

## Cardioversion of Atrial Fibrillation

# Concomitant Recovery of Atrial Mechanical and Endocrine Function After Cardioversion in Patients With Persistent Atrial Fibrillation

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<b>OBJECTIVES</b>	The purpose of this study was to evaluate left atrial mechanical function recovery and plasma atrial natriuretic peptide (ANP) release following successful cardioversion of persistent atrial fibrillation (AF).
<b>BACKGROUND</b>	Atrial fibrillation is characterized by functional deterioration, loss of atrial contraction, and elevation of plasma ANP levels. The response of ANP release toward atrial mechanical function after cardioversion of AF has not been fully examined.
<b>METHODS</b>	We examined 29 patients with successfully cardioverted persistent AF in whom sinus rhythm was maintained for at least 30 days after cardioversion. We assessed mechanical function of the left atrium at 24 h and 7 and 30 days after cardioversion and evaluated plasma ANP level at the same time. Atrial mechanical function was assessed during echocardiographic examination by means of the peak velocity of the transmitral A-wave, early transmitral to atrial flow velocity ratio, and atrial filling fraction (AFF). The plasma ANP level was determined by the radioimmunoassay method.
<b>RESULTS</b>	Plasma ANP levels were significantly reduced from $59.4 \pm 16.6$ pg/ml to $31.1 \pm 9.2$ pg/ml at 24 h after successful cardioversion. Within 30 days, we noted progressive improvement of atrial systolic function (increase in AFF from 21% to 31%, $p < 0.05$ ). At the same time, plasma ANP levels gradually increased from $31.1 \pm 9.2$ pg/ml at 24 h to $36.9 \pm 12.8$ pg/ml on day 30 following cardioversion ( $p < 0.05$ ).
<b>CONCLUSIONS</b>	Plasma ANP levels significantly decreased in patients with persistent AF after successful cardioversion. In the 30 days after cardioversion, gradual elevation of plasma ANP concentration was observed concomitantly with an increase of AFF. Plasma ANP release after successful cardioversion of persistent AF might be due to recovery of atrial mechanical function. (J Am Coll Cardiol 2003;41:1716–20) © 2003 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is primarily characterized by electrical remodeling and functional deterioration. The inappropriately rapid ventricular response, loss of atrial contribution to cardiac output, and atrial overloading lead to neurohormonal system activation (1).

Atrial natriuretic peptide (ANP), with its diuretic, natriuretic, and vasodilative actions, plays a major role in body fluid hemostasis and blood pressure (BP) control, protecting the organism from volume and pressure overload during arrhythmia (2).

The electrical, mechanical, and hormonal remodeling after cardioversion of persistent AF is related to the duration of AF and is mostly reversible (3–5). The delayed improvement in atrial contraction is associated with an initial stunning in atrial mechanical function (6). During the course of long-standing AF, a significant decline in ANP

levels (“endocrinologic silence”) has been described (7,8). However, no previous study has systematically assessed the influence of functional factors stimulating ANP secretion in patients with nonrheumatic persistent AF after successful cardioversion.

The aim of our study was to determine a time-course improvement of atrial mechanical and endocrine function after cardioversion of persistent AF and to assess the relationship between transient left atrial mechanical dysfunction and ANP secretion.

## METHODS

**Study patients.** We attempted direct-current cardioversion in 42 consecutive patients with persistent AF. Cardioversion was successful in 35 patients. However, in 6 of the 35 patients, AF reappeared within one month; 29 patients (21 men and 8 women; mean age 56.4 years) maintained sinus rhythm within 30 days after cardioversion. There were no significant differences, before cardioversion, in clinical, echocardiographic, and hemodynamic data and plasma ANP levels between the sinus rhythm group ( $n = 29$ ) and patients with unsuccessful cardioversion or recurrence of AF.

