Journal of the American College of Cardiology
© 2001 by the American College of Cardiology
Published by Elsevier Science Inc.

Vol. 37, No. 7, 2001
ISSN 0735-1097/01/$20.00
PII S0735-1097(01)01233-5

Intravenous Atrial Natriuretic Peptide Prevents Left Ventricular Remodeling in Patients With First Anterior Acute Myocardial Infarction

Masaru Hayashi, MD, Takayoshi Tsutamoto, MD, Atsuyuki Wada, MD, Keiko Maeda, MD, Naoko Mabuchi, MD, Takashi Tsutsui, MD, Hajime Horie, MD, Masato Ohnishi, MD, Masahiko Kinoshita, MD

Otsu, Japan

OBJECTIVES The study evaluates the effect of atrial natriuretic peptide (ANP) compared with nitroglycerin (GTN) on left ventricular (LV) remodeling after first anterior acute myocardial infarction (AMI).

BACKGROUND Compared with GTN, ANP suppresses the renin-angiotensin-aldosterone system and endothelin-1 (ET-1), which stimulate LV remodeling.

METHODS Sixty patients with a first anterior AMI were randomly divided into the ANP (n = 30) or GTN (n = 30) groups after direct percutaneous transluminal coronary angioplasty. We evaluated LV ejection fraction (LVEF), end-diastolic volume index (LVEDVI) and end-systolic volume index (LVESVI) at the acute phase and after one month. We also measured neurohumoral factors during study drug infusion.

RESULTS There was no difference in the baseline characteristics or LVEF (46.9 ± 1.0 vs. 46.8 ± 1.3%) between the two groups. Although there was no difference in hemodynamics during the infusion periods, the LVEF was significantly improved after one month compared with the baseline value in both groups, but it was improved more in the ANP group than in the GTN group (54.6 ± 1.1%, 50.8 ± 1.3%, $p < 0.05$). Left ventricular enlargement was prevented in the ANP group (LVEDVI, 85.8 ± 3.1 ml/m^2 to 87.3 ± 2.7 ml/m^2; p = ns, LVESVI, 45.6 ± 1.8 ml/m^2 to 41.0 ± 2.1 ml/m^2, $p < 0.05$) but not in the GTN group (LVEDVI, 86.2 ± 4.1 to 100.2 ± 3.7, $p < 0.01$; LVESVI, 46.3 ± 2.8 ml/m^2 to 51.1 ± 3.0 ml/m^2, p = ns). During the infusion, ANP suppressed plasma levels of aldosterone, angiotensin II and ET-1 compared with GTN.

CONCLUSIONS These findings indicate that in patients with a first anterior AMI, an ANP infusion can prevent LV remodeling better than can GTN, and effectively suppresses aldosterone, angiotensin II and ET-1. (J Am Coll Cardiol 2001;37:1820–6) © 2001 by the American College of Cardiology

Previous studies demonstrated that left ventricular (LV) remodeling was one of the major factors for determining long-term survival after an acute myocardial infarction (AMI) (1). Therefore, it is important to prevent LV remodeling to get a better clinical outcome and prognosis in patients with AMI. In the acute phase of AMI, nitroglycerin (GTN) has been reported to have a favorable effect in preventing LV remodeling (2). However, GTN may stimulate the renin-angiotensin-aldosterone system despite its beneficial hemodynamic effect (3). In contrast, atrial natriuretic peptide (ANP) has been demonstrated to suppress the renin-angiotensin-aldosterone system and endothelin-1 (ET-1) (4–8), which stimulate LV remodeling.

Recently, endogenous cardiac natriuretic peptides were reported to have a direct effect in inhibiting myocardial hypertrophy through the biological receptors on the myocardium (9). Moreover, the secretion of ANP during the acute phase of AMI may be insufficient relative to the chronic phase (10). If so, augmentation of the cardiac natriuretic peptide system, such as by exogenous administration of ANP, may be a useful supplementary therapy for preventing LV remodeling because of the cardioprotective actions of ANP (9,11), such as suppression of the renin-angiotensin-aldosterone system (4–8). Thus, we believe that the intravenous administration of ANP in patients with AMI may prevent LV dilation and remodeling after AMI.

METHODS

Study population. From December 1997 through August 2000, 65 patients admitted to the coronary care units of our institutions with a first anterior AMI who presented with Thrombolysis In Myocardial Infarction (TIMI) grade 0 or 1 flow at initial coronary angiography were considered for the study. Admission criteria included prolonged chest pain (>30 min), an electrocardiographic ST segment elevation >2 mV in two or more adjacent precordial leads, successful

From the First Department of Internal Medicine, Shiga University of Medical Science, Tsukinowa, Seta, Otsu, Japan. This study was partly supported by a Japanese Grant-in-Aid for Scientific Research.

Manuscript received November 1, 2000; revised manuscript received January 30, 2001, accepted February 15, 2001.

