genesis of thromboembolic complications after cardioversion. The mechanisms responsible for atrial mechanical stunning are unknown. The effects of atrial rate, isoproterenol, and calcium on atrial mechanical function in patients with atrial stunning have not been evaluated, and it is not known if atrial stunning can be reversed.

Methods and Results—Thirty-five patients with chronic atrial flutter (AFL) undergoing radiofrequency ablation were studied. Fifteen patients in sinus rhythm undergoing ablation for paroxysmal AFL were studied as control for effects of the procedure. Left atrial appendage emptying velocities (LAAEVs) and spontaneous echocardiographic contrast (LASEC) were assessed by transesophageal echocardiography during AFL, after reversion to sinus rhythm, during atrial pacing at cycle lengths of 750 to 250 ms, after a postpacing pause, and with isoproterenol or calcium. With termination of AFL, LAAEV decreased from 59.0±3.7 cm/s to 18.8±1.4 cm/s (P<0.0001) and LASEC grade increased from 0.9±0.1 to 2.2±0.2 (P<0.0001). Pacing increased LAAEV to a maximum of 38.4±3.2 cm/s (P<0.0001) and reduced LASEC grade to 1.9±0.2 (P=0.005). Isoproterenol and calcium reversed atrial mechanical stunning with LAAEV increasing to 89.3±12.6 cm/s (P=0.0007) and 50.2±10.5 cm/s (P=0.005), respectively, and LASEC grade decreasing to 0.2±0.1 (P=0.001) and 1.4±0.2 (P=0.01), respectively. The postpacing pause increased LAAEV to 69.3±3.7 cm/s (P<0.0001). No change in LAAEV was observed in the paroxysmal AFL group.

Conclusion—Atrial mechanical stunning can be reversed by pacing at increased rates and through the administration of isoproterenol or calcium. These findings suggest a functional contractile apparatus in the mechanically remodeled atrium as a result of chronic atrial flutter. (Circulation. 2002;106:1806-1813.)

Key Words: atrial flutter | cardioversion | echocardiography | remodeling

The cardioversion of chronic atrial fibrillation (AF) and atrial flutter (AFL) to sinus rhythm (SR) is associated with left atrial mechanical dysfunction.1–6 After cardioversion, transesophageal echocardiographic (TEE) studies have demonstrated the development of left atrial spontaneous echocardiographic contrast (LASEC) and thrombus. This process has been termed atrial mechanical stunning and is implicated in the development of thromboembolic stroke after cardioversion. The weight of accumulated evidence suggests that atrial mechanical remodeling relates to properties of the preceding arrhythmia rather than the mode of cardioversion, and as such, can be considered a form of tachycardia-mediated atrial cardiomyopathy.7

Why atrial mechanical function deteriorates after termination of rapid atrial rates is unknown. In isolated cardiac muscle preparations, a positive force-frequency relationship has been described (inotropic effect of rate), whereas in failing ventricular myocardium, this relationship is reversed.8 Frequency-dependent force generation appears to be mediated through intracellular calcium balance.9–10 Furthermore, with the use of isolated atrial myocardial fibers from patients with AF, Schotten and Allessie11 have demonstrated a concentration-dependent increase in the force of contraction with isoproterenol or calcium and normalization of myocardial fiber contraction with calcium. Whether a force-frequency relationship exists in the mechanically stunned...
intact human atrium and whether stimulation rates, β-adrenergic stimulation, and changes in extracellular calcium have an effect on atrial mechanical function are unknown. In this prospective clinical study, we used TEE to determine the effect of atrial rate, pacing site, isoproterenol, and calcium on the mechanical performance of the atrium in humans after the development of atrial mechanical stunning. The study was performed in patients with chronic AFL in whom cardioversion was achieved by radiofrequency ablation (RFA).4

### Methods

#### Chronic AFL Group

The study comprised 35 patients (31 men, 61.4±1.7 years of age) undergoing RFA of chronic AFL (Table 1). Structural heart disease other than atrial dilatation was present in 11 patients. All patients gave written informed consent to the study, which was approved by the Clinical Research Ethics Committee of the Royal Melbourne Hospital.

