Relationship of sustained brain natriuretic peptide release after reperfused acute myocardial infarction with gated SPECT infarct measurements and its connection with collagen turnover and left ventricular remodeling

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Background. **The relationship among plasma brain natriuretic peptide (BNP), markers of extracellular matrix (ECM) remodeling, and left ventricular (LV) dilation after reperfused acute myocardial infarction is poorly known.**

Methods and Results. **Echocardiogram, plasma BNP, and ECM degradation markers (serum amino-terminal telopeptide of type I procollagen and type III procollagen and carboxy-terminal telopeptide of type I procollagen [ICTP]) were evaluated in 34 patients at days 1, 3, and 30 after first reperfused acute myocardial infarction. At 1 month, infarct size and severity and LV volume were measured by sestamibi gated single photon emission computed tomography. Patients were stratified according to day 3 BNP levels into 2 groups: group 1 (n = 17) had BNP values over the median value, and group 2 (n = 17) had BNP values under the median value. Infarct size and severity were similar in the 2 groups. LV volumes increased in group 1 but decreased in group 2 ($P < .01$). BNP values, LV volume/mass index, and infarct size were independent predictors of 1-month LV dilation ($\beta = .58$ [$P = .001$], $\beta = .41$ [$P = .01$], and $\beta = .32$ [$P = .03$], respectively). Levels of serum amino-terminal propeptide of type I procollagen and type III procollagen were similar in both groups. The level of ICTP increased significantly in group 1 only, and after 3 days, it was higher ($P < .01$) than in group 2. In group 1 ICTP significantly interacted with the relationship between BNP release and serial changes in LV volumes ($F = 4.87$, $P = .03$).**

Conclusions. **ICTP is related to elevated BNP level independently of infarct size and severity and interacts with the relationship between BNP and LV dilation. BNP levels could play a role in LV remodeling by favoring ECM degradation. (J Nucl Cardiol 2008;15:644-54.)**

Key Words: Myocardial infarction • natriuretic peptides • collagen • remodeling

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In patients with acute myocardial infarction (AMI), plasma brain natriuretic peptide (BNP) levels rise quickly, reaching a peak at approximately 16 hours after admission, and then decline.[1,2] Patients with large AMI have higher BNP levels, showing a second peak of BNP release (biphasic pattern) about 5 days after the onset of symptoms.[2] Sustained high BNP level early after AMI has been shown to be a marker of left ventricular (LV) remodeling and adverse prognosis.[3,4] Experimental studies suggest that elevated BNP levels enhance extracellular matrix (ECM) degradation.[5,6] ECM degradation plays a key role in LV remodeling after AMI.[7] Therefore sustained high BNP level could be not just a simple marker but also a modulator of the remodeling process by enhancing ECM degradation. Studies in patients with postinfarction LV remodeling suggest a relationship between BNP and serum surrogate markers for ECM remodeling.[8-10] So far,

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this relationship has been interpreted as a consequence of their common association with infarct size.

Recently, we reported that patients in whom LV remodeling developed after AMI had significantly higher levels of BNP and carboxy-terminal telopeptide of type I procollagen (ICTP), an ECM degradation product, than patients without remodeling, and that this correlation was independent of enzymatic and echocardiographic estimates of infarct extent.[11] The latter issue is crucial, because demonstrating that, in patients with comparable infarct dimensions, LV remodeling is present only in association with high levels of BNP and serum products of collagen metabolism would suggest their causative role in the remodeling process. To support this conclusion, it is mandatory to rely on an accurate infarct measurement. The limitations of enzymatic and echocardiographic infarct estimates are well known.[12-15] Conversely, it is widely accepted that technetium 99m sestamibi single photon emission computed tomography (SPECT) is a most reliable method for measuring infarct size, with the additional advantage of assessing infarct severity as well.[16-19]

Thus the primary aim of this study was to determine whether sustained high BNP level early after AMI (sustained BNP release) is related to a different temporal profile of serum products of type I and type III procollagen independently of infarct size and severity, as assessed by Tc-99m sestamibi SPECT. A secondary aim was to examine the relationship between sustained BNP release after AMI, serum indices of collagen turnover, and early LV remodeling.