Abbreviations and Acronyms

ALD	= aldosterone
AMI	= acute myocardial infarction
Ang II	= angiotensin II
ANP	= atrial natriuretic peptide
BNP	= brain natriuretic peptide
cGMP	= cyclic guanosine monophosphate
CK	= creatine phosphokinase
ET-1	= endothelin-1
GTN	= nitroglycerin
LV	= left ventricular
LVEDVI	= left ventricular end-diastolic volume index
LVEF	= left ventricular ejection fraction
TIMI	= Thrombolysis In Myocardial Infarction

reperfusion therapy within 24 h of the onset of chest pain documented by coronary angiography and more than a threefold increase in serum creatine phosphokinase levels. Patients were excluded for the following reasons: age >80 years; cardiogenic shock or hypotension, defined as systolic blood pressure <90 mm Hg; prior myocardial infarction; treatment with an oral angiotensin-converting enzyme inhibitor within the previous two weeks; LV end-diastolic pressure >35 mm Hg or significant stenosis of the infarct-nonrelated coronary artery. All patients gave informed consent, and the study was approved by the Committee on Human Investigation at our institution.

Study design and protocol. This was a prospective randomized study. Sixty-five patients were randomly divided into two groups, ANP or GTN. All patients underwent cardiac catheterization with the femoral approach after an injection of 100 U/kg of heparin. The infarct-related artery was visualized in five views with contrast injections, and patency was determined according to the classification of the TIMI trial. Patients who had persistent occlusion of the infarct-related vessel (TIMI grade 0 or 1) underwent percutaneous transluminal coronary angioplasty following standard techniques. After revascularization (TIMI grade 3), biplane left ventriculography was performed. After angioplasty, all patients received oral aspirin and/or ticlopidine. If required, oral calcium antagonists, beta-adrenergic blocking agents and/or diuretics were added and continued. However, angiotensin-converting enzyme inhibitors and nitrates were inhibited while patients were undergoing continuous administration of ANP or GTN infusion.

Just after patients' arriving in the coronary care unit with hemodynamic stability assured (two measurements at 15-min interval), ANP or GTN infusion was started at 0.025 μg/kg/min (ANP case) or 0.4 μg/kg/min (GTN case). Continuous measurements of hemodynamic parameters such as arterial blood pressure, heart rate, cardiac output and pulmonary artery blood pressure were obtained. If the systolic arterial blood pressure was high (>150 mm Hg) or low (<90 mm Hg) within 30 min of starting the infusion, doses of ANP and GTN were changed to maintain constant blood pressure, then ANP or GTN was continuously infused for >24 h. After intravenous ANP or GTN was stopped, all patients were administrated oral angiotensin-converting enzyme inhibitor (enalapril). Repeat cardiac catheterization was performed one month after the initial catheterization to determine culprit artery patency and LV function. Patients with significant restenosis of the culprit lesion were excluded from the study.

Hemodynamic measurements. Left ventriculography performed by contrast medium was analyzed for LVEF and LV volume by cardiologists who were unaware of the patients' data at acute phase and after one month. Left ventricular ejection fraction was calculated by the area-length method. The hemodynamic measurements of pulmonary arterial blood pressure, pulmonary capillary wedge pressure, right atrial pressure, cardiac output (thermodilution method) arterial blood pressure and heart rate were made before administering the ANP or GTN infusion, 1 h after starting the infusion and just before stopping the infusion.

Neurohumoral measurements. Blood for the measurements of plasma levels of active renin, angiotensin II (Ang II), aldosterone (ALD), ET-1, norepinephrine, ANP, brain natriuretic peptide (BNP) and cyclic guanosine monophosphate (cGMP) was obtained just before intravenous ANP or GTN treatment, 1 h after starting the treatment and just before stopping the infusion. Plasma level of ANP and BNP was measured with a specific immunoradiometric assay using commercial kits (Shionogi, Osaka, Japan) as previously reported (12). The plasma ET-1 level was determined using an antibody directed against synthetic ET-1 (Peninsula Laboratories, Inc., Belmont, California) and ^{125}I ET-1 (Amersham Japan, Tokyo, Japan) as previously reported (13). Plasma cGMP levels were measured by radioimmunoassay with a commercial kit as previously reported (12). Plasma norepinephrine concentrations were measured by high-performance liquid chromatography. Plasma Ang II levels were measured by a radioimmunoassay using a specific antibody directed against synthetic Ang II (Special Research Laboratory, Tokyo, Japan) as previously reported (13). Plasma active renin and ALD levels were measured using commercial radioimmunoassay kits.

Statistical analysis. All results are expressed as mean ± SEM. Univariate analyses were performed using Student *t* test for continuous variables. Categorical data were compared against a chi-squared distribution. In patients who underwent repeat hemodynamic, neurohumoral and LV functional assessment, changes from baseline were evaluated within each treatment group with analysis of variance by Scheffé F test and between the ANP and GTN groups by two-way analysis of variance. A p-value <0.05 was regarded as significant.