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#### Abbreviations and Acronyms

AF	= atrial fibrillation
AFF	= atrial filling fraction
ANP	= atrial natriuretic peptide
BP	= blood pressure
HR	= heart rate

All of the patients had been given oral anti-arrhythmic drugs (beta-blockers, propafenone, or amiodarone) to protect them against arrhythmia recurrence. Anti-arrhythmic treatment was initiated before cardioversion.

The known duration of AF ranged from 28 days to 24 months (mean 6.9 months). Atrial fibrillation was caused by hypertension (n = 12), ischemic heart disease (n = 11), or both (n = 6). Eight of 29 patients were in New York Heart Association functional class III, and 21 were in or class I or II. All patients had controlled AF, with a mean heart rate (HR) of about 86 beats/min, normalized BP, and effective anticoagulation.

The control group in sinus rhythm comprised 11 subjects compatible in terms of age, gender, and concomitant diseases.

**Direct-current cardioversion.** After induction of general anesthesia with intravenous fentanyl and etomidate, increasing direct-current external shocks of 200, 300, and 360 J were used until the highest energy (1,000 J) was reached or sinus rhythm was achieved.

**Echocardiographic studies.** The assessments of left atrial and ventricular dimensions and left ventricular ejection fraction were performed immediately before and then 24 h and 7 and 30 days after cardioversion. All measurements were performed following the American Society of Echocardiography recommendations (9). The transmitral flow profile was recorded by continuous-wave Doppler echocardiography from the apical four-chamber view, with the sample positioned between the tips of the mitral leaflets. Peak velocities of early filling (E-wave) and atrial filling (A-wave) were determined, and ratio of peak early filling velocity to peak atrial systolic velocity was calculated. Doppler signals were digitalized using a microcomputer (IBM AT, Hewlett Packard Co., Andover, Massachusetts) and consisted of manual tracing of the velocity curves. Velocity-time integrals of the transmitral total and A-wave of the Doppler flow pattern were determined. Atrial mechanical function was assessed according to Manning et al. (10) and expressed as the percent atrial contribution to total left ventricular filling (atrial filling fraction [AFF] %).

**Blood sampling and hormone assay.** Blood samples of ANP were obtained from the antecubital vein in the supine position after a resting period of 30 min just before echocardiographic examination (before and then 24 h and 7 and 30 days after cardioversion). All specimens were collected in tubes containing ethylenediaminetetra-acetic acid (1.5 g/l) and protease inhibitor (Trasylol [aprotinin] 500 kU/ml). Plasma was separated by centrifugation for 20 min

at 4°C and kept at -35°C until measurement. Analysis of ANP plasma level was performed by means of radioimmunoassay methods (Peninsula Laboratories Inc., Belmont, California). The inter-assay coefficient of variation was 9%, and the intra-assay coefficient was 6%. Informed, written consent was obtained from each patient.