#### Paroxysmal AFL Group

To control for potential procedural effects on atrial mechanical function, 15 patients (13 men, 66.6±1.9 years of age) with paroxysmal AFL were evaluated. Paroxysmal AFL was defined by ≥3 previous episodes of typical AFL. These patients were documented to be in SR and described no symptoms attributable to AFL for ≥1 month before RFA.

#### Patient Preparation

All antiarrhythmic drugs, except amiodarone, were ceased ≥5 half-lives before RFA. In all cases, RFA was performed under general anesthesia to facilitate the performance of serial TEE. A standardized general anesthetic with endotracheal intubation and mechanical ventilation was administered with propofol induction followed by maintenance with the volatile agent isoflurane and the muscle relaxant atracurium.

#### Echocardiographic Analysis

TEE was performed with the use of a 4- to 7-MHz phased array omniplane probe connected to a Hewlett-Packard 5500 ultrasound system. Images were recorded on 0.5-inch super VHS tape and analyzed offline.

Left atrial appendage emptying velocities (LAAEVs) were assessed with the use of pulsed-wave Doppler by placing the sample volume 1 cm into the mouth of the left atrial appendage.5 The left atrial appendage was scanned in planes from 0 to 180° to establish the angle at which the maximal LAAEV could be obtained, and the resultant angle used for all subsequent analyses. All recordings were performed during apnea to control for potential velocity variations associated with ventilation. LAAEVs were measured offline and averaged over 20 consecutive cycles.

LASEC was defined as the appearance of swirling clouds of echodensity distinct from white noise artifact.12 Gain settings were reduced sequentially to distinguish LASEC from noise artifact. Changes in LASEC were assessed independently by two observers and graded from 0 to 4 according to previously published criteria.12 Differences in LASEC grading were resolved by consensus. Thrombus was defined as a mass adherent to the wall of the atrium with either independent motion or different echogenicity.12

#### AFL Definition

The characteristic 12-lead surface electrocardiographic appearance defined typical AFL and was confirmed at electrophysiological evaluation by established criteria.13 Chronicity was defined as the presence of AFL for ≥1 month before RFA. Duration of AFL was defined as the time from the initial 12-lead ECG diagnosis to the time of RFA.

#### Electrophysiological Evaluation and Ablation

Catheters were positioned after the initial TEE evaluation to avoid physical termination of AFL before collection of baseline TEE data. Catheters were placed in the coronary sinus (CS), lateral right atrium, and His position as previously described (Figure 1).11 The CS catheter was placed with the proximal electrode pair positioned at the CS ostium. After the electrophysiological mechanism of AFL was confirmed, an anatomic approach was used to create a line of conduction block between the tricuspid annulus and the eustachian ridge. Successful RFA was demonstrated by bidirectional isthmus block. At no time during the procedure were DC shocks or antiarrhythmic agents administered.

Surface ECG and bipolar endocardial electrograms were continuously monitored and stored on a computer-based digital amplifier/recorder system with optical disk storage for offline analysis. Intracardiac electrograms were filtered from 30 to 500 Hz and measured with computer-assisted calipers at a sweep speed of 200 mm/s.

#### Study Protocol

After termination of chronic AFL to SR by radiofrequency energy, a pacing protocol was initiated (Figure 2). Pacing was performed at twice the diastolic threshold (for a pacing threshold of <2 ms) with a pulse duration of 1 ms. LAAEV and LASEC were assessed during:

1. **AFL before ablation**;
2. **SR after AFL termination**; and
3. **atrial pacing at cycle lengths between 750 ms and 250 ms from**:
   - (a) distal CS;
   - (b) proximal CS;
   - (c) lateral right atrium (LRA); and
   - (d) simultaneous distal CS and LRA (bilateral).

The effect of the postpacing pause on LAAEV was determined at each pacing site after pacing at 250 ms for a 2-minute period (n=27). The mean LAAEV for the first postpacing-pause beat in each patient was determined after pacing from each of the 3 sites tested. LAAEV was determined every 15 minutes in SR to control for potential baseline variation. During the pacing protocol, LAAEV was determined 10 seconds after the commencement of pacing at each rate, and in SR, 30 seconds after the cessation of pacing to avoid recording transitional velocities.