METHODS

Patients and Study Protocol

We prospectively studied 34 patients with a first ST-elevation AMI selected among 60 patients consecutively admitted for emergency primary percutaneous coronary intervention. Prior AMI was excluded based on history, electrocardiogram, and echocardiographic pattern. Only patients with AMI and LV systolic dysfunction (left ventricular ejection fraction [LVEF] $\leq$40%)[20] were considered eligible for the study because of their increased risk of sustained BNP release early after AMI.[2] To avoid the potential confounding effect of a residual stenosis/occlusion and/or suboptimal flow in the infarct-related artery (IRA) on subsequent serum values of collagen products,[21] only patients in whom anterograde flow was fully restored (Thrombolysis in Myocardial Infarction grade 3 flow) without significant residual stenosis were included in the study. Exclusion criteria were (1) cardiogenic shock, (2) cardiac disease other than coronary artery disease, (3) renal insufficiency (serum creatinine level $>$2.0 mg/dL), (4) diseases potentially responsible for abnormal collagen turnover (alcoholic liver disease, metabolic bone disease, hyperthyroidism, pulmonary fibrosis, and connective tissue disorders), (5) life-limiting noncardiac disease, and (6) inadequate echocardiographic image quality. Of the 60 potential candidates for the study, 20 (33%) were excluded because of an LVEF greater than 40%, 2 patients (3%) were excluded because of inadequate quality of the echocardiographic images, and an additional 2 patients (3%) did not adhere to the follow-up protocol. Thus 36 patients were enrolled in the study. During the first 3 days after index AMI, 2 patients (5%) died from refractory congestive heart failure. Thus the final study group consists of 34 patients. All patients underwent serial controls including clinical status, echocardiography, and dosage of plasma BNP, carboxy-terminal propeptide of type I procollagen (PICP), ICTP, and amino-terminal propeptide of type III procollagen (PIIINP) at day 1, day 3, and month 1 after index AMI. Furthermore, at 1 month after index AMI, resting Tc-99m sestamibi gated SPECT was performed for the measurement of myocardial infarct size and severity and of LV volumes,[19] and coronary angiography was performed for the evaluation of IRA patency. The study protocol was approved by the ethics committee of our institution, and all patients gave written informed consent to participate in the study.

Echocardiography

Complete M-mode and 2-dimensional echocardiography and Doppler ultrasound examinations were performed blindly with a commercially available imaging system (Sonos 5500; Hewlett-Packard, Palo Alto, Calif). Details pertaining to modality of acquisition and analysis of echocardiographic data, as well as the agreement between LV volume index measurements (intraobserver variability, $r = 0.96$; interobserver variability, $r = 0.94$) in our laboratory, have been reported elsewhere.[22,23]

Measurement of BNP and Indices of Collagen Metabolism

Blood samples were taken at least 30 minutes before sampling, with the patient resting in a semirecumbent supine position. For BNP measurement, blood samples were collected into plastic tubes containing ethylenediaminetetraacetic acid and aprotinin (500 KIU/mL); the plasma was separated by centrifugation at 2000*g* at 4°C and stored at −80°C until analysis. Plasma BNP level was measured by a commercial immunoradiometric assay method (Shionoria BNP; CIS Bio International, Milan, Italy). The minimum sensitivity and upper limit of normal values were 2 and 18.4 pg/mL, respectively, for the BNP assay, with the highest intra-assay and interassay coefficients of variation being 2.7% and 4.2%, respectively. For PICP, ICTP, and PIIINP measurement, blood samples were collected into plastic tubes without additives and the separated sera were stored at −80°C until analysis. PICP, ICTP, and PIIINP were measured by radioimmunoassay kits (Orion Diagnostica, Espoo, Finland). The minimum sensitivity and upper limit of normal values were 1.2 and 202 ng/mL, respectively, for the PICP assay; 0.4 and 5.6 ng/mL, respectively, for ICTP; and 0.2 and 4.5 ng/mL, respectively, for PIIINP. The highest intra-

assay and interassay coefficients of variation were 3.2% and 6.6%, respectively, for PICP; 9.4% and 9.0%, respectively, for ICTP; and 1.7% and 5.3%, respectively, for PIIINP.

Gated SPECT

Gated SPECT acquisition began 60 minutes after Tc-99m sestamibi injection (740 MBq), by use of a double-head camera equipped with high-resolution collimators, with a 180° rotation arc, 32 projections, 60 seconds per projection, 8 frames per heart cycle, and 64 × 64 matrices. The studies were reconstructed via filtered backprojection without attenuation or scatter correction and realigned along the heart axis. Perfusion defects were quantified as percentage of LV wall, with the defect threshold set at 60% of peak uptake.[19,24] Infarct severity, as a measure of infarct transmurality, was defined as the lowest ratio of minimal to maximal counts in the short-axis slices evaluated for infarct size.[18,19] LV end-diastolic volume and end-systolic volume were measured by an automated and validated method.[25] Volumetric data were corrected for body surface area and expressed as indices.

