

Increased Level of Pericardial Insulin-Like Growth Factor-1 in Patients With Left Ventricular Dysfunction and Advanced Heart Failure

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OBJECTIVES	To test the hypothesis that the cardiac insulin-like growth factor-1 (IGF-1) system is up-regulated in the failing heart, we measured the pericardial (cardiac) and plasma (circulating) IGF-1 levels in coronary artery disease patients.
BACKGROUND	Local IGF-1 systems are regulated differently from the systemic IGF-1 system. The cardiac IGF-1 system is up-regulated by the increased left ventricular (LV) wall stress. However, it remains unknown how this system is affected in LV dysfunction and heart failure.
METHODS	We measured the plasma and pericardial fluid levels of IGF-1 and brain natriuretic peptide (BNP) in 87 coronary artery disease patients undergoing cardiac surgery, and examined their relationships with LV function and heart failure severity. The expressions of IGF-1 and IGF-1 receptor proteins were examined in endomyocardial biopsies obtained from other patients with normal or impaired LV function.
RESULTS	The pericardial IGF-1 and BNP levels were positively correlated with the plasma BNP level (both $p < 0.001$). The pericardial IGF-1 level was increased in heart failure patients, whereas the plasma IGF-1 level was rather decreased. The pericardial IGF-1 level was inversely correlated with the LV ejection fraction ($p < 0.001$), whereas the plasma IGF-1 level was not. Positive immunostaining for IGF-1 and IGF-1 receptor proteins was enhanced in myocardial biopsies from failing hearts compared with those from nonfailing hearts.
CONCLUSIONS	The pericardial IGF-1 level was increased in patients with LV dysfunction and heart failure, whereas the plasma IGF-1 level was decreased. These results may indicate that up-regulation of the cardiac IGF-1 system serves as a compensatory mechanism for LV dysfunction. (J Am Coll Cardiol 2006;48:1387-95) © 2006 by the American College of Cardiology Foundation

Circulating insulin-like growth factor-1 (IGF-1) is mainly released from the liver in response to growth hormone secreted from the pituitary gland, and is chiefly bound to insulin-like growth factor binding protein (IGFBP). The IGF-1-IGFBP complex is transported to target organs (or tissues), where the free form of IGF-1 binds to the IGF-1 receptor and mediates the actions of growth hormone (1). Previous experimental studies have reported several roles for IGF-1 in the heart. Particularly, cardiomyocyte apoptosis during reperfusion injury was prevented in IGF-1 transgenic mice (2); IGF-1 enhanced ventricular hypertrophy and function during the initial phase of experimental cardiac failure (3); and IGF-1 showed distinct positive inotropic properties by sensitizing myofilaments to Ca^{2+} without increasing myocyte Ca^{2+} currents (4).

On the other hand, local (tissue) IGF-1 systems exist that are regulated differently from the circulating IGF-1 system (1) and regulate tissue development (1,5-7). Both IGF-1 and IGF-1 receptor mRNA levels in the myocardium are up-regulated in an experimental angiotensin II-induced hypertension model (8). In humans, IGF-1 production in the heart, which was estimated by the difference in the

plasma concentrations between the aorta and coronary sinus, is increased in patients with valvular heart disease (9). These experimental and clinical studies suggest that the local cardiac IGF-1 system is up-regulated, presumably by increases in the left ventricular wall stress. However, it remains unknown how the cardiac IGF-1 system is involved in the pathophysiology of left ventricular dysfunction and heart failure induced by coronary artery disease (CAD). In the present study, we tested the hypothesis that the cardiac IGF-1 system is up-regulated with the progression of left ventricular dysfunction by measuring the pericardial (cardiac) and plasma (circulating) levels of IGF-1 in CAD patients, and examining their correlations with parameters for left ventricular function as well as the pericardial and plasma levels of brain natriuretic peptide (BNP), a sensitive biochemical marker for the severity of heart failure (10). Furthermore, we examined the expressions of IGF-1 and IGF-1 receptor proteins in the human endomyocardial biopsy samples obtained from the patients with or without left ventricular dysfunction.

METHODS

Study patients. The protocol of the present study was approved by the ethics committee of our institution. All of the patients gave informed consent before the study commenced.