In the paroxysmal AFL group, LAAEV and LASEC were measured in SR before and after RFA and 60 minutes after RFA to control for the effects of radiofrequency energy and procedure duration on atrial mechanical function.

#### Pharmacological Intervention

At the completion of the pacing protocol, 25 patients were randomized in a 3:2 fashion to receive either an isoproterenol infusion (n=15) or intravenous calcium chloride (n=10). Isoproterenol was
commenced at a rate of 2 μg/min for 10 minutes and titrated (maximum of 4 μg/min) to achieve a sinus cycle length of 700 ms. LAEEV was recorded during isoproterenol infusion at cycle lengths of 750 700 and during concurrent atrial pacing from the distal CS at 600, 500, 400, and 300 ms. LASEC was assessed at a cycle length of 600 ms. Calcium chloride (1 g, 7 mmol calcium ions) was administered intravenously over 60 seconds. Five minutes after injection, LAEEV was assessed at the previously stated rates by pacing from the distal CS. LASEC was assessed at a cycle length of 600 ms.

Pace Termination and Reinitiation of AFL
In 6 patients, AFL was pace-terminated to document the development of atrial stunning. To determine the effects of the arrhythmia (in addition to the rate), AFL was reinduced before RFA. RFA was then continued as in the other patients, with the study protocol on completion of the RFA.

Statistical Analysis
All variables are reported as mean±SEM. Sequential data measurements were analyzed by repeated-measures ANOVA followed by the Tukey-Kramer procedure for multiple comparisons. Comparison between groups was performed with either Student’s paired t test or the Wilcoxon rank-sum test. Statistical significance was established at P<0.05.

Results
Atrial Mechanical Function on Termination of Chronic AFL
In all 35 patients, AFL was terminated with RFA and bidirectional isthmus block was achieved. LAEEV in AFL before RFA was 59.0±3.7 cm/s. After termination of AFL, LAEEV decreased to 18.8±1.4 cm/s (P<0.0001). There was no further change in baseline LAEEV over the duration of the study (Figure 3). There was no significant change in the sinus cycle length immediately after the termination of AFL to completion of the pacing protocol (920±30 versus 923±28 ms). LASEC grade before RFA was 0.9±0.1 and increased significantly after AFL termination to 2.2±0.2 (P<0.0001; Figure 4A). No patient developed thrombus after reversion to SR.

Effect of Pacing Rate and Site on Atrial Mechanical Function
An increase in the atrial rate of stimulation achieved through pacing resulted in a significant increase in LAEEV (P<0.0001) to a peak effect of 38.4±3.2 cm/s with biatrial
pacing at a cycle length of 500 ms (Figure 5). All pacing sites studied in this protocol were comparable in terms of the significant increase in LAAEV from $18.8 \pm 1.4$ cm/s in SR after termination of AFL. There was a significant reduction in the magnitude of LASEC with pacing. LASEC grade decreased to $1.9 \pm 0.2$ with pacing at an atrial cycle length of 600 ms in the stunned atrium ($P=0.005$, Figure 4A).

**Effect of Pace Termination and Reinitiation of AFL on Atrial Mechanical Function**

Pace termination of AFL resulted in significant atrial mechanical stunning with LAAEV decreasing from $59.2 \pm 10.4$ cm/s in AFL to $19.5 \pm 3.0$ cm/s in SR ($P=0.01$). Reinitiation of pace-terminated AFL resulted in a significant improvement in atrial mechanical function with LAAEV increasing to $58.0 \pm 10.1$ cm/s ($P=0.01$). There was no significant difference in LAAEV between the 2 episodes of AFL or in SR after reversion of AFL by pace termination (19.5±3.0 cm/s) or by RFA (19.0±2.9 cm/s).

