Plasma Atrial Natriuretic Peptide Response to Direct Current Cardioversion of Atrial Fibrillation in Patients With Mitral Stenosis

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Objectives. The purpose of this study was to evaluate the effect of direct current cardioversion therapy on the plasma concentration of atrial natriuretic peptide and to determine the main factors that influence the change in plasma atrial natriuretic peptide levels in patients with atrial fibrillation.

Background. In atrial arrhythmias, whether the fast atrial rate itself or the associated elevation of atrial pressure, or both, contributes to the increase in atrial natriuretic peptide is a subject of debate.

Methods. In 15 patients with mild mitral stenosis, plasma atrial natriuretic peptide levels were measured and transmitral flow pattern was obtained by continuous wave Doppler echocardiography immediately before cardioversion and at 5 min, 4 h, 24 h and 5 days after direct current cardioversion. Mean mitral pressure gradient and atrial filling fraction were calculated on the basis of transmitral flow.

Results. In three patients who did not have a successful return to sinus rhythm, plasma atrial natriuretic peptide levels remained elevated after cardioversion. In 12 patients who maintained sinus rhythm, plasma atrial natriuretic peptide levels were significantly reduced from 79 ± 29 to 36 ± 11 pg/ml 4 h after cardioversion to sinus rhythm. However, the mitral pressure gradient did not change significantly during the observation period. There were progressive increases in atrial filling fraction throughout the observation period. From 4 h to 5 days after direct current cardioversion, plasma atrial natriuretic peptide levels gradually increased concomitantly with the recovery of atrial mechanical function.

Conclusion. The reduction of plasma atrial natriuretic peptide levels after direct current cardioversion might be due to recovery from the high rate of atrial firing and not to an alteration in the mitral pressure gradient. Direct current cardioversion itself does not seem to influence atrial natriuretic peptide secretion. The increase in atrial natriuretic peptide levels from 4 h to 5 days after cardioversion concomitantly with an increase in atrial filling fraction may be due to recovery of atrial mechanical function.

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Peptides with potent vasodilator and diuretic activities have been purified from animal and human atrial extracts (1–8). Atrial natriuretic peptide is released from atrial myocytes not only in congestive heart failure, but also in atrial and ventricular tachyarrhythmias (9–12). However, the mechanism of atrial natriuretic peptide release from the atria still remains controversial, particularly in the setting of cardiac arrhythmias. For example, in atrial arrhythmias, whether the fast atrial rate itself or the associated elevation of atrial pressure, or both, contribute to the increase in atrial natriuretic peptide is a subject of debate (13,14). It has been observed that repetitive electrical stimulation of the isolated left atrium released atrial natriuretic peptide in the bathing solution, indicating that stimulation frequency was the modulator of atrial natriuretic peptide release in this setting (13). We have consistently shown that in patients with mitral stenosis, the plasma concentration of atrial natriuretic peptide depends on left atrial pressure, whether or not there is atrial fibrillation (15,16).

The purpose of the present study was to evaluate the effect of cardioversion on the plasma concentration of atrial natriuretic peptide and to determine the main factors influencing the change in plasma atrial natriuretic peptide in patients with atrial fibrillation after direct current cardioversion to sinus rhythm.

Methods

Study patients. We studied 15 patients with atrial fibrillation and mild mitral stenosis. All patients were treated by percutaneous transvenous mitral commissurotomy. Nine had grade I/VI and three had grade II/VI mitral regurgitation after commissurotomy. All patients underwent elective direct current cardioversion for atrial fibrillation. The mean age of the 4 men and 11 women was 50 years (range 40 to 66). The known duration of atrial fibrillation ranged from 3 to 240 months (mean 52).
Percutaneous transvenous mitral commissurotomy. All patients underwent this procedure as previously described (17,18). Right and left heart pressures and mean mitral pressure gradient were measured before and after commissurotomy. Left ventriculography was performed before and after commissurotomy. The severity of mitral regurgitation from left ventriculography was graded semiquantitatively from 1+ to 4+ (19). Mitral valve area was measured by planimetry from two-dimensional echocardiograms obtained before and after the procedure.