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Abbreviations and Acronyms

ANOVA	= analysis of variance
BNP	= brain natriuretic peptide
CABG	= coronary artery bypass graft surgery
CAD	= coronary artery disease
IGF-1	= insulin-like growth factor-1
IGFBP	= insulin-like growth factor binding protein
LVEF	= left ventricular ejection fraction
LVG	= left ventriculography
NYHA	= New York Heart Association

A total of 87 consecutive patients who underwent elective coronary artery bypass graft surgery (CABG) for CAD and biplanar left ventriculography (LVG) before the surgery were enrolled between April 2001 and December 2003. The clinical profiles of these patients, including their New York Heart Association (NYHA) functional classes and left ventricular ejection fraction (LVEF), are shown in Table 1. Among the patients, 5 had single-vessel disease, 17 had double-vessel disease, 65 had triple-vessel disease, and the remaining 5 had left main trunk disease. The patients were administered angiotensin-converting enzyme inhibitor (n = 37), angiotensin II type 1 receptor blocker (n = 35), furosemide (n = 28), beta-blocker (n = 67), aspirin (n = 81), warfarin (n = 11), digoxin (n = 3), nitrates (n = 19),

Table 1. Clinical Characteristics of Study Patients

	Patients (n = 87)
Age (yrs)	66 ± 10
Gender (male/female)	54/33
Weight (kg)	60 ± 10
Height (cm)	158 ± 1
Body mass index (kg/m ²)	24.3 ± 3.0
NYHA functional class	
I	43
II	31
III	13
Laboratory data	
Blood sugar (mg/dl)	119 ± 36
Hemoglobin A1c (%)	6.1 ± 1.3
Cholinesterase (IU/l)	121 ± 30
Serum total cholesterol (mg/ml)	191 ± 42
Mean resting blood pressure (mm Hg)	128/70
Hypertension (%)	68%
Diabetes (%)	60%
Dyslipidemia (%)	47%
Smoking (%)	55%
LVEDVI (ml/m ²)	102 ± 29
LVESVI (ml/m ²)	56 ± 28
LVEF (%)	47 ± 14
Subgroups divided by LVEF	
<30%	18
30% to 50%	38
>50%	31
CI (l/min/m ²)	2.6 ± 0.7
PCWP (mm Hg)	11 ± 7

Data are given as mean values ± SD.

CI = cardiac index; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; NYHA = New York Heart Association; PCWP = pulmonary capillary wedge pressure.

and hydroxymethyl glutaryl coenzyme A reductase inhibitor (n = 55). Patients with severe renal failure, liver dysfunction, inflammatory disease, cancer, thyroid disease, or uncontrolled diabetes mellitus were excluded. Furthermore, patients who underwent emergency CABG were excluded.

Before the CABG, cardiac catheterization including coronary angiography and biplanar LVG was performed in all patients. Two cardiologists who were unaware of the results for the IGF-1 and BNP levels analyzed the LVG using an LVG analysis system (Cardio 500; Kontron Instruments, Eching, Germany) and determined the left ventricular end-diastolic volume index and LVEF.

Ideally, we would have preferred to obtain myocardial tissue biopsy samples during the CABG. However, we were unable to do it from an ethical point of view. Alternatively, we examined the expressions of IGF-1 and IGF-1 receptor proteins immunohistochemically in endomyocardial biopsy samples obtained from other patients with normal or impaired left ventricular function. These patients consisted of 4 patients with impaired left ventricular function caused by dilated cardiomyopathy and 4 with ventricular tachycardia or electrocardiographic abnormalities and with normal function. Right ventricular endomyocardial biopsy samples were obtained during diagnostic cardiac catheterization. In one particular patient with left ventricular dysfunction caused by dilated cardiomyopathy and with massive pericardial effusion, who had previously undergone transsphenoidal surgery against acromegaly and had a decreased plasma IGF-1 level (14 ng/ml), pericardial fluid was obtained via a pericardiocentesis in addition to the endomyocardial biopsy sample.

Measurements of the IGF-1 and BNP levels in blood and pericardial fluid samples. Pericardial fluid samples were obtained during CABG under general anesthesia. Immediately after the creation of a small incision in the pericardium, undiluted samples of pericardial fluid were obtained. Samples contaminated with blood were discharged. The samples were collected into sterile tubes, immediately placed on ice, clarified by centrifugation at 3,000 × g for 10 min at 4°C, and rapidly frozen and stored at -80°C until analysis. The levels of total IGF-1, free IGF-1, and BNP were measured in duplicate using sensitive and specific enzyme-linked immunosorbent assays (ELISAs; total IGF-1 by ELISA DSL-10-2800 and free IGF-1 by ELISA DSL-10-9400; Diagnostic System Laboratories, Inc., Webster, Texas), and immunoradiometric assays (Shionoria BNP RIA kit, Shionogi, Japan), respectively. The interassay coefficients of variation for total IGF-1, free IGF-1, and BNP were <15%, <6.2%, and <10%, respectively. It is known that IGF-1 is stable in frozen samples (11). The plasma total IGF-1 and BNP levels were measured in 39 of the 87 patients. Venous blood samples (10 ml) were collected in the morning between 6 and 7 AM while the patients were in a fasting state. After centrifugation at 3,000 × g for 15 min, aliquots were stored at -80°C until analysis. We also measured the serum cholinesterase level using a spectrometric assay (ChE-CL;

Serotec, Sapporo, Japan) as a marker for protein synthesis activity in the liver, and examined its relationships with the plasma IGF-1 and BNP levels.