RESULTS

Clinical characteristics (Table 1). Sixty-five consecutive patients who met entry criteria were enrolled. Thirty-three patients were randomized to GTN treatment and 32 to

Table 1. Baseline Characteristics

	ANP (n = 30)	GTN (n = 30)	p Value
Age (yrs)	60.9 ± 1.9	59.4 ± 2.1	n.s.
Gender (male/female)	19/11	21/9	n.s.
Symptom onset-reflow time (h)	5.2 ± 0.9	5.1 ± 0.8	n.s.
Max CK (IU/ml)	3322 ± 388	3518 ± 332	n.s.
LV function and volumes			
LVEF (%)	46.9 ± 1.0	46.7 ± 1.3	n.s.
LVEDVI (ml/m^2)	85.8 ± 3.1	86.2 ± 4.1	n.s.
LVESVI (ml/m^2)	45.6 ± 1.8	46.3 ± 2.8	n.s.
Collateral (grade >2)	7	4	n.s.
Risk factors			
Smoking	15	18	n.s.
Hypertension	8	9	n.s.
Hyperlipidemia	11	13	n.s.
Diabetes mellitus	14	14	n.s.
In-hospital therapy			
Catecholamine	5	7	n.s.
IABP	2	3	n.s.
Oral nitrates	28	27	n.s.
Ca antagonists	7	5	n.s.
Diuretics	3	4	n.s.
Beta-blockers	7	8	n.s.
Enalapril dose (mg)	9.1 ± 0.4	10.1 ± 0.4	n.s.
Infusion time of study drug (h)	61.5 ± 5.6	64.0 ± 4.9	n.s.
Study drug dose (μg/kg/min)	0.028 ± 0.002	0.476 ± 0.04	—

ANP = atrial natriuretic peptide; CK = creatine phosphokinase; GTN = nitroglycerin; IABP = intra-aortic balloon pumping; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; n.s. = not stated.

ANP treatment. In the GTN group, one patient had a cerebral hemorrhage, one died from lethal arrhythmia, and one was excluded because of restenosis in the culprit lesion. In the ANP group, one patient died eight days after congestive heart failure and one was excluded because of restenosis. Therefore, 60 of 65 patients enrolled in the trial completed the entire protocol. The average infusion dose was 0.028 ± 0.002 μg/kg/min in the ANP group (n = 30) and 0.48 ± 0.04 μg/kg/min in the GTN group (n = 30), respectively. There was no difference of baseline characteristics, including maximum levels of creatine phosphokinase (CK) and duration of infusion time, between the ANP group and the GTN group (Table 1). There was also no difference of therapy including the doses of enalapril between the two groups.

Hemodynamic parameters (Table 2). There was no difference in hemodynamic parameters at baseline between the two groups. Moreover, there were no significant differences between the two groups in these hemodynamic parameters after 1 h and before stopping the infusion of GTN or ANP. Serial changes of mean arterial blood pressure, pulmonary capillary wedge pressure and mean pulmonary arterial pressure, which were significantly decreased after 1 h and decreased versus baseline values until the end of infusion, were similar in both groups.

LV volume and function (Fig. 1, Table 3). There was no difference in LVEF at baseline, and it was significantly increased in both groups after one month as shown in Figure 1 and Table 3, but the increase in LVEF with ANP was greater than with GTN. The change in LVEF of the ANP group was significantly higher than that of the GTN group (7.70 ± 1.3%, 4.08 ± 1.1%, $p < 0.05$), and LVEF at one month in the ANP group was significantly higher than that in the GTN group. There was no difference in LVEDVI at baseline. However, in the GTN group the LVEDVI was significantly increased whereas LVEDVI did

Table 2. Hemodynamic Changes During the Study Drug Infusion

				p Value (analysis of variance)		
	Baseline	1 h	Before Stop	Group	Time	Interaction
HR (beats/min)						
ANP	79.2 ± 2.4	78.5 ± 2.4	75.7 ± 1.9	n.s.	n.s.	n.s.
GTN	78.2 ± 2.1	80.4 ± 2.0	79.1 ± 2.3			
MBP (mm Hg)						
ANP	93.0 ± 1.9	87.8 ± 2.0*	85.0 ± 1.0†	n.s.	<0.0001	n.s.
GTN	91.3 ± 2.0	87.2 ± 1.9‡	86.1 ± 1.3*			
CI (l/min/m^2)						
ANP	2.82 ± 0.17	2.80 ± 0.15	2.55 ± 0.09‡	n.s.	0.003	n.s.
GTN	2.75 ± 0.10	2.74 ± 0.08	2.66 ± 0.07			
PCWP (mm Hg)						
ANP	16.0 ± 0.8	13.5 ± 0.7§	11.5 ± 0.7†	n.s.	<0.0001	n.s.
GTN	16.5 ± 0.8	14.1 ± 1.0*	13.2 ± 0.8§			
MPA (mm Hg)						
ANP	19.8 ± 0.8	16.2 ± 0.7†	13.7 ± 0.5†	n.s.	<0.0001	n.s.
GTN	20.0 ± 1.2	17.0 ± 1.1*	14.4 ± 0.7†			
RA (mm Hg)						
ANP	6.3 ± 0.4	5.6 ± 0.4	5.6 ± 0.4	n.s.	<0.0001	n.s.
GTN	6.8 ± 0.5	6.2 ± 0.5	5.5 ± 0.4*			