Direct current cardioversion. All patients underwent direct current cardioversion 9 days after percutaneous transvenous mitral commissurotomy. Anticoagulant therapy was started at least 1 week before cardioversion, with doses of oral warfarin sufficient to maintain a prothrombin time of 30% to 40%. Moreover, to confirm the absence of left atrial thrombus, all patients underwent transesophageal echocardiography within 48 h before cardioversion. There was no evidence of significant left atrial thrombus in any patient. Eleven of 15 patients had been receiving digoxin, which was withheld before elective cardioversion. Treatment with disopyramide (300 mg/day) was started a few days before cardioversion in all patients. After induction of general anesthesia with intravenous pentobarbital calcium, direct current cardioversion was performed with initial 100-J shocks. In the unsuccessful cases, we repeated the procedure with added 50-J shocks. However, we terminated the protocol in three patients after cardioversion with 200-J shocks was unsuccessful. Twelve patients were continued on maintenance doses of the medications they were taking before cardioversion throughout the observation period.

Echocardiographic studies. Two-dimensional and continuous wave Doppler echocardiographic examinations were performed with a Toshiba 140A Doppler system with a 2.5- or 3.75-MHz phased array transducer. Patients were examined in the supine position after sedation immediately before cardioversion and at 5 min, 4 h, 24 h and 5 days after cardioversion. Left atrial dimension at end-systole was measured in the parasternal long-axis view with use of the leading edge technique from M-mode tracings (20,21). Transmitral flow profile was recorded by continuous wave Doppler echocardiography from the apical two-chamber view. Hard copy recordings were made at paper speeds of 50 mm/s. Doppler signals were digitalized with use of a microcomputer (NEC 9800). The mean mitral pressure gradient was obtained from the integral of the instantaneous pressure gradient along the velocity profile. The atrial filling fraction (i.e., the percent atrial contribution to total left ventricular filling) was determined by extrapolating the early diastolic descent of the mitral velocity profile to end-diastole in order to separate the atrial component. The atrial filling fraction was calculated as the quotient of the atrial component and the total left ventricular filling time-velocity integral (lower panel).

Blood sampling and hormone assay. Blood samples were drawn from a peripheral vein into the tube containing ethylenediaminetetraacetic acid and aprotinin as reported (25). Blood samples were obtained immediately before cardioversion and at 5 min, 4 h, 24 h and 5 days after cardioversion. Plasma concentration of atrial natriuretic peptide was determined by specific radioimmunoassay after extraction with octadecylsilane cartridges as previously described (26).

Statistical analysis. Data are expressed as mean value ± SD. Statistical significance of serial changes in the plasma concentration of atrial natriuretic peptide, Doppler echocardiographic variables, left atrial dimension and hemodynamic variables during the study period were assessed by multiple comparison analysis (ANOVA, followed by the Scheffé F test). The statistical significance of changes in hemodynamic variables during percutaneous transvenous mitral commissurotomy was assessed by Student t tests. A probability value < 0.05 was considered significant.
Results

Results of percutaneous transvenous mitral commissurotomy. Mitral valve area evaluated by two-dimensional echocardiography increased from 1.1 ± 0.4 to 1.9 ± 0.4 cm² after percutaneous transvenous mitral commissurotomy in all 15 patients (p < 0.01). Mean transmitral pressure gradient calculated by cardiac catheterization decreased from 9.5 ± 3 to 4.1 ± 2.2 mm Hg (p < 0.01). Mitral regurgitation increased in nine patients. However, there were no patients with severe mitral regurgitation > grade III/VI.

Direct current cardioversion. In 12 of 15 pts sinus rhythm was restored immediately after direct current cardioversion and maintained beyond 5 days. In three patients in whom cardioversion was unsuccessful with 200-J shocks, no further cardioversion was attempted.