Immunohistochemistry for IGF-1 and IGF-1 receptor proteins. Endomyocardial biopsy samples were fixed in 10% formalin, embedded in paraffin, serially cut into 5- μ m-thick sections, and subjected to immunoenzymatic staining using the DAKO LSAB system (K0679; DakoCytomation, Carpinteria, California) (12). Briefly, the sections were pre-incubated with 0.3% hydrogen peroxide, washed, and incubated with a rabbit polyclonal anti-IGF-1 antibody (5345-0225; Biogenesis, Oxford, United Kingdom; 1:50 dilution) or rabbit polyclonal anti-IGF-1R α antibody (sc-712; Santa Cruz Biotechnology, Santa Cruz, California; 1:100 dilution) containing 1% bovine serum albumin for 30 min. After washing, the sections were sequentially incubated with biotinylated anti-rabbit immunoglobulins for 15 min and horseradish peroxidase-conjugated streptavidin for 15 min. Peroxidase activity was visualized with a diaminobenzidine chromogen solution. Each stained histological section was examined under a microscope (Carl Zeiss, Jena, Germany) connected to a computerized image-analysis system (AxioVision; Carl Zeiss). The degrees of protein expression were estimated according to the following scale: 0, samples without any staining; 1+, samples with weak staining; 2+, samples with moderate staining; 3+, samples with markedly enhanced staining. This estimation was

performed by 2 independent investigators without any knowledge of the patient profiles.

Statistical analysis. All data are shown as mean values \pm 1 SD, with the exception of the IGF-1 and BNP levels. Because the IGF-1 and BNP levels were not normally distributed, they are shown as the median with an interquartile range. For comparison of the data between the 2 groups, nonparametric analysis (Mann-Whitney *U* test) was used. For comparison among the 3 groups, analysis of variance (ANOVA) with post hoc Bonferroni comparisons was used. A linear regression analysis was performed to examine the correlations between each of the LVG parameters and the BNP and IGF-1 levels. We performed a multiple regression analysis to examine whether age affects association of plasma total IGF-1 level with heart failure or the LVEF. The degrees of immunostaining for IGF-1 and IGF-1 receptor proteins in the biopsy samples were compared between the groups with left ventricular dysfunction and normal function using the chi-square test. We used log-transformed values of BNP (log BNP) for statistical regression analysis because of the skewed distribution. Values of $p < 0.05$ were considered significant.

RESULTS

Plasma and pericardial levels of BNP and IGF-1. The pericardial total IGF-1 median level was 27 ng/ml with an

