

## Comparison of Secretion Pattern Between A-Type and B-Type Natriuretic Peptides in Patients With Old Myocardial Infarction

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**Objectives.** The present study was designed to compare the secretion patterns of two cardiac hormones—A-type (atrial) and B-type (brain) natriuretic peptides—from the ventricles in patients with old myocardial infarction.

**Background.** Plasma levels of these two natriuretic peptides are increased, and their secretion from the ventricles is augmented, in patients with congestive heart failure.

**Methods.** We measured the plasma levels of these two types of natriuretic peptides at the aortic root and the anterior interventricular vein in 42 patients with old myocardial infarction (anterior in 22 and inferior in 20) and 18 control subjects.

**Results.** The difference between the plasma levels of both A- and B-type natriuretic peptide in the anterior interventricular vein and aortic root was significantly greater in the groups with anterior and inferior infarction than in the control group (A-type [mean  $\pm$  SD]  $380 \pm 290$  and  $247 \pm 205$  pg/ml in the infarction groups vs.  $11 \pm 14$  pg/ml; B-type  $497 \pm 445$  and  $75 \pm 73$  pg/ml vs.

$23 \pm 16$  pg/ml, respectively). The difference between the plasma levels of each peptide at the anterior interventricular vein and aortic root had a significant negative linear correlation with left ventricular ejection fraction in both groups with infarction. The slope of the regression line of the arteriovenous difference of B-type natriuretic peptide at the anterior interventricular vein was significantly steeper in the anterior than in the inferior infarction group (left ventricular ejection fraction  $-12.801$  vs.  $-1.891$ ,  $p < 0.01$ ).

**Conclusions.** These results indicate that 1) the secretion of A- and B-type natriuretic peptide from the left ventricle increases in proportion to the severity of left ventricular dysfunction, and 2) secretion of B-type natriuretic peptide is much greater from the infarct than from the noninfarct region, suggesting that the regional ventricular wall stretch caused by infarction strongly stimulates secretion of B-type natriuretic peptide.

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A-type (atrial) natriuretic peptide is a hormone with a wide range of biologic effects, including natriuresis, diuresis, vasodilation and inhibition of the renin-angiotensin-aldosterone and sympathetic nervous systems (1-6). A-type natriuretic peptide is mainly synthesized in and secreted from the atria in adult mammals and its plasma levels are increased in patients with congestive heart failure (1-5,7-10). We and others (11-15) have shown that A-type natriuretic peptide is also synthesized in and secreted from the ventricles in patients with congestive heart failure, and the amount secreted has a positive correlation with left ventricular dysfunction in dilated cardiomyopathy (11-15).

B-type (brain) natriuretic peptide, first isolated from a

porcine brain (16) and subsequently from human hearts (17), forms a peptide family with A-type natriuretic peptide and may be involved in the regulation of blood pressure and fluid volume. The plasma levels of B-type natriuretic peptide are markedly increased in patients with congestive heart failure (17-20) and in those with acute myocardial infarction (21,22). B-type natriuretic peptide is reported to be mainly synthesized in and secreted from the ventricles (17,23). However, the precise mechanisms of the secretion of A-type and B-type natriuretic peptides in living humans is not known.

We (7,13,15) have shown that A-type natriuretic peptide is released into the general circulation mainly by way of the coronary sinus. Because the anterior interventricular vein drains blood mainly from the left anterior ventricle (24-26), the difference between plasma levels of A- and B-type natriuretic peptide in the anterior interventricular vein and the aortic root reflects the amount of the peptides released mainly from the anterior ventricle.