Plasma atrial natriuretic peptide levels. In three patients who did not have a successful return to sinus rhythm, plasma concentration of atrial natriuretic peptide was 42 ± 8, 39 ± 6 and 41 ± 10 pg/ml immediately before cardioversion and at 5 min and 4 h after cardioversion, respectively. In 12 patients who maintained sinus rhythm, plasma concentration of atrial natriuretic peptide was 79 ± 29, 69 ± 27, 36 ± 11, 44 ± 13 and 55 ± 19 pg/ml immediately before cardioversion and at 5 min, 4 h, 24 h and 5 days after cardioversion to sinus rhythm, respectively (Table 1, Fig. 2). Plasma concentration of atrial natriuretic peptide was significantly reduced from 79 ± 29 to 36 ± 11 pg/ml 4 h after cardioversion to sinus rhythm (p < 0.05). From 4 h to 5 days after cardioversion, the plasma concentration of atrial natriuretic peptide gradually increased to 55 ± 19 pg/ml (p < 0.05).

Serial changes of transmitral flow profile. Mean mitral pressure gradient was 4.7 ± 1.5, 4.0 ± 1.2, 4.0 ± 1.6, 4.0 ± 1.5, 4.1 ± 1.2 mm Hg immediately before cardioversion and at 5 min, 4 h, 24 h and 5 days after cardioversion to sinus rhythm, respectively. Mean mitral pressure gradient did not change during study period. Atrial filling fraction (in %) was 0, 1.4 ± 3.4, 3.4 ± 4.1, 6.1 ± 4.9, 9.3 ± 3.9 immediately before cardioversion and at 5 min, 4 h, 24 h and 5 days after cardioversion. Atrial filling fraction was significantly increased from 4.5% 4 h after cardioversion to 13.3% 5 days after cardioversion to sinus rhythm. Bar at right represents velocity.

Figure 2. Plots of changes in plasma atrial natriuretic peptide immediately before (prior) cardioversion and at 5 min, 4 h, 24 h and 5 days after cardioversion to sinus rhythm. (p < 0.05 before vs. 4 h, before vs. 24 h, before vs. 5 days, 5 min vs. 4 h, 5 min vs. 24 h and 4 h vs. 5 days.) Squares and dashed lines indicate mean values for the group as a whole. Short bars indicate SD. Circles and lines indicate values for individual patients.

Table 1. Changes in Atrial Natriuretic Peptide and Other Hemodynamic Data

<table>
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<tr>
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<th>Prior</th>
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<td>ANP (pg/ml)</td>
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<td>69 ± 27</td>
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<td>LAD (mm)</td>
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<td>46 ± 4</td>
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<td>HR (beats/min)</td>
<td>82 ± 22</td>
<td>72 ± 8</td>
<td>67 ± 6</td>
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<tr>
<td>SBP (mm Hg)</td>
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<td>123 ± 13</td>
<td>126 ± 13</td>
<td>119 ± 9</td>
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Statistical analysis by analysis of variance, followed by the Schef¿e F test. Atrial filling fraction (AFF): p < 0.05 5 min vs. 24 h, 5 min vs. 5 days, 4 h vs. 5 days, 24 h vs. 5 days. Atrial natriuretic peptide (ANP): p < 0.05 before cardioversion vs. 4 h, before cardioversion vs. 24 h, before cardioversion vs. 5 days, 4 h vs. 24 h, before cardioversion vs. 5 days, 5 min vs. 24 h. Left atrial dimension (LAD): p = NS. Mean mitral pressure gradient (MPG): p = NS. Systolic blood pressure (SBP): p = NS.
ATRIAL NATRIURETIC PEPTIDE RESPONSE TO CARDIOVERSION

August 1993:575-80

Figure 4. Plots of changes in mean mitral pressure gradient (upper panel) and atrial filling fraction (lower panel) immediately before (prior) cardioversion and at 5 min, 4 h, 24 h and 5 days after cardioversion to sinus rhythm. (p < 0.05, atrial filling fraction: 5 min vs. 24 h, 5 min vs. 5 days, 4 h vs. 24 h, 4 h vs. 5 days and 24 h vs. 5 days.) Symbols as in Figure 2.

cardioversion to sinus rhythm, respectively. Identifiable atrial filling wave was seen in 3 of 12 patients on the transmitral flow recording performed at 5 min after cardioversion. At 4 h after cardioversion, an identifiable atrial filling wave was seen in 6 patients. Atrial filling fraction was increased continuously over the observation period (Table 1, Fig. 3 and 4).