**Effect of Isoproterenol on Atrial Mechanical Function**

After the infusion of isoproterenol, LAAEV in the mechanically stunned atrium increased from $19.1 \pm 2.1$ cm/s to $89.3 \pm 12.6$ cm/s at an atrial cycle length of 400 ms ($P<0.0001$, Figure 6). Isoproterenol augmented the previously described increases in LAAEV with pacing at cycle lengths between 600 and 300 ms ($P<0.01$, Figure 6). LASEC grade decreased from $2.3 \pm 0.2$ to $0.2 \pm 0.1$ with complete elimination of LASEC in 85% of cases in this subset of patients ($P=0.001$, Figure 4).

![Figure 3. LAAEV at baseline, during AFL pre-RFA, post-RFA in SR, and at 15-minute intervals in SR.](image)

![Figure 4. LASEC grade in AFL, SR, pacing, calcium, and isoproterenol (A). LASEC grade before and after isoproterenol (B).](image)
Effect of Calcium on Atrial Mechanical Function

After the administration of intravenous calcium, LAAEV increased significantly from $17.4\pm2.3$ cm/s to $31.6\pm5.5$ cm/s ($P<0.005$) with no change in the sinus cycle length (Figure 7). The maximum effect of calcium on LAAEV was observed at a cycle length of 500 ms; LAAEV increased from $17.4\pm2.3$ cm/s in SR to $50.2\pm10.5$ cm/s ($P<0.005$). Intravenous calcium also resulted in a significant reduction in LASEC grade from $2.9\pm0.1$ to $1.4\pm0.2$ ($P=0.01$, Figure 4A).

Figure 5. Effect of atrial pacing on LAAEV in SR and with distal CS pacing at cycle lengths of 750 to 250 ms (A). Representative LAAEV with pacing (B). Representative postpacing-pause potentiation of LAAEV (C). RAP indicates rapid atrial pacing.

Figure 6. Effect of isoproterenol on LAAEV. Atrial cycle lengths of 750 to 250 ms (A). Representative LAAEV with isoproterenol (B). *$P<0.01$ compared with the equivalent pacing rate.

Effect of the Postpacing Pause on Atrial Mechanical Function

After the predefined pacing train at 250 ms, the LAAEV for the first beat after the pause was $69.3\pm3.7$ cm/s. This was significantly higher than the LAAEV observed in SR in the stunned atrium of $19.2\pm1.7$ cm/s ($P<0.0001$). The LAAEV...
observed with the first postpacing-pause beat was similar to that observed during AFL preceding the development of stunning (61.3±4.2 cm/s, P=NS). The effect seen with the postspacing pause gradually diminished over the ensuing beats to that of the mechanically stunned atrium (Figure 5C).

Paroxysmal AFL Group
All patients in this group underwent successful RFA in SR. AFL was not induced and no arrhythmics or electrical cardioversion were used during the procedure. LAAEV in SR before RFA was 70.1±5.7 cm/s. Immediately after and 60 minutes after RFA, the LAAEV in SR was 70.2±5.7 cm/s and 68.8±7.9 cm/s, respectively (P=NS). There was no significant difference in the sinus cycle length at baseline (1034±53 ms) and after completion of the protocol (1043±48 ms). No patient had evidence of LASEC or thrombus.

Discussion
New Findings
The present study presents new information about atrial mechanical function in the remodeled atrium after termination of chronic AFL. First, the present study demonstrates a positive force-frequency relationship in the mechanically stunned atrium in humans. We have demonstrated that pacing the atrium at rates higher than SR results in improvement in function and reversal of atrial stunning. In addition, pharmacological modulation of this force-frequency relationship has been demonstrated. In the mechanically stunned atrium, isoproterenol led to a marked increase in LAAEV and the extinction of LASEC. Calcium was associated with an increase in LAAEV and reduction in LASEC. Second, despite marked impairment of atrial mechanical function after reversion to SR from chronic AFL, immediate and significant improvement of function to pre-RFA levels has been demonstrated with both reinitiation of AFL and observing the first postspacing-pause beat on LAAEV, thus suggesting the presence of an intact contractile apparatus. Third, the development of significant atrial mechanical stunning on pace termination of AFL provides further evidence that this process is independent of the mode of cardioversion.