Definitions and Outcome Measures

Sustained BNP release during AMI was defined as the presence of a plasma BNP value over the median value 3 days after index AMI. The choice of the third day for the last measurement of BNP levels during the early phase of AMI was based on prior studies in the same setting showing that day 3 is the optimal timing for the prognostic value of BNP.[3,4] LV dilation was defined as a change in left ventricular end-diastolic volume index (LVEDVI) from baseline to 1 month (ΔLVEDVI).

Statistical Analysis

Continuous data were expressed as mean ± SEM, and categorical data as frequencies. Continuous variables were tested by unpaired *t* test once normality was demonstrated (Shapiro-Wilk test); otherwise, a nonparametric test was used (Mann-Whitney *U* test). Categorical variables were compared by the χ^2 or Fisher exact test when appropriate. Linear correlations were tested by use of the Pearson correlation coefficient once normality was demonstrated; otherwise, Spearman correlation was used. We tested partial correlations between BNP and procollagens, controlling for SPECT measures of infarct size and severity. Analysis of variance with the Bonferroni post hoc test and Friedman analysis of variance were used to analyze changes in echocardiographic measures (LV volumes, LVEF, and deceleration time of early transmitral flow [DT]) and neurohormonal measures (BNP, ICTP, PICP, and PIIINP), respectively, over time. Forward stepwise linear multivariate regression analysis was used to evaluate the predictors of change in LVEDVI from baseline to 1 month (ΔLVEDVI). The variables submitted to the stepwise procedure were age, sex, symptom-to-balloon time, anterior infarct location, pattern of BNP release, DT, LV volume–mass ratio, SPECT infarct size, and SPECT infarct severity. Hierarchic multiple regression analysis was performed to test the value of a clinical-imaging model versus a clinical-serum model in predicting 1-month LV remodeling. Repeated-measures analysis was used to evaluate the interaction of procollagens on the relationship between time course of LVEDVI and different pattern of BNP release. $P < .05$ was considered statistically significant. All statistical calculations were performed by use of SPSS for Windows software (release 11.5; SPSS, Chicago, Ill).

RESULTS

Patient Characteristics

The patient clinical, echocardiographic, and therapeutic data are shown in Table 1. Patients with sustained BNP release during AMI (group 1, n = 17) had a longer symptom-to-balloon time, lower LVEF, and higher LV volume/mass index than patients without sustained BNP release (group 2, n = 17). There were no significant differences between groups regarding risk factors and drug regimen. In the angiographic follow-up the IRA patency rate was 100% in both groups. Moderate to severe mitral regurgitation was registered in 3 patients in group 1 and 2 in group 2.

Gated SPECT

One-month gated SPECT showed similar infarct size and infarct severity in the 2 groups of patients (23% ± 3% vs 19% ± 2% [$P = .256$] and 0.33 ± 0.03 vs 0.40 ± 0.02 [$P = .158$], respectively) (Figure 1). Individual SPECT measures of infarct size and severity are presented in Table 2. In the presence of similar infarct size and severity, LVEDVI and left ventricular end-systolic volume index (LVESVI) in group 1 were significantly larger than those in group 2 (80 ± 8 mL vs 61 ± 4 mL [$P = .04$] and 51 ± 6 mL vs 35 ± 3 mL [$P = .04$], respectively). A significant correlation was found between SPECT measures of infarct severity and plasma value of BNP at day 3 ($r = 0.36$, $P = .04$) and at month 1 ($r = 0.56$, $P = .001$).

Serial Changes in Echocardiographic LV Volumes and Function

The changes in LVEDVI, LVESVI, and LVEF from baseline to 1 month were significantly different between groups (Figure 2). Individual values of 6-month LV volumes and ejection fraction are presented in Table 2. A significant relationship was found between concurrent echocardiographic and SPECT measures of LV end-diastolic volume and end-systolic volume ($r = 0.50$, $P = .003$ for both).