*$p < 0.01$, †$p < 0.0001$, ‡$p < 0.05$, §$p < 0.001$: difference between baseline and 1 h or before stop within each group.

ANP = atrial natriuretic peptide; CI = cardiac index; GTN = nitroglycerin; HR = heart rate; MBP = mean arterial blood pressure; MPA = mean pulmonary arterial pressure; n.s. = not stated; PCWP = pulmonary capillary wedge pressure; RA = right atrial pressure.

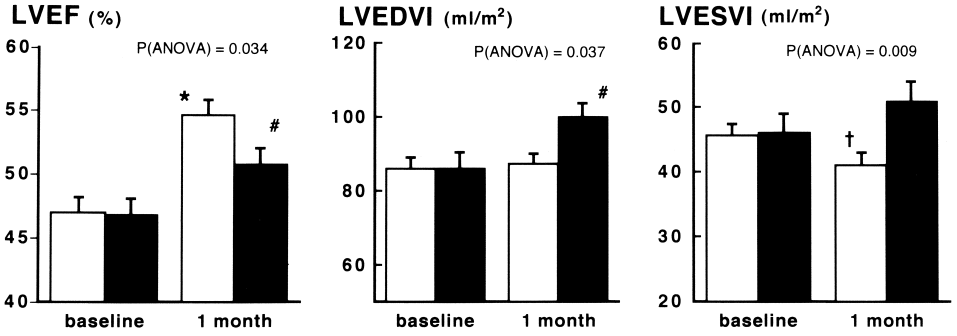

Figure 1. Changes in the ejection fraction (EF), left ventricular end-diastolic volume index (LVEDVI) and left ventricular end-systolic volume index (LVESVI) in the two randomized treatment groups from baseline to one month after. P(ANOVA) indicates the p value for time-group interaction. The **white bars** indicate the ANP group and the **black bars** the GTN group. *$p < 0.001$: difference between baseline and one-month values (within each group), †$p < 0.05$, #$p < 0.01$.

not change in the ANP group. Atrial natriuretic peptide but not GTN prevented the increase in LVEDVI. There was no difference of LVESVI at baseline, and LVESVI tended to increase in the GTN group but was significantly decreased in the ANP group. The changes in LVEDVI (1.50 ± 3.5 ml/m^2 vs. 14.0 ± 4.7 ml/m^2: $p < 0.05$) and LVESVI (-4.57 ± 2.0 ml/m^2 vs. 4.87 ± 2.8 ml/m^2: $p < 0.01$) were significantly smaller in the ANP group than in the GTN group.

Comparison of plasma neurohumoral factors during the infusion of GTN or ANP. At baseline, there were no significant differences between the two groups in plasma levels of ANP, BNP and cGMP (Table 4). Plasma levels of ANP and cGMP were increased after 1 h and increased compared with the baseline value during infusion in the ANP group but not in the GTN group. There was no difference of plasma ANP levels at 1 h and before stopping, but the plasma cGMP level was significantly lower before stopping compared with the value after 1 h.

At baseline, there was no significant difference in plasma levels of norepinephrine, active renin, Ang II, ALD or ET-1 between the two groups (Fig. 2, Table 4). After 1 h of infusion, the plasma ALD level was significantly suppressed in the ANP group. Plasma levels of Ang II, ALD and ET-1 were significantly suppressed in the ANP group compared with the GTN group. On the other hand, plasma norepinephrine and active renin levels were not different between the two groups during the infusion periods.

DISCUSSION

Our findings demonstrate for the first time that treatment with an ANP infusion started immediately from the onset after direct percutaneous transluminal coronary angioplasty can prevent LV dilation more effectively than GTN and better improve the LVEF in patients with a first anterior AMI.

Although there was no difference in the baseline characteristics, including the maximum level of CK and LVEF, and there was no difference in hemodynamics between the two groups during the infusion periods, LVEF and LVEDVI were more improved in the ANP group than the GTN group. Moreover, plasma levels of ALD, Ang II and ET-1 were suppressed in the ANP group compared with the GTN group. These findings indicate that treatment with an ANP infusion can prevent LV remodeling in patients with a first anterior AMI compared with GTN partly due to the suppression of ALD, Ang II and ET-1.