The present study was designed to examine the sites and mechanism of the secretion of A- and B-type natriuretic peptides from the anterior ventricle by sampling blood for these peptides from the aortic root, anterior interventricular

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**Table 1.** Clinical Characteristics of the Patients With Old Myocardial Infarction

	Anterior MI (n = 22)	Inferior MI (n = 20)
Age (yr) (mean; range)	64; 46-80	64; 45-75
M/F ratio	17/5	17/3
NYHA class		
I/II	7/7	13/3
III/IV	6/2	4/0
Drug therapy		
Aspirin	22	19
Calcium channel blockers	16	15
Alone	2	3
With nitrates	6	9
With nitrates, beta-blockers	3	1
With nitrates, ACEI	3	2
With nitrates, ACEI, diuretic drugs	2	0
Nitrates without calcium channel blockers	3	0
Alone	1	0
With ACEI	2	0

Unless otherwise indicated, all data are expressed as number of patients. ACEI = angiotensin-converting enzyme inhibitor; Anterior MI = patients with old anterior myocardial infarction; F = female; Inferior MI = patients with old inferior myocardial infarction; M = male; NYHA class = New York Heart Association functional class.

vein and coronary sinus in patients with old myocardial infarction and control subjects.

## Methods

**Patients.** Three groups of patients were studied: patients with anterior or inferior old myocardial infarction and a control group.

*Patients with old myocardial infarction.* The clinical characteristics of the 42 patients with old myocardial infarction are shown in Table 1. Diagnostic cardiac catheterization, performed  $\geq 1$  month after the onset of infarction (mean 65 days, range 31 to 375), revealed that the infarct-related artery was the left anterior descending coronary artery in the patients with anterior infarction and the right coronary artery in those with inferior infarction. The infarct region was also assessed by left ventriculography and thallium-201 myocardial scintigraphy.

In all patients, angiotensin-converting enzyme inhibitors were withdrawn 3 to 5 days before the study; all other drugs were withheld  $\geq 1$  day before the study.

*Control group.* The control group comprised 18 patients (11 men and 7 women with a mean age of 62 years [range 46 to 74]) in whom diagnostic cardiac catheterization including coronary angiography and left ventriculography was performed and insertion of a catheter into the anterior interventricular vein was possible. Nine control patients had atypical chest pain syndrome with normal coronary arteriographic findings and nine had stable angina pectoris. None had old myocardial infarction, cardiac hypertrophy or other heart muscle disease, renal impairment (serum creatinine level  $>2.0$  mg/dl), hyper-

tension or ventricular hypertrophy. All drugs were withheld  $\geq 1$  week before the study.

*Ethical guidelines.* This study protocol was in an agreement with the guideline by the ethics committee at our institution, and written informed consent was obtained from each patient.

**Cardiac catheterization.** Cardiac catheterization was performed in the morning with patients in the fasting state. Cardiac output was determined by the thermodilution technique in triplicate. After completion of right heart catheterization, a 6F Goodale-Lubin catheter was placed in the coronary sinus by way of the brachial vein. The catheter was then advanced to the anterior interventricular vein under fluoroscopy by using a guide wire, as previously reported (13,15). The position of the catheter tip in the anterior interventricular vein was confirmed by injection of contrast material. A Sones catheter was placed at the aortic root by way of a right brachial artery. Sampling of blood for A- and B-type natriuretic peptide levels was performed simultaneously from the aortic root, the anterior interventricular vein and the coronary sinus; special care was taken to draw blood samples slowly from the anterior interventricular vein. Coronary arteriography and left ventriculography were performed in each patient.

**Hormonal analysis.** All blood samples were withdrawn into plastic syringes and transferred to chilled siliconized disposable tubes with aprotinin (1,000 kallikrein inactivator units/ml) (Ohkura Pharmaceutical, Kyoto, Japan) and ethylenediaminetetraacetic acid (1 mg/ml), then immediately placed on ice and centrifuged at 4°C. An aliquot of plasma was immediately frozen at -80°C and thawed only once at the time of assay within 1 week.

Plasma A-type natriuretic peptide concentration was measured by a specific immunoradiometric assay for alpha-human A-type natriuretic peptide (Shionoria ANP kit, Osaka, Japan) as previously reported (15). The minimal detectable quantity of alpha-human A-type natriuretic peptide is 5 pg/ml. The intraassay and interassay coefficients of variation were 4.7% and 5.8%, respectively. The cross-reactivity with human B-type natriuretic peptide was  $<0.001\%$  on a molar basis.

Plasma B-type natriuretic peptide concentration was measured with a new and specific immunoradiometric assay for human B-type natriuretic peptide as previously reported (15). The minimal detectable quantity of human B-type natriuretic peptide is 2 pg/ml. The intraassay and interassay coefficients of variation were 5.3% and 5.9%, respectively. The cross-reactivity with alpha-human A-type natriuretic peptide was  $<0.001\%$  on a molar basis.