Table 1. Baseline clinical, echocardiographic, and therapeutic characteristics

	All patients (n = 34)	Group 1 (n = 17)	Group 2 (n = 17)	*P* value
Age (y)	62 ± 2	64 ± 3	61 ± 2	.24
Male (%)	28 (82)	14 (82)	14 (82)	>.99
Diabetes (%)	9 (27)	6 (35)	3 (17)	.43
Hypertension (%)	17 (50)	6 (35)	11(65)	.16
Anterior infarct location (%)	27 (79)	14 (82)	13 (77)	>.99
Multivessel disease (%)	11 (61)	11 (61)	5 (31)	.10
Symptom-to-balloon time (h)	4.8 ± 0.3	5.4 ± 0.5	4.2 ± 0.3	.04
Mass index (g/m^2)	90 ± 3	86 ± 4	94 ± 5	.34
Heart rate (beats/min)	77 ± 3	81 ± 3	72 ± 4	.07
Systolic BP (mm Hg)	125 ± 4	117 ± 5	133 ± 4	.06
LVEDVI (mL/m^2)	58 ± 2	60 ± 4	56 ± 3	.60
LVESVI (mL/m^2)	37 ± 2	40 ± 2	34 ± 2	.13
LV volume–mass ratio	0.60 ± 0.03	0.73 ± 0.03	0.58 ± 0.04	.01
LVEF (%)	36 ± 1	33 ± 2	38 ± 1	.02*
IZWMSI	2.3 ± 0.07	2.4 ± 0.06	2.3 ± 0.05	.13*
DT (ms)	168 ± 7	154 ± 11	182 ± 8	.08
E/A	0.9 ± 0.07	1 ± 0.1	0.9 ± 0.07	.18*
BNP (pg/mL)	213 ± 27	306 ± 42	121 ± 14	<.01*
Aspirin	34 (100)	17 (100)	17 (100)	>.99
Thienopiridines	34 (100)	17 (100)	17 (100)	>.99
Statins	17 (50)	6 (35)	11 (65)	.17
Loop diuretic	29 (85)	15 (88)	14 (82)	.62
Spironolactone	12 (35)	6 (36)	5 (29)	.66
ACE inhibitors	32 (94)	16 (94)	16 (94)	>.99
β-Blockers	5 (15)	1 (6)	4 (24)	.33
Coronary stent	34 (100)	17 (100)	17 (100)	>.99

BP, Blood pressure; *IZWMSI*, infarct zone wall motion score index; *DT*, wave deceleration time of early transmitral flow; *E/A*, ratio between peak flow velocities at rapid filling and at atrial contraction of transmitral flow; *ACE*, angiotensin-converting enzyme; *BNP*, brain natriuretic peptide; *LVEDVI*, left ventricular end-diastolic volume index; *LVESVI*, left ventricular end-systolic volume index; *LVEF*, left ventricular ejection fraction.
*Variables for which nonparametric test was used.

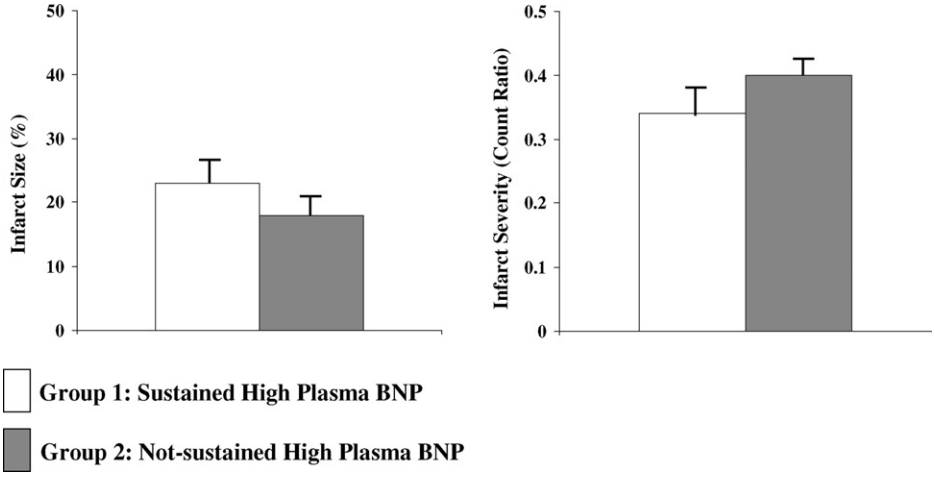

Figure 1. One-month gated SPECT infarct size and infarct severity in the 2 groups with and without sustained plasma BNP release.