Left atrial dimension and hemodynamic changes. Left atrial dimension did not change during study period. Mean heart rate was 82 ± 22, 72 ± 8, 67 ± 6, 63 ± 7, 65 ± 12 beats/min immediately before cardioversion and at 5 min, 4 h, 24 h and 5 days after cardioversion to sinus rhythm, respectively. Mean heart rate was significantly reduced 4 h after cardioversion to sinus rhythm (p < 0.05). Systemic systolic blood pressure did not change during study period (Table 1, Fig. 5).

Changes in plasma atrial natriuretic peptide and in hemodynamic variables. The plasma concentration of atrial natriuretic peptide was significantly reduced 4 h after direct current cardioversion to sinus rhythm. Mean mitral pressure gradient did not differ significantly between immediately before cardioversion and 4 h after cardioversion. From 4 h to 5 days after cardioversion plasma concentration of atrial natriuretic peptide gradually increased. Atrial filling fraction gradually increased to 9.3 ± 3.9% 5 days after cardioversion. Left atrial dimension, heart rate and systolic blood pressure did not change from 4 h to 5 days after cardioversion.

Discussion

Reduction of atrial natriuretic peptide after cardioversion. Recent studies (27-30) have demonstrated increased plasma concentrations of atrial natriuretic peptide in patients with atrial fibrillation. Roy et al. (29) reported that plasma atrial natriuretic peptide levels were high in patients with atrial fibrillation and decreased 1 h after cardioversion to sinus rhythm. The authors (29) suggested that high atrial pressure and chronic atrial stretch contributed to the high plasma atrial natriuretic peptide concentration during atrial fibrillation, although they did not measure atrial pressure in this setting. An increase in plasma atrial natriuretic peptide concentration in atrial arrhythmias may be attributed to an associated elevation of atrial pressure in these circum-

Figure 5. Plots of changes in left atrial dimension (upper panel), mean heart rate (middle panel) and systemic systolic blood pressure (lower panel) immediately before (prior) cardioversion and at 5 min, 4 h, 24 h and 5 days after cardioversion to sinus rhythm. (p < 0.05, heart rate: before vs. 4 h, before vs. 24 h, before vs. 5 days and 5 min vs. 24 h.) Symbols as in Figure 2. bpm = beats per minute.
Atrial natriuretic peptide response to cardioversion

Fujiwara et al.

August 1993:575-80

JACC Vol. 22, No. 2

ATRIAL NATRIURETIC PEPTIDE RESPONSE TO CARDIOVERSION

stances. Likewise, the decrease after cardioversion in atrial natriuretic peptide concentration has been explained by the decrease in atrial pressure resulting from restoration of sinus rhythm. We (15) have already reported the rapid reduction of plasma atrial natriuretic peptide concentration with a concomitant rapid decrease in left atrial pressure and indicated that left atrial pressure was the most important factor influencing atrial natriuretic peptide secretion in patients with mitral stenosis. Dussaule et al. (31) also indicated that there was an increase in atrial natriuretic peptide secretion, depending on left atrial pressure, in patients with mitral stenosis and sinus rhythm. In our present study, we measured mean mitral pressure gradient estimated by Doppler echocardiography instead of evaluating left atrial pressure. We showed that during exercise, the most important factor influencing the secretion of atrial natriuretic peptide may be the alteration of transmural pressure gradient in patients with mitral stenosis (16).