**Statistical analysis.** All values are expressed as mean value  $\pm$  SD. Statistical significance was defined as a p value  $<0.05$ . Variables were compared between two groups by unpaired *t* test. Hormonal levels at the aortic root, anterior interventricular vein and coronary sinus within the group were compared by using one-way analysis of variance (ANOVA) with repeated measurements followed by the Fisher test. Stepwise regression analysis was undertaken to determine which hemodynamic variable was most closely correlated with the plasma levels of A- and B-type natriuretic peptide. The correlation of these

**Table 2.** Hemodynamic Data in the Control Group and Groups With Old Anterior and Inferior Myocardial Infarction

	Control (n = 18)	Anterior MI (n = 22)	Inferior MI (n = 20)
HR (beats/min)	73 ± 12	74 ± 12	70 ± 11
AOP (mm Hg)	95 ± 13	100 ± 13	96 ± 14
RAP (mm Hg)	2 ± 2	4 ± 2*	4 ± 2†
PCWP (mm Hg)	5 ± 2	14 ± 9*‡	10 ± 5†
CI (liters/min per m <sup>2</sup> )	2.9 ± 0.6	2.6 ± 0.7	2.7 ± 0.3
LVEF (%)	78 ± 4	39 ± 18*§	50 ± 13*

\*p < 0.01 versus the control group. †p < 0.05 versus the control group. ‡p < 0.05 versus the old inferior myocardial infarction group. §p < 0.01 versus the old inferior myocardial infarction group. Values are expressed as mean value ± SD. Anterior MI = old anterior myocardial infarction group; AOP = aortic mean pressure; CI = cardiac index; Control = control group; HR = heart rate; Inferior MI = old inferior myocardial infarction group; LVEF = left ventricular ejection fraction; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure.

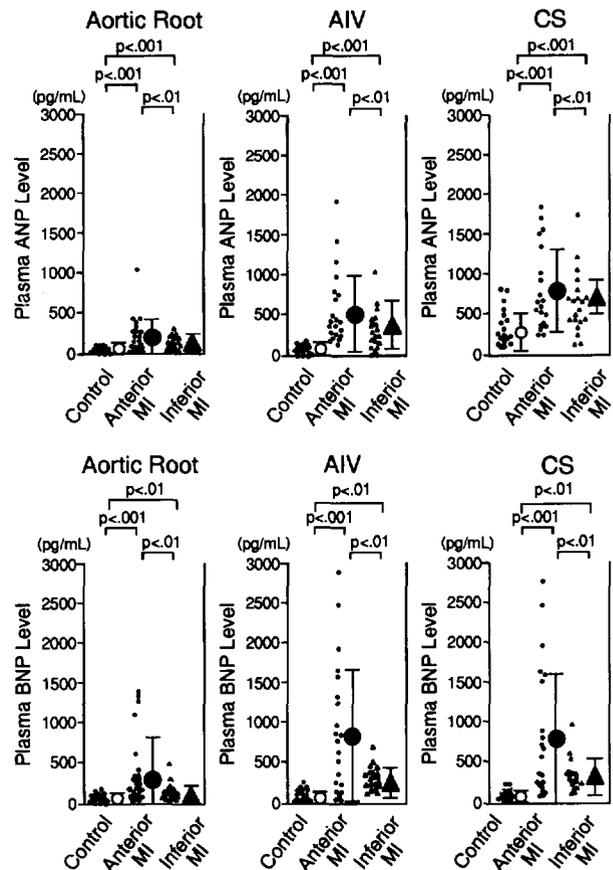
plasma levels with hemodynamic variables was examined by using linear regression analysis. The slopes of the linear regression lines were compared between the anterior and the inferior infarction groups by analysis of covariance (27).