Table 2. Individual patient data

Patient No.	BNP (pg/mL): Day 3	Infarct size (%)	Infarct severity	ICTP (ng/mL)			PICP (ng/mL)		
				Day 1	Day 3	Month 1	Day 1	Day 3	Month 1
Group 1									
1	192	34	0.10	7	12	9	57	106	95
2	190	0	0.75	4	5	5	84	114	62
3	177	5	0.42	3	4	4	107	114	160
4	207	30	0.19	2	7	11	134	102	122
5	206	12	0.49	5	7	7	106	137	187
6	297	38	0.11	3	6	4	63	85	96
7	866	9	0.29	13	16	9	124	197	194
8	259	20	0.30	3	6	4	151	92	177
9	909	8	0.49	4	11	3	130	58	118
10	221	37	0.22	6	8	6	93	111	85
11	194	38	0.41	2	4	2	49	81	98
12	161	24	0.43	9	6	8	109	167	143
13	270	21	0.36	4	6	5	95	88	119
14	296	28	0.24	4	6	5	99	79	100
15	212	40	0.21	7	7	4	83	91	133
16	668	22	0.42	10	13	9	103	144	132
17	219	36	0.26	5	5	9	42	122	159
Mean ± SEM	326 ± 58	23 ± 3	0.33 ± 0.03	5 ± 0.7	8 ± 0.8	6 ± 0.6	96 ± 7	111 ± 9	128 ± 9
Group 2									
18	78	18	0.45	2	3	4	76	107	126
19	98	21	0.37	4	7	2	130	89	200
20	39	14	0.30	3	3	3	103	114	192
21	30	26	0.22	3	5	5	139	161	158
22	65	3	0.59	4	5	4	104	122	138
23	64	6	0.49	8	8	7	132	142	175
24	30	6	0.51	4	3	3	162	191	200
25	126	17	0.31	7	6	4	89	79	159
26	131	25	0.26	4	4	6	139	160	146
27	69	18	0.45	2	3	3	137	121	99
28	72	19	0.51	2	3	2	113	98	33
29	70	38	0.23	6	6	5	139	167	169
30	86	25	0.31	9	2	1	131	122	160
31	54	16	0.48	3	4	9	115	121	183
32	158	30	0.44	3	4	3	110	128	153
33	122	25	0.51	4	5	3	97	94	104
34	157	17	0.43	4	5	2	56	65	87
Mean ± SEM	85 ± 10	19 ± 2.1	0.40 ± 0.02	4 ± 0.5	4 ± 0.4	4 ± 0.5	116 ± 6	122 ± 9	146 ± 11
Total (mean ± SEM)	206 ± 36	21 ± 1.9	0.37 ± 0.02	5 ± 0.4	6 ± 0.5	5 ± 0.4	106 ± 5	117 ± 6	137 ± 7

LVEDVI, Left ventricular end-diastolic volume index; *LVESVI,* left ventricular end-systolic volume index.

Serial Changes in Serum Products of Type I and Type III Collagen

From baseline to month 1, PICP significantly ($P < .05$) increased in both groups with and without sustained BNP release, and no significant differences in PICP and PIIINP values were found between groups at each time point of measurement (Figures 3*A* and 3*C*). ICTP significantly increased from day 1 to month 1 in group 1 patients but remained unchanged in group 2. Furthermore, since day 3, serum ICTP was significantly ($P < .01$) higher in group 1 than in group 2 (Figure 3*B*). Individual serum values of type I and type III procollagen at each time point of measurement are presented in Table 2.

Table 2. Continued

PIIINP (μg/mL)			LVEDVI (mL/m^2):	LVESVI (mL/m^2):	LVEF (%):
Day 1	Day 3	Month 1	Month 1	Month 1	Month 1
2	3	2	94	63	33
3	4	3	40	15	62
3	3	4	61	31	49
3	3	4	60	28	53
4	4	7	77	46	40
2	2	2	72	46	36
7	6	6	65	39	40
5	3	4	70	41	42
3	6	4	69	48	30
2	4	2	65	39	41
2	2	2	79	46	42
4	6	4	108	63	42
4	5	5	74	48	35
4	3	5	57	32	43
4	2	3	89	64	28
6	7	6	65	44	32
2	2	5	74	42	43
3.4 ± 0.4	3.9 ± 0.4	4 ± 0.3	72 ± 4	43 ± 3	41 ± 2
2	3	2	61	29	53
3	4	4	41	18	56
2	3	4	60	33	44
2	3	3	51	33	34
4	4	3	24	10	56
4	5	5	42	15	64
3	4	3	57	20	64
4	4	5	65	38	41
2	6	3	57	31	45
1	2	3	58	33	43
4	2	2	65	35	46
6	7	5	68	29	57
2	4	3	54	24	55
3	2	6	68	39	42
2	2	3	45	26	43
3	6	3	40	18	55
3	3	3	68	26	62
2.8 ± 03	3.7 ± 0.4	3.5 ± 0.3	54 ± 3	27 ± 2	51 ± 2.1
3.1 ± 0.2	3.8 ± 0.3	3.7 ± 0.2	63 ± 3	35 ± 2.3	46 ± 1.7

Relationship Between Plasma BNP and Serum Products of Type I and Type III Collagen

From baseline to month 1, plasma BNP decreased in both groups of patients but was significantly higher ($P = .001$) in group 1 patients than in group 2, and the greater difference between groups occurred at day 3 (326 ± 58 pg/mL vs 85 ± 58 pg/mL). Individual values of plasma BNP at each time point of measurement are presented in Table 2.