Dose setting of ANP or GTN. We chose an ANP starting dose of 0.025 μg/kg/min because in our preliminary study, a reduction of the preload and blood pressure had a mild acute effect; the more preload and afterload reduction the more varoreflex activation, which diminished the beneficial effects of suppressing sympathetic nerve activity and the renin-angiotensin-aldosterone system. Then, we chose the starting dose of GTN at a comparative dose to decrease the preload. As a result, the plasma level of ANP increased within the pathophysiologic range that is observed in severe heart failure (12), and the acute effects of ANP and GTN on hemodynamic parameters were the same.

Table 3. Changes in LVEF, EDVI and ESVI from Baseline to One Month

	ANP (n = 30)		GTN (n = 30)		p Value (analysis of variance)		
	Baseline	One Month	Baseline	One Month	Group	Time	Interaction
LVEF (%)	46.9 ± 1.0	54.6 ± 1.1*	46.8 ± 1.3	50.8 ± 1.3†	n.s.	<0.0001	0.034
LVEDVI (ml/m^2)	85.8 ± 3.1	87.3 ± 2.7	86.2 ± 4.1	100.2 ± 3.7†	n.s.	0.011	0.037
LVESVI (ml/m^2)	45.6 ± 1.8	41.0 ± 2.1‡	46.3 ± 2.8	51.1 ± 3.0	n.s.	n.s.	0.009

*$p < 0.001$, †$p < 0.01$, ‡$p < 0.05$: difference between baseline and one-month values (within each group).
ANP = atrial natriuretic peptide; EDVI = end-diastolic volume index; ESVI = end-systolic volume index; GTN = nitroglycerin; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; n.s. = not stated.

Table 4. Changes in the Neurohumoral Factors During the Study Drug Infusion

	ANP (n = 30)			GTN (n = 30)			p Value (analysis of variance)		
	Baseline	1 h	Before Stop	Baseline	1 h	Before Stop	Group	Time	Interaction
ANP (pg/ml)	60.3 ± 7.8	473 ± 59*	483 ± 57*	70 ± 11	53 ± 8	90 ± 31	<0.0001	<0.0001	<0.0001
BNP (pg/ml)	156 ± 35	215 ± 41†	209 ± 35	140 ± 30	161 ± 38	219 ± 41†	n.s.	0.012	n.s.
cGMP (pmol/l)	6.7 ± 0.7	21.2 ± 1.6*	14.3 ± 1.0*	7.5 ± 0.7	6.0 ± 0.7	6.5 ± 0.8	<0.0001	<0.0001	<0.0001
NE (pg/ml)	456 ± 40	480 ± 40	431 ± 39	575 ± 118	576 ± 82	465 ± 48	n.s.	n.s.	n.s.
PARC (pg/ml)	37.9 ± 13.0	35.0 ± 12.8	30.0 ± 7.3	38.6 ± 12.1	43.1 ± 17.9	42.9 ± 10.6	n.s.	n.s.	n.s.
Ang II (pg/ml)	10.4 ± 2.0	9.6 ± 1.7	9.0 ± 0.9	7.5 ± 0.6	12.4 ± 3.8	17.9 ± 3.2‡	n.s.	0.025	0.002
ALD (pg/ml)	67.6 ± 9.3	44.8 ± 4.6†	37.9 ± 7.5‡	65.5 ± 8.9	78.4 ± 13.5	67.1 ± 8.4	n.s.	0.048	0.012
ET-1 (pg/ml)	4.37 ± 0.28	4.06 ± 0.32	2.38 ± 0.13*	4.23 ± 0.34	4.84 ± 0.44	3.34 ± 0.27	n.s.	<0.0001	0.049

*$p < 0.0001$, †$p < 0.05$, ‡$p < 0.01$ vs. baseline values (within each group).
ALD = aldosterone; Ang II = angiotensin II; ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; cGMP = cyclic guanosine monophosphate; ET-1 = endothelin-1; NE = norepinephrine; n.s. = not stated; PARC = plasma active renin concentration.

Possible mechanism of beneficial effects of ANP on LV remodeling. Because ANP has an inhibitory effect on sympathetic nerve activity (14), we hypothesized that the indexes of sympathetic nerve activity were different during infusion periods between the two groups. However, there was no difference of plasma norepinephrine or heart rates, which was probably because of the relatively small dose of ANP or GTN and the slight reduction of the mean arterial blood pressure in this study.