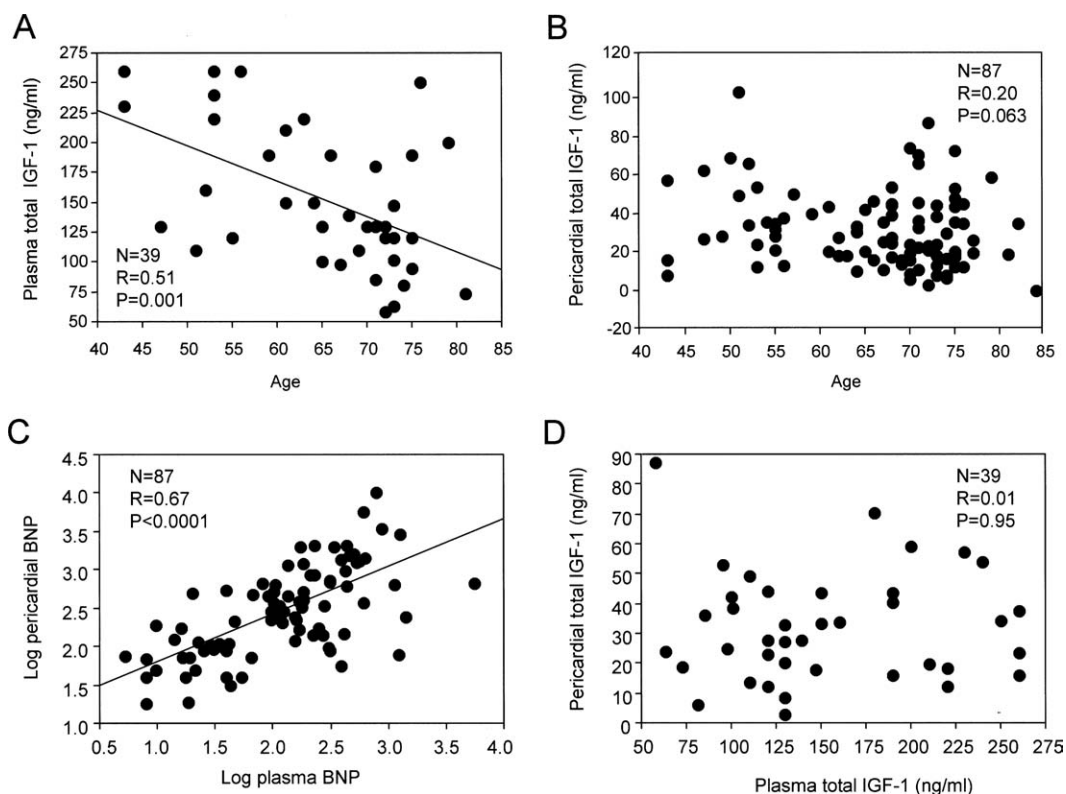


Figure 1. (A) Relationship between age and the plasma total insulin-like growth factor-1 (IGF-1) level. (B) Relationship between age and the pericardial total IGF-1 level. (C) Relationship between the plasma and pericardial brain natriuretic peptide (BNP) levels. (D) Relationship between the plasma and pericardial total IGF-1 levels.

interquartile range of 27 ng/ml, and was lower than the plasma IGF-1 median level of 130 ng/ml with an interquartile range of 88 ng/ml ($p < 0.0001$ by Mann-Whitney U test). The pericardial free IGF-1 median level was 1.0 ng/ml with an interquartile range of 1.0 ng/ml, and was lower than the pericardial total IGF-1 median level ($p < 0.0001$ by Mann-Whitney U test). In contrast, the pericardial BNP median level was 286 pg/ml with an interquartile range of 607 pg/ml for all patients, and was 2-fold higher than the plasma median level of 153 pg/ml with an interquartile range of 285 pg/ml ($p < 0.0001$ by Mann-Whitney U test).

Correlations between age and the plasma and pericardial levels of IGF-1 and BNP. There was a significant negative correlation between age and the plasma total IGF-1 level (Fig. 1A). In contrast, the pericardial total IGF-1 level was not correlated with age (Fig. 1B). Neither the plasma nor the pericardial BNP level was correlated with age (data not shown). The pericardial BNP level was well correlated with the plasma BNP level (Fig. 1C). However, the pericardial total IGF-1 level was not correlated with the plasma total IGF-1 level (Fig. 1D).

Relationships of the IGF-1 and BNP levels with LVEF. Both the total and free pericardial IGF-1 levels were negatively correlated with LVEF (total IGF-1: $r = 0.45$, $p < 0.0001$; free IGF-1: $r = 0.37$, $p < 0.001$), whereas the

plasma total IGF-1 level was not ($r = 0.12$, $p = \text{NS}$). The plasma BNP level was negatively correlated with the LVEF ($r = 0.53$, $p < 0.0001$).

Figure 2 shows the pericardial total IGF-1 levels (Fig. 2A), free IGF-1 levels (Fig. 2B), plasma total IGF-1 levels (Fig. 2C), and plasma BNP levels (Fig. 2D) in patient groups with LVEF values of $>50\%$, 30% to 50% , and $<30\%$. The pericardial total and free IGF-1 levels were significantly higher in the LVEF $<30\%$ group than in the LVEF $>50\%$ group (by ANOVA). The plasma total IGF-1 levels did not differ among the 3 groups. The plasma BNP level was significantly higher in the LVEF $<30\%$ group than in the LVEF $>50\%$ group (by ANOVA).

Relationships of the IGF-1 and BNP levels to NYHA functional classes. The pericardial total and free IGF-1 levels were significantly higher in the patient group with NYHA functional class III than in the patient group with NYHA functional class I (Figs. 3A and 3B) (by ANOVA). On the other hand, the plasma total IGF-1 level was significantly lower in the patient group with NYHA functional class III than in the patient group with NYHA functional class I (Fig. 3C) (by ANOVA). The plasma BNP level was significantly higher in the patient group with NYHA functional class III than in the patient groups with NYHA functional classes I and II (Fig. 3D) (by ANOVA). After age was adjusted, the plasma total IGF-1 level was