A significant linear relationship between BNP and ICTP occurs at day 1 and day 3 in group 1 patients but not in group 2 (Table 3). We further calculated the partial correlation coefficient of BNP and ICTP controlling for

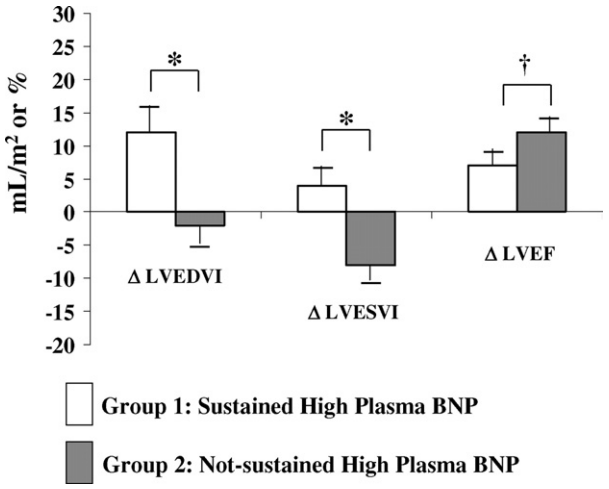

Figure 2. Changes in LVEDVI, LVESVI, and LVEF from baseline to first month (Δ) in the 2 groups with and without sustained plasma BNP release. *$P < .01$ between groups; †$P < .05$ between groups.

SPECT infarct size and severity (Table 3) and found that the relationship remained significant in group 1 patients and not significant in group 2 patients. No relationship was observed between BNP and PICP as well as PIIINP in both groups of patients.

Predictors of 1-Month LV Remodeling

Univariate linear regression analysis of variables potentially responsible for 1-month LV dilation is presented Table 4. On stepwise multiple linear regression analysis, sustained pattern of high plasma BNP release, baseline values of LV volume/mass index, and SPECT infarct size emerged as independent predictors of 1-month LV remodeling (Table 5). The power of a clinical-serum model and a clinical-imaging model was also tested in hierarchic order (clinical-imaging model first, then clinical-serum model) to predict 1-month LV dilation. The R^2 change obtained by the addition of the clinical-serum model was significant (R^2 change, 0.305 [from 0.173 to 0.478]; $P = .004$) (Table 6).

Interaction of ICTP on Relationship Between Pattern of Plasma BNP Release Early After AMI and Time Course of LVEDVI

Repeated-measures analysis showed that serum changes from baseline to day 3 of ICTP, but not of PICP and PIIINP, significantly interact with the relationship between serial changes in LV volumes from baseline to month 1 and different pattern of plasma BNP release early after AMI ($F = 4.87$, $P = .03$).

DISCUSSION

Study Findings

This study shows that (1) in the presence of similar SPECT infarct size and severity, only higher ICTP levels discriminate patients with or without sustained BNP release early after AMI with regard to the pattern of collagen metabolism; (2) only in patients with sustained BNP release, serum ICTP during the first 3 days after reperfused AMI is significantly related to concurrent values of BNP and interacts with the relationship between BNP and 1-month LV dilation; and (3) sustained BNP release and LV volume/mass ratio (a marker of wall tension) are the two most important predictors of early postinfarction LV dilation. These findings exclude that combined BNP and ICTP increases are just the joint consequence of larger and more severe infarctions. Our results would support the hypothesis that sustained BNP could be not just a marker but also a potential modulator of LV remodeling through a favoring effect on ECM degradation.

Comparison with Previous Studies

ECM remodeling plays a key role in postinfarction LV remodeling.[7] However, the relationship between BNP and surrogate markers of ECM remodeling in AMI patients is poorly understood. Tziakas et al[8] showed a significant association between circulating levels of *N*-terminal pro–B-type natriuretic peptide and metalloproteinases (MMPs) in early and late postinfarction remodeling. Squire et al[9] reported a correlation between MMP-9 levels and *N*-terminal pro–B-type natriuretic peptide and between MMP-9 levels and echocardiographic LV dilation in patients soon after AMI. Magga et al[10] showed a significant relationship between BNP and serum products of type I collagen after AMI, and they suggest a possible regulatory role of BNP on ECM degradation. In patients with LV remodeling, we observed an increase in BNP and type I collagen turnover, which was apparently not influenced by enzymatic and echocardiographic estimates of infarct extent.[11] Differently from that report, in the present study we also examined the turnover of soft-tissue type III collagen, as assessed by changes in PIIINP. Changes in PIIINP have been shown to be induced by AMI in humans[26] and may reflect both synthesis and degradation of soft-tissue collagen,[27] whereas PICP reflects synthesis and ICTP degradation of bone-tissue collagen (type I).[27,28] We observed that only higher circulating levels of ICTP, which represent collagen degradation,[28] discriminate patients with or without sustained BNP