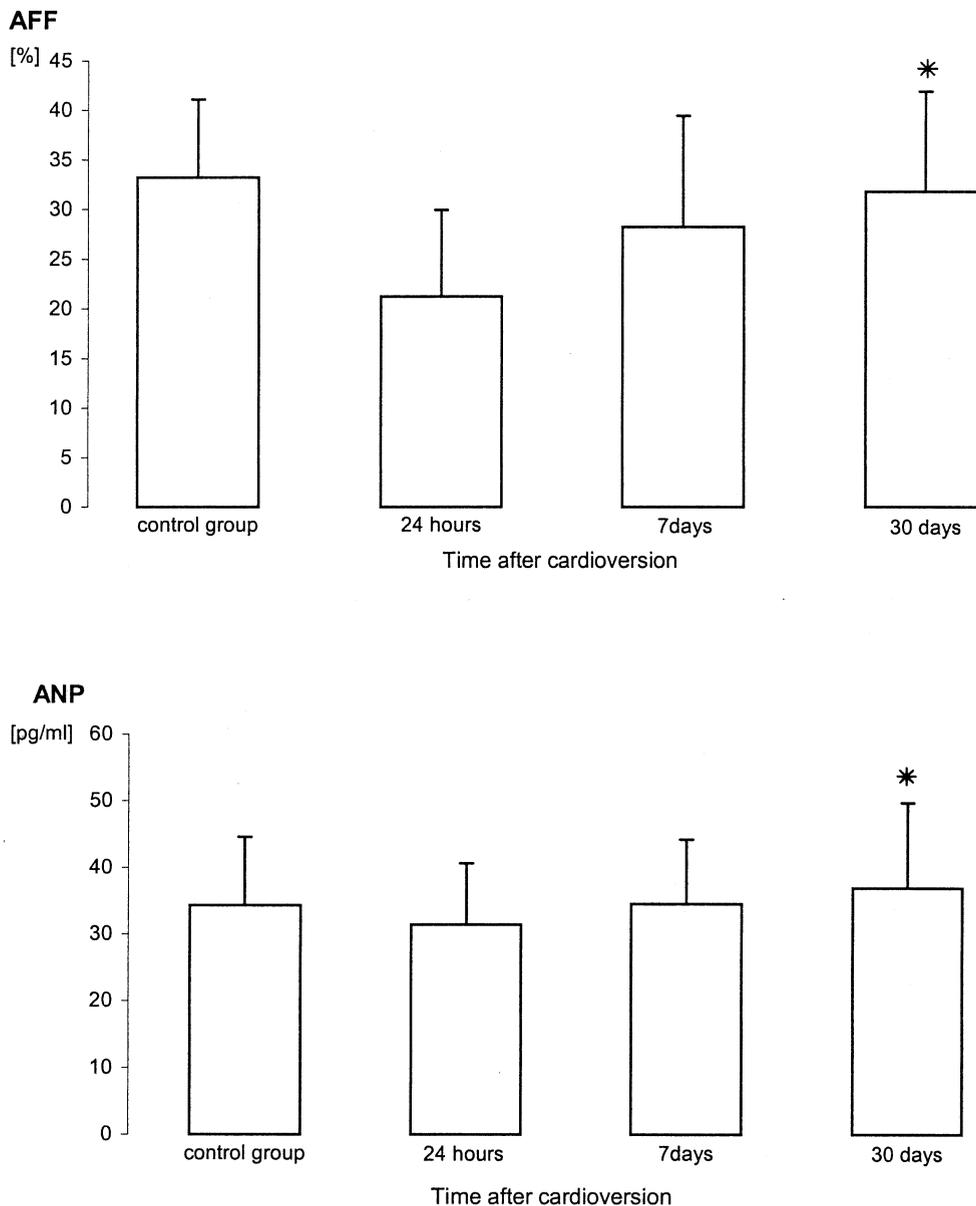
**Statistical analysis.** Data are expressed as the mean value  $\pm$  SD (variables were normally distributed). Statistical significance of serial changes in the plasma concentration of ANP, echocardiographic variables, and hemodynamic data during the study period was assessed by using the Student paired *t* test and analysis of variance for repeated measures, followed by the Scheffé F test. Correlations between two parameters were tested by linear regression analysis using the least-squares method. A level of  $p < 0.05$  was accepted as statistically significant.

## RESULTS

**Echocardiographic studies.** Left atrial and ventricular dimensions remained unchanged at 24 h after cardioversion of AF. In the 30 days after cardioversion, left atrial volume decreased and left ventricle ejection fraction increased significantly compared with measurements before cardioversion ( $102.5 \pm 24.9$  ml vs.  $86.6 \pm 25.8$  ml [ $p < 0.05$ ] and  $52.6 \pm 10.9\%$  vs.  $58.6 \pm 9.1\%$  [ $p < 0.05$ ], respectively).