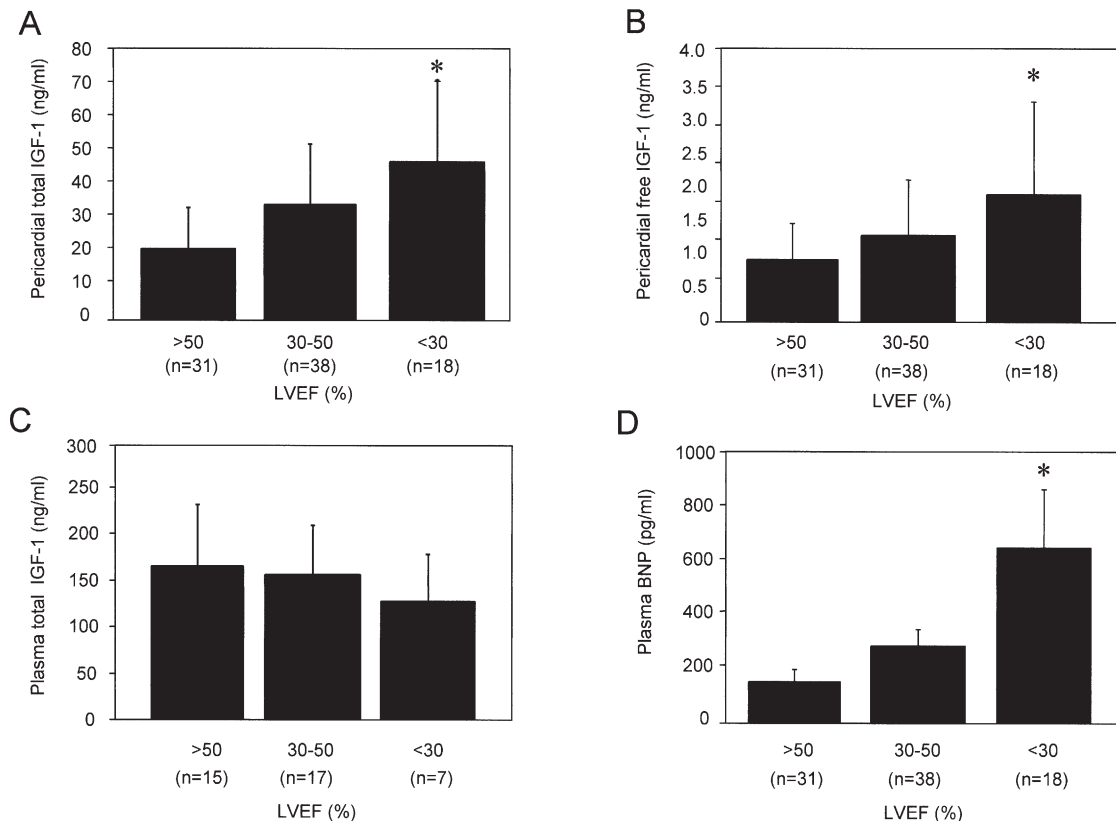


Figure 2. Pericardial total insulin-like growth factor-1 (IGF-1) levels (A), pericardial free IGF-1 levels (B), plasma total IGF-1 levels (C), and plasma brain natriuretic peptide (BNP) levels (D) in patient groups with left ventricular ejection fraction (LVEF) values of $>50\%$, 30% to 50% , and $<30\%$. * $p < 0.01$ compared with the LVEF $>50\%$ group.

