Rapid Reduction of Plasma Atrial Natriuretic Peptide Levels During Percutaneous Transvenous Mitral Commissurotomy in Patients With Mitral Stenosis

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To clarify the direct contribution of the left atrial pressure to secretion of human atrial natriuretic peptide (hANP), we have attempted to study the relations between plasma hANP levels, neurohumoral factors, and hemodynamic changes in 13 patients with mitral stenosis undergoing percutaneous transvenous mitral commissurotomy (PTMC). After PTMC, the left atrial pressure fell from 14.7±1.9 (mean±SEM) to 6.5±0.7 mm Hg in all patients studied (p<0.0005), whereas there were no remarkable changes in either the right atrial pressure, mean arterial pressure, or heart rate. Plasma immunoreactive hANP levels obtained from the pulmonary artery decreased from 278±51 to 137±31 pg/ml after PTMC (p<0.0005). There was a significant correlation between the decrement of hANP levels and that of left atrial pressure (r=0.72, p<0.005). Neither plasma renin activity nor norepinephrine levels changed. In contrast, plasma aldosterone concentrations significantly increased from 11.3±1.5 to 16.4±2.7 pg/ml after PTMC (p<0.01), although there was no causal relation between plasma concentrations of aldosterone and hANP. The present result with PTMC-induced rapid fall of the left atrial pressure with a concomitant reduction in hANP secretion strongly suggests the importance of the left atrial pressure on hANP secretion in humans. (Circulation 1989;79:47–50)

Human atrial natriuretic peptide (hANP), a 28-amino acid polypeptide hormone with potent natriuretic and vasodilatory effect, has been recently isolated from human heart.1 Secretion of hANP is mainly influenced by hemodynamic factors, especially the right atrial pressure or pulmonary artery wedge pressure or both, suggesting that increase in atrial pressure or atrial distention or both are the predominant stimulus for hANP secretion.2–5 To our knowledge, however, there have been no reports to demonstrate whether the rapid change of the left atrial pressure directly contributes to the secretion of hANP in humans.

Percutaneous transvenous mitral commissurotomy (PTMC) is a new therapeutic technique for mitral stenosis by extending the mitral orifice with a rapid fall of the left atrial pressure without changes in other hemodynamic parameters.6 Therefore, the present study was designed to investigate the relations between hemodynamic factors, plasma levels of hANP, and other neurohumoral factors in patients with mitral stenosis during PTMC.

Subjects and Methods

Subjects

Subjects studied were 13 patients (three men and 10 women) with symptomatic mitral stenosis. Their ages ranged from 36 to 66 years with an average of 50 years. Informed consents were obtained from each patient. All patients were in New York Heart Association functional Class II. Six patients were in normal sinus rhythm, and seven had atrial fibrilla-
Sampling and Analysis

Plasma concentrations of hANP were determined by specific radioimmunoassay after extraction with octadecylsilane cartridges as previously described. Plasma renin activity and plasma aldosterone concentrations were measured by radioimmunoassays. Plasma concentrations of norepinephrine were measured by high-performance liquid chromatography combined with the trihydroxyindole fluorometric procedure.

Statistical Analysis

Data were expressed as mean ± SEM. Linear regression analysis was used to determine the correlations between plasma levels of hANP and hemodynamic parameters. Statistical comparisons were made by paired Student’s t test. A probability value less than 0.05 was considered statistically significant.

Results

Changes in Hemodynamic Parameters and Plasma hANP Levels

The mean left atrial pressure after commissurotomy significantly fell in all patients from 14.7 ± 1.9 to 6.5 ± 0.7 mm Hg after commissurotomy (p < 0.0005) (Table 1 and Figure 1). However, there were no significant changes in the mean right atrial pressure (2.8 ± 0.9 compared with 1.6 ± 0.4 mm Hg), the mean arterial pressure (94.3 ± 3.1 compared with 91.0 ± 3.1 mm Hg), or heart rate (78.7 ± 3.1 compared with 76.2 ± 4.1 beats/min) before and after PTMC. Plasma hANP levels in the pulmonary artery ranged from 88 to 795 pg/ml with an average of 278 ± 51 pg/ml before balloon inflation, but they significantly decreased to 137 ± 31 pg/ml, ranging from 44 to 455 pg/ml, 30 minutes after commissurotomy (p < 0.0005). There was a positive correlation between the decrement ratio of hANP and that of the mean left atrial pressure (r = 0.72, p < 0.005) (Figure 2). However, there was no significant correlation between changes of hANP and those of the mean right atrial pressure.

Changes of Plasma Renin Activity, Norepinephrine, and Plasma Aldosterone Concentration

Neither plasma renin activity nor plasma norepinephrine levels significantly changed, being 3.5 ± 1.1 ng/ml/hr and 348 ± 46 pg/ml before and 3.3 ± 1.0 ng/ml/hr and 313 ± 41 pg/ml after commissurotomy.