## Results

**Hemodynamic variables.** Table 2 shows the hemodynamic variables in the two groups with myocardial infarction and the control group. There were no significant differences in heart rate, aortic mean pressure or cardiac index among the three groups. Pulmonary capillary wedge and right atrial pressures were significantly higher and the left ventricular ejection fraction was significantly lower in the two infarction groups than in the control group. Pulmonary capillary wedge pressure was significantly higher and the left ventricular ejection fraction was significantly lower in the anterior than in the inferior infarction group.

**Plasma A- and B-type natriuretic peptide levels at three sampling sites.** The plasma A-type natriuretic peptide levels at the three sampling sites were significantly higher in the groups with anterior (p < 0.001) and inferior (p < 0.001) infarction than in the control group (aortic root 174 ± 248 and 97 ± 76 pg/ml vs. 35 ± 27 pg/ml; anterior interventricular vein 554 ± 468 and 344 ± 234 pg/ml vs. 46 ± 26 pg/ml; coronary sinus 779 ± 508 and 727 ± 187 pg/ml vs. 278 ± 187 pg/ml) (Fig. 1, upper panel). The plasma A-type natriuretic peptide levels were significantly higher (p < 0.01) in the anterior group than in the inferior group at all three sampling sites.

The plasma B-type natriuretic peptide levels at all three sampling sites were significantly higher in the anterior (p < 0.001) and inferior (p < 0.01) infarction groups than in the control group (aortic root 340 ± 472 and 125 ± 81 pg/ml vs. 12 ± 8 pg/ml; anterior interventricular vein 853 ± 817 and 198 ± 125 pg/ml vs. 35 ± 21 pg/ml; coronary sinus 806 ± 826 and 331 ± 227 pg/ml vs. 34 ± 17 pg/ml) (Fig. 1, lower panel).

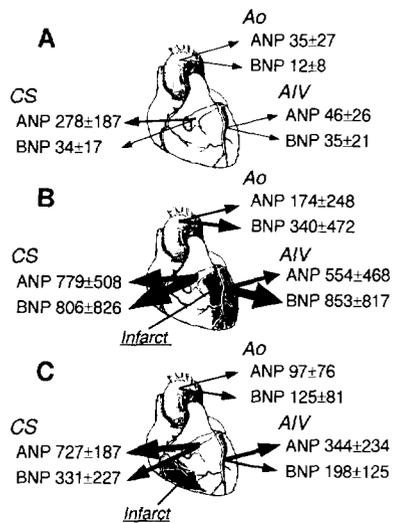


**Figure 1.** Plasma levels of A-type (ANP) and B-type (BNP) natriuretic peptide at three sampling sites in the groups with old anterior myocardial infarction (Anterior MI) and old inferior myocardial infarction (Inferior MI) and the control group (Control). The mean value ± SD for each plasma level at each sampling site is also shown (large symbols and bars). AIV = anterior interventricular vein; CS: coronary sinus.

The plasma B-type natriuretic peptide levels at all three sampling sites were significantly higher (p < 0.01) in the anterior than in the inferior infarction group.

Figure 2 shows schematically the changes in both plasma A- and B-type natriuretic peptide levels from the aortic root to the anterior interventricular vein and coronary sinus in the three groups. In the control group (Fig. 2A), the plasma A-type natriuretic peptide level did not differ between the aortic root and anterior interventricular vein, but increased significantly (p < 0.001) from the anterior interventricular vein to the coronary sinus. In contrast, the plasma B-type natriuretic peptide level in the control group increased significantly (p < 0.001) from the aortic root to the anterior interventricular vein (p < 0.001) but did not differ between the anterior interventricular vein and the coronary sinus.

In the anterior myocardial infarction group (Fig. 2B), the plasma A-type natriuretic peptide level increased significantly between the aortic root and anterior interventricular vein (p < 0.001) and between the anterior interventricular vein and coronary sinus (p < 0.01). The plasma B-type natriuretic



**Figure 2.** Schematic presentation of the changes in the plasma levels of A-type (ANP) and B-type (BNP) natriuretic peptides at the three sampling sites in the control group (A) and the groups with old anterior (B) and inferior (C) myocardial infarction. Values are expressed as mean value  $\pm$  SD in pg/ml. AIV = anterior interventricular vein; Ao = aortic root; CS = coronary sinus.

peptide level in this group increased significantly ( $p < 0.001$ ) between the aortic root and anterior interventricular vein, but did not differ between the anterior interventricular vein and coronary sinus.