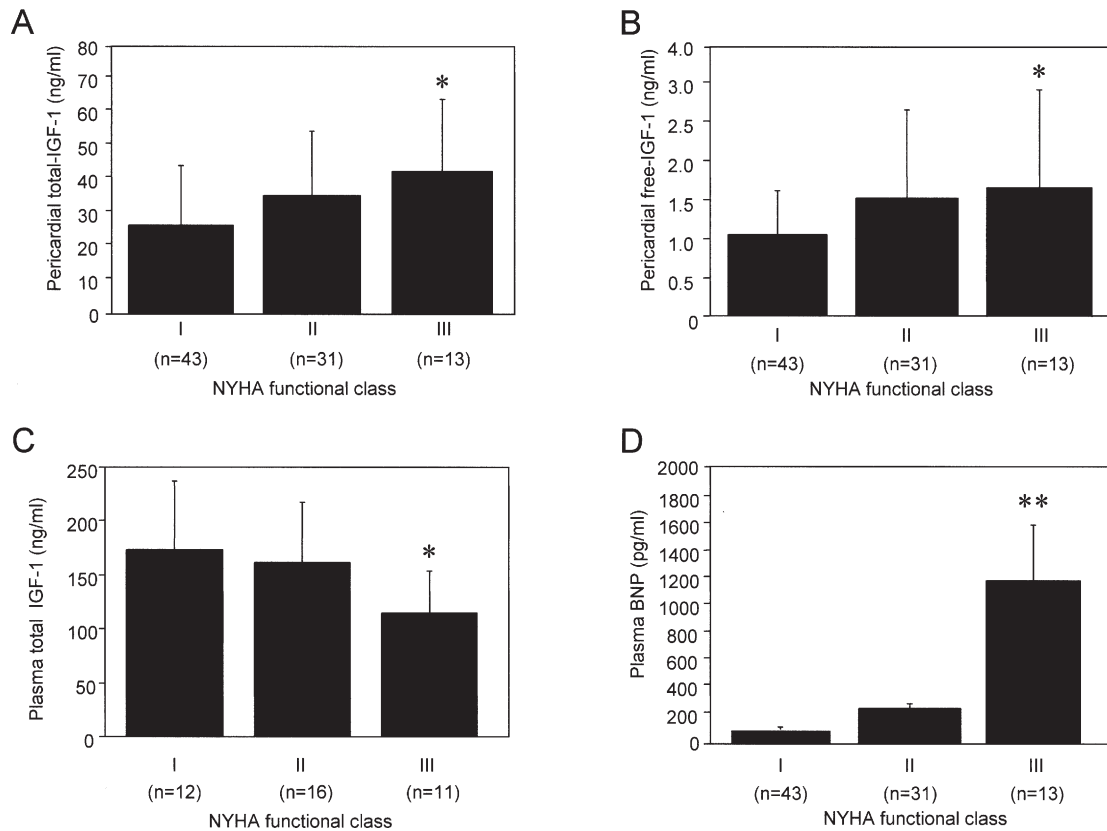


Figure 3. Pericardial total insulin-like growth factor-1 (IGF-1) levels (A), pericardial free IGF-1 levels (B), plasma total IGF-1 levels (C), and plasma brain natriuretic peptide (BNP) levels (D) in patient groups with New York Heart Association (NYHA) functional classes I, II, and III. * $p < 0.05$ compared with class I. ** $p < 0.001$ compared with classes I and II.

still significantly lower in the patient group with NYHA functional class III than in the patient group with NYHA functional class I ($p < 0.05$).

Relationships between IGF-1 and BNP levels. The pericardial total and free IGF-1 levels were both positively correlated with the plasma BNP level (Figs. 4A and 4B). In contrast, the plasma IGF-1 level was negatively correlated with the plasma BNP level (Fig. 4C).

Relationships among the plasma total IGF-1 and BNP levels and the serum cholinesterase level. The serum cholinesterase level (IU/l) was significantly lower in the patient group with NYHA functional class III (99 ± 19) than in the patient groups with NYHA functional classes I (128 ± 28) and II (120 ± 33) (both $p < 0.05$). There was a significant positive correlation between the plasma total IGF-1 level and the serum cholinesterase level ($r = 0.47$, $p < 0.01$, $n = 39$) and a significant negative correlation between the plasma BNP level and the serum cholinesterase level ($r = 0.37$, $p < 0.01$, $n = 87$).

Immunohistochemical analyses of IGF-1 and IGF-1 receptor proteins in the endomyocardial biopsy samples. Figure 5 shows the different degrees of staining for IGF-1 and IGF-1 receptor proteins in the endomyocardial biopsy samples obtained from 3 patients. In the left panels, brown positive immunostaining signals for IGF-1 and IGF-1

receptor proteins were distinct in both cardiomyocytes and interstitial cells and were assessed as 3+. In the center panels, the degrees of positive staining for IGF-1 and IGF-1 receptor proteins were assessed as 2+, whereas in the right panels, the degrees were assessed as 1+. Table 2 shows the clinical profiles and the degrees of immunostaining in 4 patients with left ventricular dysfunction (cases 1 to 4) and 4 patients with normal left ventricular function (cases 5 to 8). In all patients, some degrees of positive staining for IGF-1 and IGF-1 receptor proteins were observed. In the patients with normal left ventricular function, the degrees of staining for IGF-1 protein were all 1+, whereas those for IGF-1 receptor protein were 1+ in 2 patients and 2+ in the other 2 patients. In the patients with left ventricular dysfunction, the degrees were all increased as $\geq 2+$. The degrees of staining for IGF-1 and IGF-1 receptor proteins in the group with left ventricular dysfunction were higher than those in the group with normal left ventricular function (IGF-1: $p < 0.05$, IGF-1 receptor: $p = 0.06$ by chi-square test).

In one patient with dilated cardiomyopathy who previously underwent trans-sphenoidal surgery, the plasma total IGF-1 level was 14 ng/ml, whereas the pericardial total IGF-1 level was 72 ng/ml. The degrees of positive staining for IGF-1 and IGF-1 receptor proteins were both assessed as 2+ (center panel in Fig. 5).