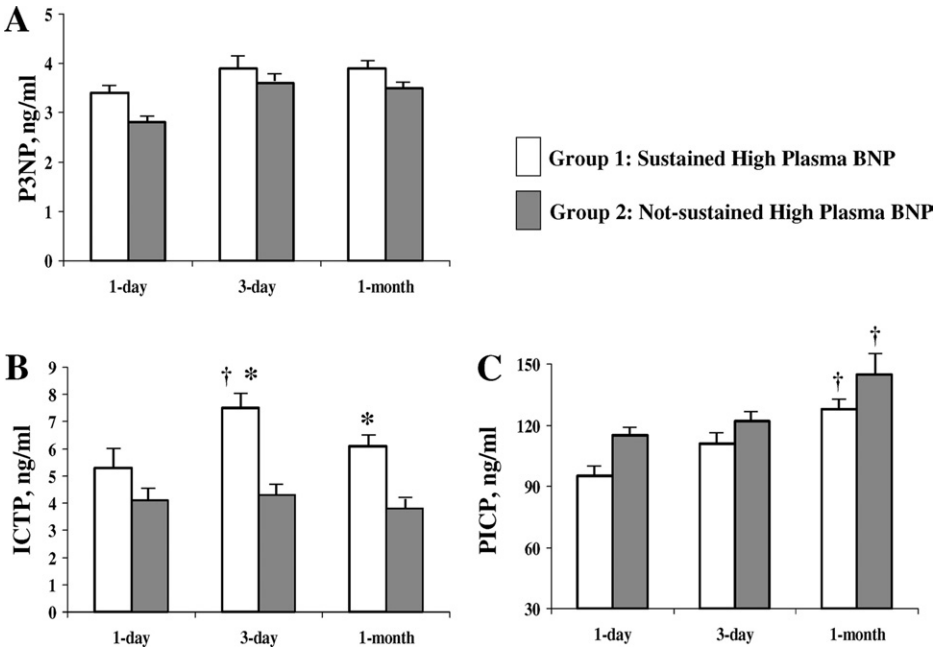

Figure 3. Serial changes in plasma PIIINP (**A**), ICTP (**B**), and PICP (**C**) levels in the 2 groups with and without sustained plasma BNP release. *$P < .01$ between groups; †$P < .05$ versus baseline.

Table 3. Correlation between BNP and ICTP in patients with (group 1) or without (group 2) sustained plasma BNP release and partial correlation coefficients between BNP and ICTP after controlling for SPECT measures of infarct size and severity

	Day 1		Day 3		Month 1	
	r	*P* value	*r*	*P* value	*r*	*P* value
Correlation coefficients between BNP and ICTP in patients with (group 1) or without (group 2) sustained plasma BNP release						
Group 1	0.57	.002	0.79	<.01	0.33	.14
Group 2	0.5	.85	0.17	.52	0.35	.17
Partial correlation coefficients between BNP and ICTP after controlling for SPECT measures of infarct size and severity						
Group 1	0.56	.02	0.77	.001	0.31	.25
Group 2	0.3	.92	0.24	.44	0.37	.19

release early after AMI with regards to the pattern of collagen metabolism. A possible explanation for this finding is that in the presence of high concentrations of BNP, there is increased MMP activity and ECM degradation.[5] Another novel point of this study is that we used Tc-99m sestamibi gated SPECT to accurately evaluate the influence of both infarct size and infarct severity on BNP and collagen degradation. In the setting of reperfusion the limitations of enzymatic estimates of infarct dimensions are particularly important.[12,13] Similarly, there are major problems in defining the extent of infarction by use of methods based on wall motion abnormalities.[14,15] Conversely, Tc-99m sestamibi SPECT infarct size measurements have been shown to be reliable and have been accepted as surrogate endpoints for studies comparing different therapeutic strategies in AMI patients.[16,17,29] We also considered infarct severity, which is related to infarct transmurality and therefore has implications for LV remodeling.[18,19]

Table 4. Univariate linear regression of predictors of 1-month LV dilation

Variable	B	SE	*P* value
Age	0.09	0.24	.71
Sex	7.46	7.05	.29
Symptom-to-balloon time	2.09	1.61	.20
Anterior infarct location	−4.54	6.72	.50
Pattern of BNP release	14.15	4.92	.007
DT	−0.13	0.06	.05
LV volume–mass ratio	31.74	14.66	.03
SPECT infarct size	0.50	0.24	.04
SPECT infarct severity	−27.56	19.44	.16

DT, Wave deceleration time of early transmitral flow; *BNP*, brain natriuretic peptide.