**PULSED DOPPLER TRANSMITRAL RECORDINGS.** Identifiable atrial filling waves on the pulsed Doppler transmitral recordings performed 24 h after successful cardioversion were seen in all 29 patients. The initial value of the mean A-wave velocity, however, was significantly lower than those values at 7 and 30 days ( $p < 0.05$ ) after cardioversion or in those of control subjects ( $p < 0.05$ ). Thirty days after cardioversion, the peak A-wave velocity had markedly increased compared with 24-h data ( $0.28 \pm 0.11$  vs.  $0.42 \pm 0.2$ ,  $p < 0.05$ ). Twenty-four hours after cardioversion, AFF was significantly lower than that in the control group ( $21.2 \pm 8.7\%$  vs.  $33.2 \pm 7.9\%$ ,  $p < 0.05$ ). From 24 h to 30 days after cardioversion, AFF increased significantly ( $21.2 \pm 8.7\%$  vs.  $31.7 \pm 10.1\%$ ,  $p < 0.05$ ) (Fig. 1).

**Plasma ANP levels.** The mean plasma ANP level before cardioversion was  $59.4 \pm 16.6$  pg/ml in the examined group and  $34.3 \pm 10.7$  pg/ml in the control group ( $p < 0.001$ ). The mean systolic BP at the time of tube collecting before cardioversion was  $126.9 \pm 14.5$  mm Hg. At the same time, the HR measured by electrocardiography was  $82.1 \pm 8.5$  beats/min and  $74.7 \pm 9.8$  beats/min in the examined and control groups, respectively ( $p = \text{NS}$ ). The HR decreased 24 h following cardioversion to  $64.1 \pm 9.5$  beats/min, but it did not reach statistical significance (borderline significance:  $p = 0.06$ ). Plasma ANP levels were significantly reduced from  $59.4 \pm 16.5$  pg/ml to  $31.4 \pm 15.0$  pg/ml at 24 h following cardioversion ( $p < 0.001$ ). The plasma ANP concentration gradually increased from 24 h to 30 days after cardioversion ( $31.4 \pm 15.0$  pg/ml to  $36.9 \pm 12.8$  pg/ml,  $p < 0.05$ ) (Fig. 1). The mean systolic BP and HR did not



**Figure 1.** (Top) Changes in atrial filling fraction (AFF) after cardioversion in 29 patients with persistent atrial fibrillation (\* $p < 0.05$  vs. 24 h after cardioversion). (Bottom) Changes in plasma atrial natriuretic peptide (ANP) level in 29 patients (\* $p < 0.05$  vs. 24 h after cardioversion).

change during this period ( $115.6 \pm 14.9$  mm Hg vs.  $126 \pm 13.4$  mm Hg [ $p = \text{NS}$ ] and  $64.1 \pm 9.5$  beats/min at 24 h vs.  $65.7 \pm 8.2$  beats/min on day 30 [ $p = \text{NS}$ ], respectively). A significant positive linear correlation was found between plasma ANP level and maximal atrial volume ( $r = 0.60$ ,  $p < 0.05$ ).

## DISCUSSION

The left atrium is important in the maintenance of left ventricular function and in hormonal secretion. After short periods of AF, electrical remodeling and mechanical dysfunction are completely reversible, and normal values are reached within two to three days after sinus rhythm recovery (5). Atrial chamber and appendage “stunning” after electrical cardioversion of AF is related to its duration (11). After

longer periods of AF, recovery from contractile dysfunction may take several weeks to months (6,8).

In the present study, left atrial contractility increased progressively, becoming comparable to values in the control group by 30 days after successful cardioversion.

Atrial fibrillation is associated with activation of ANP. Previous studies have demonstrated that plasma ANP levels are markedly elevated in patients with chronic AF and decrease substantially after conversion to sinus rhythm (1,3,4). Although the trigger for release of ANP is still being discussed, experimental and clinical studies have suggested that atrial volume, pressure, and wall stretch are the main determinants of ANP activation (1,10).