In the present study, the plasma concentration of atrial natriuretic peptide decreased significantly without changes in mean mitral pressure gradient and left atrial dimension 4 h after cardioversion. The reduction in atrial natriuretic peptide does not seem to be due to the change in mean mitral pressure gradient.

Effect of cardioversion itself on atrial natriuretic peptide secretion. To ascertain if cardioversion itself might influence plasma atrial natriuretic peptide levels, we studied three patients who did not recover from atrial fibrillation. The plasma concentration of atrial natriuretic peptide in those three patients did not significantly change after cardioversion. Therefore, direct current cardioversion itself does not seem to influence atrial natriuretic peptide secretion.

Main factor influencing the reduction of atrial natriuretic peptide. Dussaule et al. (31) showed that the atrial natriuretic peptide level was also high in patients with mitral stenosis and atrial fibrillation but did not respond appropriately to changes in left atrial pressure. They tried to estimate the relation of left atrial dimension to plasma atrial natriuretic peptide release. Left atrial dimension tended to be greater in patients with atrial fibrillation than in those with sinus rhythm. They concluded that it was likely that high plasma atrial natriuretic peptide levels and the inappropriate response of plasma atrial natriuretic peptide to the decrease in left atrial pressure observed in patients with atrial fibrillation were due to several related factors such as a high rate of atrial firing, abnormal stretch of the atrial wall and larger atrial volume (31). Microelectrode studies (32) have indicated that cells in the fibrillating atrium may fire 500 times/min. This very high rate could participate in the pathophysologic effects we observed. The reduction of atrial natriuretic peptide concentration after cardioversion to sinus rhythm might be reflected by recovery from the high rate of atrial firing. Although we did not assess atrial pressure directly, our noninvasive data strongly suggested that a high rate of firing alone could cause an elevation in plasma atrial natriuretic peptide without changes in mitral pressure gradient and atrial size in patients with mitral stenosis.

Increase in atrial natriuretic peptide after restoration of sinus rhythm. Manning et al. (33) reported that the percent atrial contribution to left ventricular filling did not return to normal until 3 weeks after cardioversion in patients with atrial fibrillation. The present study indicated that full recovery of atrial mechanical function did not occur immediately after successful direct current cardioversion of atrial fibrillation to sinus rhythm, but it increased from 4 h to 5 days after cardioversion. Plasma concentrations of atrial natriuretic peptide gradually increased from 4 h to 5 days after cardioversion. Other variables such as mean mitral pressure gradient, left atrial dimension, heart rate and systolic blood pressure did not change from 4 h to 5 days. The increase in atrial natriuretic peptide from 4 h to 5 days after cardioversion was concomitant with the increase in atrial filling fraction and might be due to changes in atrial mechanical function. Thus, recovery of atrial mechanical function seems to play a role in atrial natriuretic peptide secretion.

Limitations of the study. We could not assess left atrial pressure because of practical limitations. Instead, we measured mean mitral pressure gradient obtained by Doppler echocardiography because there was a close correlation between this variable and left atrial pressure.

The improvement in atrial mechanical function might appear to continue for up to several weeks after cardioversion in most patients. In this study, we could not evaluate the changes in atrial natriuretic peptide up to the time of full recovery of atrial function. However, the improvement in atrial mechanical function within 1 week may be larger than that during the next several weeks. Thus, the relation between the improvement in atrial mechanical function and the changes in plasma atrial natriuretic peptide levels could be sufficiently evaluated within 1 week.

Conclusions. Plasma atrial natriuretic peptide levels decreased after direct current cardioversion in patients with mitral stenosis and atrial fibrillation. The reduction of atrial natriuretic peptide was independent of mean mitral pressure gradient and left atrial size. The reduction of atrial natriuretic peptide after direct current cardioversion may be due to recovery from the high rate of atrial firing. In cases where sinus rhythm was maintained, atrial mechanical function recovered gradually from 5 min to 5 days after cardioversion. The increase in atrial natriuretic peptide from 4 h to 5 days after cardioversion may be due to recovery of atrial mechanical function.

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References