In the inferior infarction group (Fig. 2C), the A-type natriuretic peptide level increased significantly ( $p < 0.001$ ) between the aortic root and anterior interventricular vein and also between the anterior interventricular vein and coronary sinus. The plasma B-type natriuretic peptide level in this group increased significantly between the aortic root and anterior interventricular vein ( $p < 0.01$ ) and between the anterior interventricular vein and coronary sinus ( $p < 0.001$ ).

The difference between the plasma levels of A-type natriuretic peptide in the anterior interventricular vein and aortic root was significantly greater in the anterior and inferior infarction groups than in the control group ( $380 \pm 290$  and  $247 \pm 205$  pg/ml vs.  $11 \pm 14$  pg/ml,  $p < 0.001$  and  $p < 0.001$ , respectively). The difference between these plasma levels in the coronary sinus and aortic root was also significantly greater in the infarction groups than in the control group ( $606 \pm 348$  and  $622 \pm 345$  pg/ml vs.  $244 \pm 175$  pg/ml,  $p < 0.001$  and  $p < 0.001$ , respectively).

The difference between the plasma levels of B-type natriuretic peptide in the anterior interventricular vein and aortic root was similarly significantly greater in the anterior and inferior infarction groups than in the control group ( $497 \pm 445$  and  $75 \pm 73$  pg/ml vs.  $23 \pm 16$  pg/ml,  $p < 0.001$  and  $p < 0.01$ , respectively). The difference between these plasma levels in the coronary sinus and aortic root was also significantly greater in the infarction groups than in the control group ( $470 \pm 412$  and  $208 \pm 158$  pg/ml vs.  $23 \pm 15$  pg/ml,  $p < 0.001$  and  $p < 0.01$ , respectively).

**Correlation of the increases in A- and B-type natriuretic peptide levels at the anterior interventricular vein with hemodynamic variables.** Stepwise linear regression analysis was undertaken to determine which hemodynamic variable was most closely correlated with the differences between the plasma A- and B-type natriuretic peptide levels in the anterior interventricular vein and the aortic root. Ejection fraction was found to be most significantly correlated in the anterior infarction group ( $F = 38.8$  for A-type;  $F = 38.4$  for B-type natriuretic peptide), whereas pulmonary capillary wedge pressure was most significantly correlated in the inferior infarction group ( $F = 29.1$  for A-type;  $F = 17.2$  for B-type).

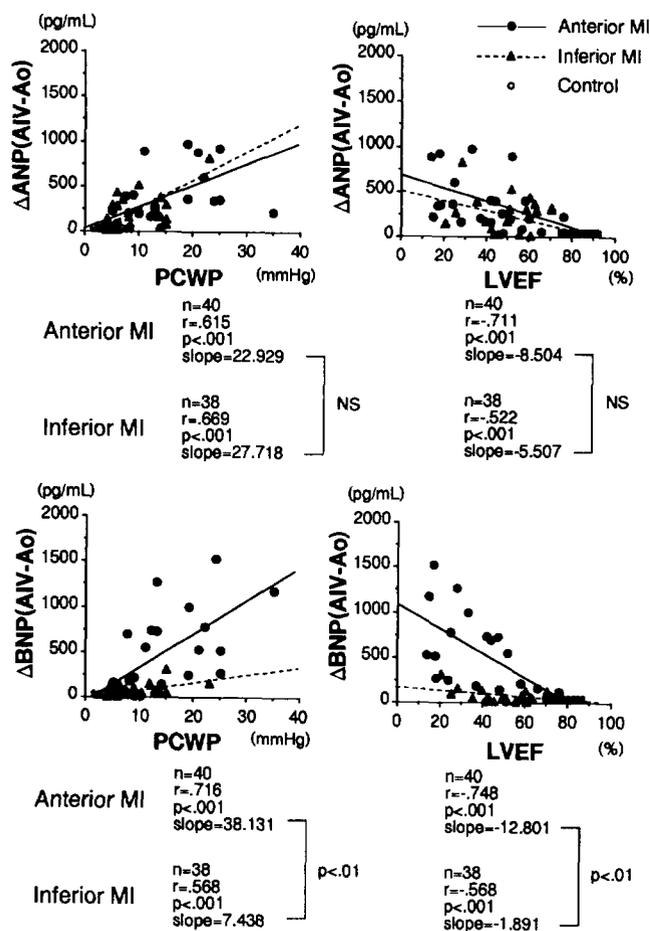
The difference between plasma A-type natriuretic peptide level in the anterior interventricular vein and aortic root showed a significant positive linear correlation with pulmonary capillary wedge pressure (anterior infarction group  $r = 0.615$ ,  $p < 0.001$ ; inferior infarction group  $r = 0.669$ ,  $p < 0.01$ ). It also showed a significant negative linear correlation with left ventricular ejection fraction (anterior infarction group  $r = -0.711$ ,  $p < 0.001$ ; inferior infarction group  $r = -0.522$ ,  $p < 0.001$ ) (Fig. 3, upper panel).