In our study, the plasma levels of ALD, Ang II and ET-1 were significantly suppressed in the ANP group compared with the GTN group. Especially, the plasma ALD level was significantly decreased after 1 h and suppressed during the infusion of ANP. Aldosterone levels have been found to be increased in patients with AMI, and aldosterone shows both myocardial and renal effects that may have profound implications for LV remodeling (15,16). We recently reported that plasma ALD is extracted through the heart in patients with heart failure, and that a positive correlation exists between the transcardiac gradient of ALD, which correlates with plasma ALD level, and LVEDVI. We also demonstrated that transcardiac ALD extraction is an important modulator of LV remodeling (17). In this earlier study, 60% of the population consisted of old myocardial infarctions. Therefore, the significant suppression of plasma ALD by ANP compared with that by GTN may have passively prevented LV remodeling in the present study. In rat models, after myocardial infarction, tissue-specific activation of myocardial ALD synthesis was reported (18). Aldosterone has been shown to stimulate cardiac collagen synthesis and fibroblast proliferation via activation of local mineralocorticoid receptors (19). Atrial natriuretic peptide

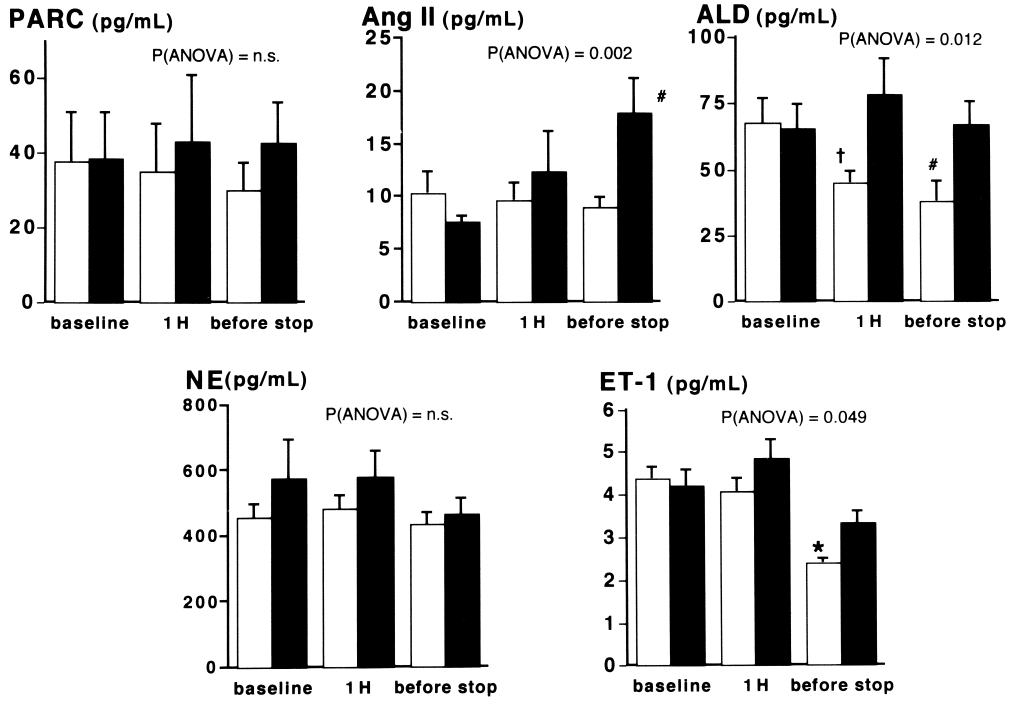

Figure 2. Effects of intravenous atrial natriuretic peptide (ANP) and nitroglycerin (GTN) on norepinephrine (NE), plasma active renin concentration (PARC), angiotensin II (Ang II), aldosterone (ALD) and endothelin-1 (ET-1). P(ANOVA) indicates the p value for time-group interaction. **White bars** indicate ANP group and **black bars** the GTN group. Baseline and 1 H indicate just before and after 1 H starting ANP or GTN. Before stop indicates just before stopping ANP or GTN. †$p < 0.05$, #$p < 0.01$, *$p < 0.001$, §$p < 0.0001$: difference between baseline and before stop values (within each group).

directly inhibits ALD secretion (7) and attenuates the stimulatory effect of Ang II on ALD release (6). The great success of spironolactone for the treatment of heart failure suggests the important role of ALD on the progression of LV remodeling and LV dysfunction (20). Therefore, the beneficial effect of ANP on the LV remodeling is partly due to the suppression of the plasma ALD level.

The significant reductions of plasma Ang II and ET-1 in the ANP group compared with the GTN group may also have beneficial effects on LV remodeling because of the important role of myocardial hypertrophy and the LV remodeling process via a direct effect and/or interaction (21,22). The previous study demonstrated that Ang II and ALD each play a role in promoting structural remodeling of the myocardium. Although fibrosis was seen in ventricles in each model, combined elevation in the circulating Ang II and ALD more rapidly induced fibrous tissue response than elevation of plasma ALD (23). In the present study, ANP significantly suppressed plasma levels of both Ang II and ALD, so this effect of ANP may play a role in preventing LV remodeling in the ANP group. Exposure of myocardial fibroblasts to Ang II in a cell culture produces a mitogenic effect, apparently triggered by immediate early gene expression, with increased proliferation and collagen synthesis (24). Atrial natriuretic peptide inhibits Ang II-stimulated proliferation of cardiac fibroblast (25).