TABLE 1. Clinical and Hemodynamic Data Before and After Percutaneous Transvenous Mitral Commissurotomy in 13 Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
<th>Diagnosis</th>
<th>HR (beats/min)</th>
<th>MAP (mm Hg)</th>
<th>RAP (mm Hg)</th>
<th>LAP (mm Hg)</th>
<th>ANP (pg/ml)</th>
</tr>
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<tr>
<td></td>
<td></td>
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<td>Post</td>
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<tr>
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<td>77</td>
<td>76</td>
<td>107</td>
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</tbody>
</table>

Mean ± SEM 50 ± 3

HR, heart rate; MAP, mean arterial pressure; RAP, mean right atrial pressure; LAP, mean left atrial pressure; ANP, atrial natriuretic peptide.

F, female; M, male; MS, mitral stenosis; AR, aortic regurgitation; ASR, aortic stenosis and regurgitation.

*p < 0.0005.
respectively. Plasma aldosterone concentration significantly increased from $11.3 \pm 1.5$ to $16.4 \pm 2.7$ pg/ml ($p<0.01$), although three of 13 patients had decreased plasma aldosterone concentration after PTMC (Figure 1). However, there was no significant correlation between increment of plasma aldosterone concentration and decrement of hANP levels ($r=0.44$, $p<0.1$).

**Discussion**

It has recently been reported that the basal plasma hANP levels are approximately 30–50 pg/ml in healthy subjects. In contrast, patients with mitral stenosis and congestive heart failure have higher plasma hANP levels, and there are positive correlations between hANP levels and atrial and pulmonary artery pressures. Dietz et al. have reported a close relation between the mean left atrial pressure and plasma hANP level in patients with mitral stenosis. It has been shown that plasma hANP levels fall concomitantly with reduction in the atrial pressure in patients with congestive heart failure after treatment. These data suggest that an increase in atrial pressure is a potent stimulant for hANP secretion.

In dogs, acute elevation of the left atrial pressure with experimental maneuvers like occlusion of mitral valve or the ascending aorta induced ANP secretion. Andersson et al. have reported that plasma hANP levels gradually fall in a patient with patent ductus arteriosus after ligation of the ductus. Schwab et al. have recently demonstrated that plasma hANP levels increased in association with simultaneous short-term increases in the right atrial pressure in human recipients of artificial hearts. However, there have been no reports to study the changes in plasma hANP levels during the acute fall of the left atrial pressure in humans. Thus, the present study is the first report for investigating the direct effect of the left atrial pressure on hANP secretion by the use of PTMC in humans.

PTMC is a new technique developed for treating mitral stenosis by extending the mitral orifice with a rapid fall of the left atrial pressure, and it proves to be a useful noninvasive procedure. It should be noted that this procedure requires only local anesthesia without significant changes in other hemodynamic parameters, such as the right atrial pressure, systemic blood pressure, or heart rate (Table 1), although pulmonary artery pressure only transiently
increased and left ventricular pressure decreased during balloon inflation. The present study was intentionally designed to obtain blood samples at 30 minutes after commissurotomy when the left atrial pressure consistently decreased. In fact, Andersson et al.\textsuperscript{16} showed that plasma hANP levels almost stabilized about 30 minutes after ligating the ductus. However, simultaneous study for collecting blood samples and monitoring the hemodynamic changes with more frequent time intervals should be needed.

In the present study, plasma norepinephrine did not change during PTMC, and there were no significant relations between plasma levels of hANP and norepinephrine. It has been suggested that hANP has an inhibitory effect on renin secretion in vitro,\textsuperscript{18} whereas its inhibitory effect on renin secretion is controversial in vivo.\textsuperscript{19} The present result does not support any direct relation between plasma hANP and plasma renin activity.

It has been reported that ANP has a direct inhibitory effect on aldosterone secretion in vitro\textsuperscript{20} as well as in vivo.\textsuperscript{21} In the present study, although plasma aldosterone concentration significantly increased after commissurotomy, there was no causal relation between plasma aldosterone concentration and hANP levels. It has been suggested that atrial stretch receptors exert a tonic inhibition of renin release.\textsuperscript{22} However, the neurally mediated activation of the renin-angiotensin system resulting from a decrease in the left atrial pressure seems unlikely because plasma renin activity did not change during PTMC. Therefore, neurohumoral factors other than the renin-angiotensin system and hANP may be involved in the mechanism of increased aldosterone secretion after PTMC. For example, stress-induced release of adrenocorticotropic hormone and proopi melanocortin-related peptides from the pituitary may stimulate aldosterone secretion.\textsuperscript{23} Alternatively, reflex-mediated decrease in dopaminergic activity may lead to diminished tonic inhibitory effect on aldosterone secretion.\textsuperscript{24}

In addition to the importance of the right atrial pressure on hANP secretion as demonstrated by Schwab et al.,\textsuperscript{17} the present study provides the direct evidence that the left atrial pressure also participates in the mechanism of hANP secretion in humans.

References


Key Words • plasma aldosterone concentration • plasma renin activity • plasma norepinephrine concentration • left atrial pressure
Rapid reduction of plasma atrial natriuretic peptide levels during percutaneous transvenous mitral commissurotomy in patients with mitral stenosis.
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Circulation. 1989;79:47-50
doi: 10.1161/01.CIR.79.1.47

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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