The difference between the plasma B-type natriuretic peptide level in the anterior interventricular vein and aortic root showed a significant positive linear correlation with pulmonary capillary wedge pressure (anterior infarction group  $r = 0.716$ ,  $p < 0.001$ ; inferior infarction group  $r = 0.568$ ,  $p < 0.001$ ). It also showed a significant negative linear correlation with left ventricular ejection fraction (anterior infarction group  $r = -0.748$ ,  $p < 0.001$ ; inferior infarction group  $r = -0.568$ ,  $p < 0.001$ ) (Fig. 3, lower panel).

**Comparison of linear regression line slope between the anterior and inferior myocardial infarction groups.** There was no significant difference in the slopes of the regression lines of the arteriovenous difference of the plasma A-type natriuretic level at the anterior interventricular vein between the anterior and inferior infarction groups (pulmonary capillary wedge pressure 22.929 vs. 27.718; left ventricular ejection fraction  $-8.504$  vs.  $-5.507$ ) (Fig. 3, upper panel). In contrast, the slopes of the regression lines of the arteriovenous difference of the plasma B-type natriuretic level at the anterior interventricular vein were significantly steeper in the anterior than in the inferior infarction group (pulmonary capillary wedge pressure 38.131 vs. 7.438,  $p < 0.01$ ; left ventricular ejection fraction  $-12.801$  vs.  $-1.891$ ,  $p < 0.01$ ) (Fig. 3, lower panel).

## Discussion

B-type natriuretic peptide, a cardiac hormone synthesized mainly in the ventricles, forms a natriuretic peptide family with A-type natriuretic peptide (16–18). We and others (17–20) have shown that plasma levels of these two peptides are increased in patients with congestive heart failure. There has been no systematic study of the secretion of A- and B-type natriuretic peptides from the heart of patients with an old myocardial infarction. In this study, we measured the plasma



**Figure 3.** Correlation of arteriovenous difference of plasma A-type (ANP) and B-type (BNP) natriuretic peptide levels at the anterior interventricular vein (AIV) [ $\Delta$ ANP(AIV-Ao),  $\Delta$ BNP(AIV-Ao)] with pulmonary capillary wedge pressure (PCWP) and left ventricular ejection fraction (LVEF) in patients with old anterior and inferior myocardial infarction (MI). There was no significant difference in the slopes of the regression lines of the arteriovenous difference of the plasma A-type natriuretic peptide levels at the anterior interventricular vein between the two infarction groups. The slopes of the regression lines of the arteriovenous difference of the plasma B-type natriuretic peptide levels at the anterior interventricular vein were significantly steeper in the anterior than in the inferior infarction group. Ao = aortic root.

levels of these peptides at the aortic root, anterior interventricular vein and coronary sinus in patients with anterior and inferior myocardial infarction and control patients. The results showed that the plasma levels of both peptides were significantly greater at all three sites in both groups with infarction than in the control patients.