Regarding ET-1 in patients with AMI, ET-1 levels increase and their elevation is associated with infarct size and a poor prognosis (26). In infarcted rat models, ET-1 promotes LV fibrosis, and remodeling and ventricular remodeling were prevented and cardiac function improved by blocking the endothelin receptors (27,28). Atrial natriuretic peptide has been shown to inhibit the biosynthesis and release of ET-1 (8). We demonstrated that elevated circulating ET-1 is extracted across the failing heart in patients with heart failure, of which 73% had old myocardial infarction, and that there is positive correlation between the transcardiac extraction of plasma ET-1 and the LVEDVI. The transcardiac gradient of plasma ET-1 correlated with the plasma level (29). Taken together, therefore, the effect of ANP in decreasing plasma ET-1 may also have contributed to the prevention of ventricular remodeling in the present study.

Finally, ANP has been demonstrated to play a role in the regulation of cardiac myocyte growth because endogenous ANP inhibits myocyte hypertrophy (9) and cardiac fibroblast collagen synthesis (11) through a cGMP-dependent process. Therefore, exogenous ANP may have direct effect on LV remodeling through biological receptors on the myocardium.

Study limitations. In this study, patients with high LV end-diastolic pressure (>35 mm Hg) were excluded for ethical reasons to avoid performing left ventriculography at the acute phase. Therefore, patients with very severe and large infarctions may have been excluded from this study population. Pfeffer et al. (30) reported that treatment effects appeared to be highest in patients with intermediate-sized infarcts, and also demonstrated that the greatest treatment benefit of captopril occurred in medium-sized infarcts in rat infarct models after long-term follow-up. In the Captopril and Thrombolysis Study, captopril was effective in preventing LV remodeling in those with small and medium infarcts (31). In the present study, it may have influenced the results of ANP because those with very severe and large infarcts were excluded.

Conclusions. The findings of the present study demonstrate that treatment with an ANP infusion started immediately after direct PTCA can prevent LV dilation and improve LVEF in patients with a first anterior AMI. The mechanism of the beneficial effects remains uncertain, but the effects of ANP may be partly due to the suppression of plasma levels of ALD, Ang II and ET-1.

Acknowledgments

We thank Iwao Mashiro, MD, Masanori Fujii, MD, Tomohiro Doke, MD, Katsuzo Yamaguchi, MD, Takako Murata, MD and Naoki Morigami, MD for their advice in the study protocol. We also thank Ms. Ikuko Sakaguchi for her excellent technical assistance, and Mr. Daniel Mrozek for his assistance in preparing the manuscript.

Reprint requests and correspondence: Dr. Takayoshi Tsutamoto, First Department of Internal Medicine, Shiga University of Medical Science, Tsukinowa, Seta, Otsu 520-2192, Japan. E-mail: tutamoto@belle.shiga-med.ac.jp.

REFERENCES

1. Hammermeister KE, DeRouen TA, Dodge HT. Variables predictive of survival in patients with coronary artery disease: selection by univariate and multivariate analysis from the clinical, electrocardiographic, exercise, arteriographic, and quantitative angiographic evaluations. Circulation 1979;59:421–30.
2. Jugdutt BI, Warnica LW. Intravenous nitroglycerin therapy to limit myocardial infarction size, expansion and complications: effect of timing, dosage and infarct location. Circulation 1988;78:906–19.
3. Kosuge M, Miyajima E, Kimura K, Ishikawa T, Tochikubo O, Ishii M. Comparison of atrial natriuretic peptide versus nitroglycerin for reducing blood pressure in acute myocardial infarction. Am J Cardiol 1998;81:781–4.
4. Scriven TA, Burnett JC, Jr. Effects of synthetic atrial natriuretic peptide on renal function and renin release in acute experimental heart failure. Circulation 1985;72:892–7.
5. Cody RJ, Atlas SA, Laragh JH, et al. Atrial natriuretic factor in normal subjects and heart failure patients: plasma levels and renal, hormonal, and hemodynamic responses peptide infusion. J Clin Invest 1986;78: 1362–74.
6. Brans MW, Freeman RH. Aldosterone and renin inhibition by physiological levels of atrial natriuretic factor. Am J Physiol 1988;254: R1011–6.
7. Wada A, Tsutamoto T, Matsuda Y, Kinoshita M. Cardiorenal and neurohumoral effects of endogenous atrial natriuretic peptide in dogs with severe congestive heart failure using a specific antagonist for guanylate cyclase-coupled receptors. Circulation 1994;89:2232–40.
8. Emori T, Hirata H, Imai T, Eguchi S, Kanno K, Marumo F. Cellular mechanism of natriuretic peptide-induced inhibition of endothelin-1 biosynthesis in rat endothelial cells. Endocrinology 1993;133:2474–80.
9. Horio H, Nishikimi T, Yoshihara F, et al. Inhibitory regulation of