Effect of Heart Rate (Bowditch-Treppe Effect)
That an increase in the heart rate can lead to an increase in the force of contraction (inotropic effect of rate) has been well described for ventricular myocardium in normal hearts and has been termed the Bowditch-Treppe effect.8 In the failing heart, this inotropic effect of rate is either not found or is reversed.8 Evidence implicates intracellular calcium homeostasis in frequency-dependent force generation,9 in particular the sarcoplasmic storage and release of calcium.10 In the failing heart, sarcoplasmic reticulum calcium-ATPase has been demonstrated to be abnormal in function and is implicated in the observed negative force-frequency relationship.8 The efficiency of this storage and release of calcium from the sarcoplasmic reticulum is also implicated in the negative force-frequency relationship seen at higher rates.14 Whether heart rate has any effect on atrial mechanical function in the intact human heart is unknown.

In an observational study, Agmon et al15 observed a positive relation between heart rate and LAAEV. However, in patients with sinus tachycardia, a reduction in LAAEV was noted. The effect of atrial rates representative of that seen in atrial tachyarrhythmias or the effect of rate in the mechanically stunned atrium have not been studied. After cardioversion of AF, Fatkin et al16 found that worsening LASEC was accompanied by a variable degree of bradycardia or impairment of atrial contraction or both.

In the present study, we observed the development of marked atrial stunning after the cardioversion of chronic AFL to SR. With increasing pacing rates, there was a stepwise improvement in LAAEV at atrial cycle lengths between 750 ms and 500 ms, reaching a peak LAAEV at cycle lengths of 600 ms or 500 ms. This was associated with significant reduction in LASEC. Atrial mechanical stunning could therefore be reversed by atrial pacing with a positive force-frequency relationship. Further increases in the pacing rate caused a decrease in LAAEV or a failure to improve. At a cycle length of ~400 ms, a trough was noted in the force-frequency curve. It is unclear whether or not this decrease resulted from impaired cardiac filling because of changes in atrioventricular conduction at high rates or a negatively inotropic effect in the force-frequency curve as a result of impairment of calcium release.

Effect of Pacing Site
Evidence suggesting that alternate and multiple sites of atrial pacing may result in less site-dependent conduction delay16 and AF17 has stimulated the development of pacing techniques for the prevention of atrial arrhythmias.18 The effects of alternate and multiple pacing sites on atrial mechanical function are unknown. The present study presents the effect of several alternative sites and multisite pacing on atrial mechanical function over a range of atrial rates. We have demonstrated a comparable effect on atrial mechanical function from all pacing sites tested.

Effect of Isoproterenol and Calcium
No previous study has evaluated the inotropic effect on atrial mechanical function in the stunned mechanically remodeled intact human atrium. Schotten and Allessie11 have demonstrated that atrial myocardial fibers isolated from patients with chronic AF required a 10-fold greater isoproterenol concentration than those in SR to reach the same positive inotropic effect. A small clinical study of the effect of dobutamine in patients with chronic AF reported a modest improvement in left atrial appendage function and a decrease in LASEC in 2 of 5 patients.19 In the present study, isoproterenol resulted in a significant increase in LAAEV, returning stunned atrial mechanical function to magnitudes in excess of pre-RFA values (62% greater) with the disappearance of LASEC. To our knowledge, the disappearance of LASEC by pharmacological maneuvers has not previously been described in the human atrium.

In isolated atrial myocardial fiber preparations, increasing concentrations of calcium resulted in complete reversal of myocardial fiber contractile dysfunction as a result of AF.11 In the present study, a single dose of calcium administered
intravenously to patients with atrial stunning was associated with an increase in LAAEV at all stimulation frequencies evaluated. The administration of calcium was also associated with a significant reduction in LASEC grade. However, unlike the study by Schotten et al.,\textsuperscript{11} calcium did not return the LAAEV to that observed during AFL.

**Effect of AFL**

The peak effect of pacing on atrial mechanical function was reached at longer atrial cycle lengths than observed during the preceding AFL. Furthermore, while pacing at cycle lengths equivalent to that of the preceding AFL, the LAAEV was significantly lower than during AFL. We have demonstrated that the reinitiation of pace-terminated AFL, however, resulted in LAAEV of the same magnitude as during AFL before the development of atrial stunning. This finding may implicate factors other than rate alone for atrial mechanical function during atrial arrhythmias. The effect observed with isoproterenol may implicate a role for catecholamine stimulation in the improved atrial mechanical function during atrial arrhythmias. Indeed, Jayachandran et al.\textsuperscript{20} demonstrated increased sympathetic activity within the atrium during pacing-induced AF.