**Augmented secretion of A- and B-type natriuretic peptides from the ventricle in myocardial infarction.** The anterior interventricular vein drains the anterior ventricle (24-26). The difference between plasma levels of natriuretic peptides in the anterior interventricular vein and aortic root thus reflects the amount of the peptides secreted from the anterior ventricle. In the control group, plasma A-type natriuretic

peptide level did not differ significantly between these two sampling sites, whereas plasma B-type natriuretic peptide level increased significantly from the aortic root to the anterior interventricular vein. These findings are consistent with previous data (13,15,17).

In the anterior infarction group, the secretion of A- and B-type natriuretic peptides from the anterior ventricle reflects the amount of the peptides released from the infarct region, whereas in the inferior infarction group it reflects the amount released from the noninfarct region. The amount of A- and B-type natriuretic peptides secreted from the anterior ventricle was significantly higher in both infarction groups than in the control group. Thus, secretion of these peptides from the ventricle is augmented in both infarct and noninfarct areas in patients with myocardial infarction.

The amount of A- and B-type natriuretic peptides secreted from the anterior ventricle had a significant positive linear correlation with pulmonary capillary wedge pressure and a significant negative linear correlation with left ventricular ejection fraction in both infarction groups. These results indicate that increasing deterioration of left ventricular function is accompanied by an increased release of both peptides from the ventricle not only in the infarct region but also in the noninfarct region. The increased wall tension or stretch as a consequence of ventricular dilation may stimulate the secretion of A- and B-type natriuretic peptides from the ventricle.

**Regional stretch as a possible cause of increased secretion of B-type natriuretic peptide.** To compare the amount of B-type natriuretic peptide secreted from the infarct and noninfarct regions, we compared the slope of the linear regression line of B-type natriuretic peptide secretion from the anterior ventricle in the anterior and inferior infarction groups. The slope was significantly steeper in the anterior than in the inferior infarction group. This finding indicates that the secretion of B-type natriuretic peptide was greater in the infarct than in the noninfarct region even when left ventricular dysfunction was comparable.

Because the amount of B-type natriuretic peptide secreted from the anterior ventricle is also significantly greater in the inferior infarction group than in control subjects, the increased secretion of the peptide from the infarct region cannot be explained solely by secretion from the viable cells within the infarct. Rather, the myocytes surrounding the infarct are likely to be the source of the increased secretion of B-type natriuretic peptide. Because secretion of the peptide from the anterior ventricle is greater in the anterior than in the inferior infarction group, it appears that B-type natriuretic peptide secretion is augmented by the regional stretch, which is greatest around the infarct.

In the anterior infarction group, there was no significant difference between the plasma B-type natriuretic peptide level in the anterior interventricular vein and the coronary sinus. This finding suggests that in patients with myocardial infarction as in normal adult humans, B-type natriuretic peptide is secreted mainly from the ventricles and not from the atria. However, in the inferior myocardial infarction group, there

was a significant increase in the level of B-type natriuretic peptide between the anterior interventricular vein and coronary sinus. We believe that this increase is due to increased secretion of B-type natriuretic peptide from the inferior infarct region because the coronary sinus partly drains the inferior ventricle. This finding further supports our conclusion that B-type natriuretic peptide secretion is markedly greater in the area regionally stretched by myocardial infarction.

In contrast, the slope of the regression line of A-type natriuretic peptide secretion from the anterior ventricle did not differ between the anterior and inferior infarction groups. This finding suggests that A-type natriuretic peptide secretion is less sensitive than B-type natriuretic peptide secretion to the regional ventricular stretch caused by myocardial infarction.

**Conclusions.** 1) Significant secretion of A-type natriuretic peptide from the ventricles occurs in patients with old myocardial infarction but not in normal adult humans. 2) B-type natriuretic peptide is secreted mainly from the ventricles both in normal adult humans and in patients with old myocardial infarction. 3) Secretion of A-type and B-type natriuretic peptide from the ventricles increases in proportion to the severity of left ventricular dysfunction. 4) Secretion of B-type natriuretic peptide is significantly greater from the infarct region than from the noninfarct region, whereas this not the case with A-type natriuretic peptide. These findings suggest that the regional ventricular wall stretch caused by myocardial infarction strongly stimulates B-type natriuretic peptide secretion and that B-type natriuretic peptide is more sensitive than A-type natriuretic peptide as a marker of regional ventricular stretch.

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