hypertrophy by endogenous atrial natriuretic peptide in cultured cardiac myocytes. Hypertension 2000;35:19–24.
10. Maeda K, Tsutamoto T, Wada A, et al. Insufficient secretion of atrial natriuretic peptide at acute phase of myocardial infarction. J Appl Physiol 2000;89:458–64.
11. Redondo J, Bishop JE, Wilkins MR. Effect of atrial natriuretic peptide and cyclic GMP phosphodiesterase inhibition on collagen synthesis by adult cardiac fibroblasts. Br J Pharmacol 1998;124:1455–62.
12. Tsutamoto T, Wada A, Maeda K, et al. Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure: prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. Circulation 1997;96:509–16.
13. Tsutamoto T, Wada A, Hisanaga T, et al. Relationship between endothelin-1 extraction in the peripheral circulation and systemic vascular resistance in patients with severe congestive heart failure. J Am Coll Cardiol 1999;33:530–7.
14. Takeshita A, Imaizumi T, Nakamura N, et al. Attenuation of reflex forearm vasoconstriction by alpha human atrial natriuretic peptide in men. Circ Res 1987;61:555–9.
15. White PC. Disorders of aldosterone biosynthesis and action. N Engl J Med 1994;331:250–8.
16. Weber KT, Sun Y, Campbell SE, et al. Chronic mineralocorticoid excess and cardiovascular remodeling. Steroids 1995;60:125–32.
17. Tsutamoto T, Wada A, Maeda K, et al. Spironolactone inhibits the transcardiac extraction of aldosterone in patients with congestive heart failure. J Am Coll Cardiol 2000;36:838–44.
18. Silvestre JS, Heymes C, Oubenaissa A, et al. Activation of cardiac aldosterone production in rat myocardial infarction: effect of angiotensin II receptor blockade and role in cardiac fibrosis. Circulation 1999;99:2694–701.
19. Weber KT, Brilla CG. Pathological hypertrophy and cardiac interstitium: fibrosis and renin angiotensin aldosterone system. Circulation 1991;83:1849–65.
20. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999;341:709–17.
21. Harada K, Sugaya T, Murakami K, Yazaki Y, Komuro I. Angiotensin II type 1A receptor knockout mice display less left ventricular remodeling and improved survival after myocardial infarction. Circulation 1999;100:2093–9.
22. Ito H, Hirata Y, Adachi S, et al. Endothelin-1 is an autocrine/paracrine factor in the mechanism of angiotensin II-induced hypertrophy in cultured rat cardiomyocytes. J Clin Invest 1993;92:398–403.
23. Sun Y, Ratajska A, Zhou G, Weber KT. Angiotensin converting enzyme and myocardial fibrosis in the rat receiving angiotensin II or aldosterone administration. J Lab Clin Med 1993;122:395–403.
24. Brilla CG, Zhou G, Matsubara L, Weber KT. Collagen metabolism in cultured adult rat cardiac fibroblasts: response to angiotensin II and aldosterone. J Mol Cell Cardiol 1994;15:809–20.
25. Fujisaki H, Ito H, Hirata Y, et al. Natriuretic peptides inhibit angiotensin II-induced proliferation of rat cardiac fibroblasts by blocking endothelin-1 gene expression. J Clin Invest 1995;96:1059–65.
26. Omland T, Lie RT, Aakvaag A, Aarsland T, Dickstein K. Plasma endothelin determination as a prognostic indicator of 1-year mortality after acute myocardial infarction. Circulation 1994;89:1573–9.
27. Guarda E, Katwa LC, Myers PR, Tyagi SC, Weber KT. Effects of endothelins on collagen turnover in cardiac fibroblasts. Cardiovasc Res 1993;27:2130–4.
28. Fraccarollo D, Hu K, Galuppo P, Gaudron P, Ertl G. Chronic endothelin receptor blockade attenuates progressive ventricular dilation and improves cardiac function in rat with myocardial infarction: possible involvement of myocardial endothelin system in ventricular remodeling. Circulation 1997;96:3963–73.
29. Tsutamoto T, Wada A, Maeda K, et al. Transcardiac extraction of circulating endothelin-1 across the failing heart. Am J Cardiol 2000; 86:254–8.
30. Pfeffer MA, Pfeffer JM, Steinberg C, Finn P. Survival after an experimental myocardial infarction: beneficial effect of long-term therapy with captopril. Circulation 1985;72:406–12.
31. van GilstWH, Kingma JH, Peels KH, Dambrink JH, St. John Sutton M. Which patient benefits from early angiotensin-converting enzyme inhibitor after myocardial infarction? Results of one-year serial echocardiographic follow-up from the Captopril And Thrombolysis Study (CATS). J Am Coll Cardiol 1996;28:114–21.