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

The development of atrial mechanical stunning after the cardioversion of AF and AFL has been well documented.\textsuperscript{1-6} The present study confirms the development of significant stunning on termination of chronic AFL by RFA or pacing, adding to the evidence implicating the preceding arrhythmia rather than the mode of cardioversion in the development of atrial stunning.

We have demonstrated that increased pacing rates, isoproterenol, and calcium can improve atrial mechanical function after cardioversion, thereby reversing atrial stunning. This would suggest that the atrial contractile apparatus is intact and functional in patients with atrial stunning after termination of AFL. Postpacing-pause potentiation is dependent on the functional capacity of the sarcoplasmic reticulum to store and release calcium.\textsuperscript{14} We have demonstrated significant postpacing-pause potentiation of LAAEV in the mechanically stunned intact atrium, providing evidence for the presence of a functional sarcoplasmic reticulum. These findings are consistent with the observations of Schotten et al.\textsuperscript{11,21} in isolated atrial myocardial fibers and extend their findings to the whole atrium, suggesting that atrial mechanical stunning is not caused by the disruption of the contractile apparatus itself.

A positive force-frequency relationship and preserved sarcoplasmic reticulum function suggest that atrial mechanical dysfunction associated with AFL may have a different mechanism to the mechanical dysfunction associated with heart failure. Maneuvers increasing intracellular calcium (pacing, isoproterenol, and calcium) improved atrial mechanical dysfunction, suggesting an actual or relative intracellular calcium deficiency to be responsible for the observed atrial mechanical dysfunction. Previous studies have demonstrated atrial arrhythmias to result in altered calcium handling\textsuperscript{22} and intracellular calcium accumulation,\textsuperscript{23} 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.\textsuperscript{11,24} Schotten and Allessie\textsuperscript{21} have also demonstrated an upregulation of the sodium-calcium exchanger, which removes calcium from the cell. We speculate, therefore, that extrusion of calcium from the cell with chronic AFL results in relative cellular calcium depletion, which becomes clinically apparent as atrial mechanical stunning on slowing of the rate of atrial stimulation by termination of arrhythmia.

As a functional contractile apparatus has been demonstrated in these patients with mechanical stunning of the atria, it is possible that in AFL, sufficiently severe structural changes may not have occurred in the atrium, thus allowing contraction to return to normal with appropriate stimulation. It cannot be determined from the present study whether or not this applies to longer-duration AFL or AF.

**Clinical Implications**

Atrial mechanical stunning has been implicated as an important pathogenetic factor for cardioembolic stroke after cardioversion of chronic atrial arrhythmias. This process underscores the importance of postcardioversion anticoagulation. The demonstration that atrial mechanical remodeling as a result of atrial arrhythmias is functional and can be reversed creates an opportunity for the development of alternative strategies to anticoagulation for the prevention of thromboembolic complications after cardioversion of chronic atrial arrhythmias. The demonstration that heart rate may be important for atrial mechanical function after cardioversion to SR may also have implications for the choice of antiarrhythmic drugs with variable chronotropic effects at the time of cardioversion\textsuperscript{25} and postcardioversion pacing rates in patients with implanted devices.

**Limitations**

Although we have demonstrated the reversal of atrial mechanical stunning by increased pacing rates and pharmacological modulation, these maneuvers were performed during the first hour after cardioversion. Whether the improvement in atrial mechanical function could be sustained with continued stimulation or the effects of these maneuvers on the time course of recovery of atrial mechanical function are important issues that have not been addressed in the present study. Also, the assessment of the effect of calcium in the present study was limited to a single dose. Given the effects of calcium observed in atrial myocardial fiber preparations,\textsuperscript{11} the effect of increasing calcium concentrations in reversing atrial mechanical stunning is of significant interest.

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