In our patients, left atrial dimensions were markedly enlarged compared with controls. Within 30 days after

successful cardioversion, atrial volume significantly diminished. A relationship was found between plasma ANP levels and atrial volumes. Our result confirms the hypothesis that increased atrial volumes, with an associated increase in atrial stretch, cause ANP secretion (12).

Atrial mechanical overload may lead to atrial qualitative changes in electrical, mechanical, and neurohormonal functions. Some studies have demonstrated that plasma ANP levels in patients with AF were a function of time and were lower among patients with AF of longer duration (7,8,13). During the course of prolonged AF, extensive degenerative changes (atrophy and fibrosis) of the atrial myocytes develop, as found in biopsy specimens (14). The degeneration or exhaustion of atrial cells that secrete ANP may be the explanation for decreased plasma ANP levels among patients with long-standing AF. These findings suggest that plasma ANP levels reflect the qualitative change of atrial myocardium. We have shown recently that patients who had an increase in plasma ANP levels from rest to peak exercise before cardioversion had a better outcome (15).

In the present study, the mean plasma ANP concentration before cardioversion was nearly two times higher than that in the control group and decreased significantly during 24 h after successful cardioversion of AF. From 24 h to 30 days, the plasma ANP level gradually increased. Other variables, such as left atrial and ventricular dimension (except for left atrial volume), HR, and systolic BP, did not change during this period. The increase in ANP concentration from 24 h to 30 days after cardioversion was concomitant with an increase in AFF and might be due to changes in atrial mechanical function. There seems to be a significant difference between the lack of mechanical function during AF, when the highest ANP levels were observed, and the atrial stunning during sinus rhythm immediately after cardioversion. Nevertheless, after successful cardioversion, recovery of atrial contraction is delayed and deranged mitral and tricuspid valve closure and irregular ventricular rate are reversed, which leads to an improvement of left ventricular function, a reduction of volume overloading and filling pressures, and a decrease in stretch of the atrial and ventricular walls. Normalization of hormonal secretion in conjunction with atrial contractility occurred in our study at 30 days after cardioversion. Our results confirm the hypothesis that recovery of atrial mechanical function plays a role in ANP secretion.

Comparable findings were reported by Fujiwara et al. (16) in patients with mitral stenosis. They demonstrated an increase in plasma ANP levels from 4 h to 5 days after cardioversion of AF, owing to recovery of atrial mechanical function, concomitantly with an increase in AFF. However, Kalra et al. (17) investigated differences in the time course of initial "stunning" in mechanical and endocrine function in patients undergoing electrical cardioversion. Although endocrine function fully recovered by 7 days, mechanical function (determined by sequential measurements of peak A-wave velocity) continued to improve until 28 days.

A transient deficiency of the atria to produce ANP after successful cardioversion was described by Arakawa et al. (3). Passive leg elevation led to an increase in the mean pulmonary artery wedge pressure but did not result in an increased plasma ANP concentration. According to the authors, this dysregulation of ANP release during an early period after cardioversion of AF might be related to the decreased sensitivity of the atrial receptors for ANP release following volume overloading, as well as transient atrial contractile dysfunction after cardioversion.

Pulmonary edema has been reported to be a potential complication after successful cardioversion of AF (18). Thus, left atrial systolic dysfunction associated with left atrial overload mismatch, closely related to the impairment of ANP release soon after cardioversion of AF, may lead to pulmonary edema after cardioversion of AF. Further studies will show whether atrial mechanical and endocrine function parameters in patients with AF after cardioversion have prognostic importance regarding the risk of stroke.

Neurohormonal activation in atrial pathophysiology represents a challenging, poorly understood problem of modern arrhythmias and needs further investigations.

## CONCLUSIONS

Plasma ANP levels significantly decreased in patients with persistent AF after successful cardioversion and were comparable to those of the control group. Within 30 days after cardioversion, atrial mechanical contractility improved gradually, with a concomitant increase in ANP. The increase in ANP from 24 h to 30 days after cardioversion may be due to recovery of atrial mechanical function.

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