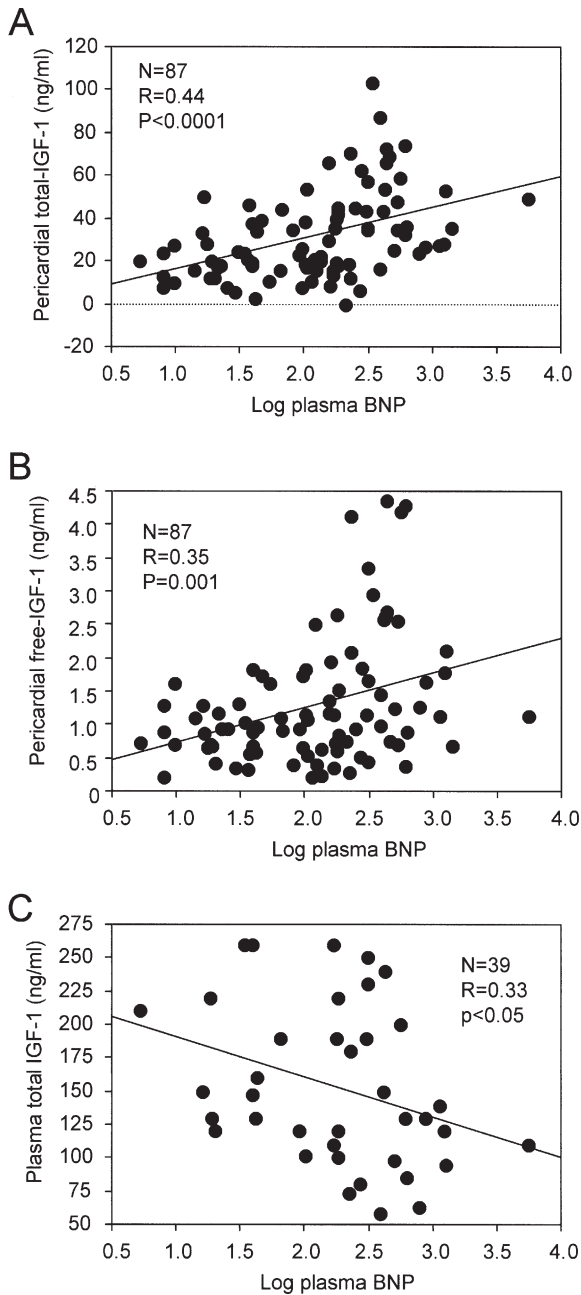


Figure 4. (A) Relationship between the plasma brain natriuretic peptide (BNP) and pericardial total insulin-like growth factor-1 (IGF-1) levels. (B) Relationship between the plasma BNP and pericardial free IGF-1 levels. (C) Relationship between the plasma BNP and plasma total IGF-1 levels.

DISCUSSION

The major findings of the present study are as follows: the pericardial total and free IGF-1 levels were increased in patients with left ventricular dysfunction and advanced heart failure, and were positively correlated with the plasma BNP level. In contrast, the plasma total IGF-1 level was inversely correlated with the plasma BNP level. Furthermore, the expressions of IGF-1 and IGF-1 receptor protein were enhanced in patients with decreased left ventricular function compared with patients with normal left ventricular func-

tion. These results indicate that the local cardiac IGF-1 system is up-regulated with progression of left ventricular dysfunction, but is regulated differently from the circulating IGF-1 system, which is rather attenuated in advanced heart failure.

Circulating and local IGF-1 systems in cardiovascular disease. To estimate the cardiac IGF-1 system, we measured the pericardial IGF-1 level because many studies have shown that pericardial fluid is useful for investigating the severity of ischemic or failing hearts in humans (13,14). Brain natriuretic peptide is mainly produced by the failing heart, and is released into the systemic circulation or pericardial fluid. Moreover, both the plasma and the pericardial BNP levels were increased with the severity of the NYHA functional class, and the pericardial BNP level was 2-fold higher than the plasma level. These results are consistent with those of a previous study (15), and indicate that the pericardial fluid strongly reflects the circumstances in the myocardial tissue.

Recently, IGF-1 was suggested to be locally produced in various tissues, such as the heart, skeletal muscle, and bone, and this local IGF-1 seems to play significant roles in tissue development (1,6,7). Sjögren et al. (5) showed that circulating liver-derived IGF-1 is not required for postnatal body growth in mice, and that locally produced IGF-1 acting in an autocrine/paracrine fashion is more important than liver-derived IGF-1. Neri Serneri et al. (9) confirmed the existence of a tissue IGF-1 system in the human heart by showing a difference in the plasma concentrations between the aorta and coronary sinus, and by reverse transcriptase-polymerase chain reaction and in situ hybridization analyses in ventricular biopsy samples from patients with valvular heart disease. To the best of our knowledge, the present study is the first report to compare the pericardial (local) and plasma (systemic) levels of IGF-1 in patients with CAD and to suggest a role for the cardiac IGF-1 system in the pathophysiology of heart failure.