Table 5. Multivariate analysis: Predictors of 1-month LV dilation

	Multiple stepwise regression analysis		
	B	SE	*P* value
Pattern of BNP release	18.24	4.93	.001
LV volume–mass ratio	−38.05	14.30	.01
SPECT infarct size	0.44	0.20	.03

Table 6. Multivariate analysis: Clinical-imaging and clinical-serum model in predicting 1-month LV dilation

	Hierarchic multiple regression analysis		
Model	R^2	R^2 change	*P* value
1° Step: Clinical-imaging	0.17	—	.39
2° Step: Clinical-serum	0.48	0.31	.004

The clinical-imaging model comprises infarct anterior location, symptom-to-balloon time, LV volume/mass index, SPECT infarct size, and SPECT infarct severity. The clinical-serum model comprises infarct anterior location, symptom-to-balloon time, LV volume/mass index, pattern of BNP release, and serum ICTP.

Plasma BNP Release, Collagen Degradation, ECM Remodeling, and LV Remodeling

Even in patients with low LVEF after AMI, progressive LV dilation is not always observed.[30] A number of factors other than infarct size probably contribute to prevent LV dilation in these subjects.[30-34] In this study patients with sustained release of BNP early after AMI and those without sustained release of BNP had similar SPECT infarct size and severity. This is not surprising because BNP may reflect the size or severity of the ischemic insult even when myocardial necrosis has not occurred.[35] Accordingly, our patients with sustained BNP release had longer symptom-to-balloon time and greater impairment of LV function and more frequently had multivessel disease as compared with patients without sustained BNP release. For the same reason, we observed that baseline values of plasma BNP did not correlate with SPECT infarct size.

In our group of patients with sustained high BNP and serum ICTP levels early after AMI, LV dilation occurred at month 1 after index AMI. Of note, serum increase in ICTP release during the early stage of index AMI (from day 1 to day 3) significantly interacts with the relationship between pattern of BNP release and subsequent LV dilation. To our knowledge, this interaction has not been reported previously in AMI patients. The patients with sustained BNP release show higher baseline values of LV volume–mass ratio and shorter values of mitral DT, which are markers of increased wall tension,[30] as well as LV filling pressure.[36] Furthermore, we found the sustained pattern of BNP release and the LV volume–mass ratio to be the 2 most important predictors of 1-month LV dilation. We also determined how well a clinical-serum model performs when a clinical-imaging model has already been taken into account. Although the results of this observational study are associative findings in a small patient population, they are suggestive for generating the following hypothesis. Because higher concentrations of BNP are likely needed to induce ECM degradation,[5] it is possible that sustained high BNP level early after AMI might be potentially harmful by allowing greater type I collagen degradation, as well as consequent LV dilation, under the effect of mechanical force.[37] Thus MMP inhibitors have the potential for postinfarction LV dilation prevention.[38]

Study Limitations

Temporal changes in serum levels of procollagens are only surrogate markers of ECM remodeling; however, the biochemical method we used has been validated by other groups.[39] Several strategies currently used to prevent remodeling after myocardial infarction, such as angiotensin-converting enzyme inhibitors with or without aldosterone antagonists, β-blockers, and angiotensin II receptor blockers, exert pleiotropic effects that can potentially affect collagen turnover.[40] However, there were no differences in treatment between the 2 study groups. It must be acknowledged that magnetic resonance imaging via delayed contrast enhancement is probably more accurate than Tc-99m sestamibi SPECT

in the assessment of small infarction and infarct transmurality.[41] However, the large number of studies based on Tc-99m sestamibi SPECT infarct size still justifies the use of this approach that offers major advantages in terms of ease and wide availability. Finally, this study included only patients who had LV systolic dysfunction (LVEF ≤40%) for a first ST–segment elevation AMI and who were treated with percutaneous coronary intervention. Whether our results can be extrapolated to the broad population of AMI patients remains to be shown.

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