It should be pointed out that the pericardial total IGF-1 level was lower than the plasma level. The pericardial space is a large lymphatic sac, and the composition of the pericardial fluid is influenced by the myocardial interstitial fluid (16). Laham et al. (17) reported that intrapericardial delivery provides markedly higher myocardial deposition and retention than intracoronary or intravenous delivery. In the present study, we measured not only the pericardial total IGF-1 level, but also the free IGF-1 level, because free IGF-1 separated from the IGF-1-IGFBP complex is bioactive. The free IGF-1 level accounted for 4.2% of the total IGF-1 level in the pericardial fluid, whereas it is generally <1% of the total IGF-1 level in the plasma in healthy subjects (18–20). These findings suggest that even a lower level of pericardial IGF-1, such as that in the present study, may function against the failing heart.

Increased pericardial total and free IGF-1 levels in left ventricular dysfunction. Both the pericardial total and free IGF-1 levels were inversely correlated with the LVEF in the present study. Ideally, we would have preferred to obtain

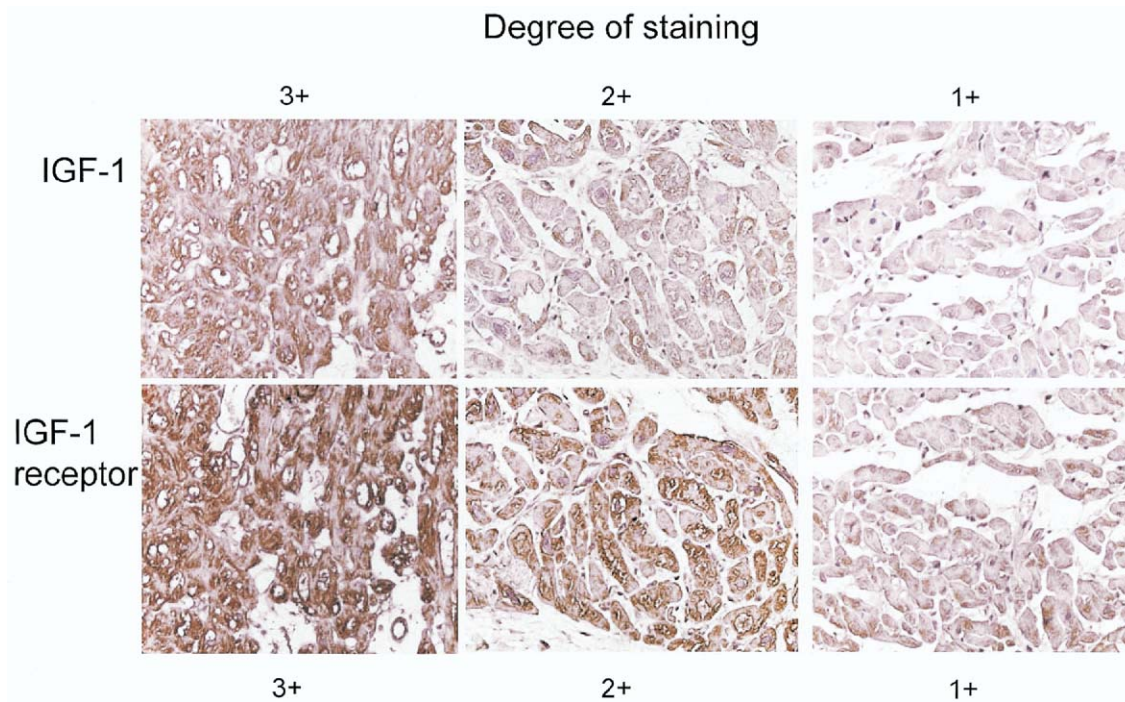


Figure 5. Different degrees of immunostaining for insulin-like growth factor-1 (IGF-1) and IGF-1 receptor proteins in endomyocardial biopsy samples obtained from 3 patients. 3+ = markedly enhanced staining; 2+ = moderate staining; 1+ = weak staining. See text for discussion.

myocardial tissue biopsy samples during CABG. However, we were unable to do it from an ethical point of view. Alternatively, we examined the expressions of IGF-1 and IGF-1 receptor proteins immunohistochemically in the endomyocardial biopsy samples obtained from other patients with normal (4 patients) or impaired (4 patients) left ventricular function. This immunohistochemical results showed that IGF-1 and IGF-1 receptor proteins were present in the myocardial tissue, and their expressions were enhanced in patients with decreased left ventricular function compared with those in patients with normal left ventricular function. These findings strongly suggest that a high pericardial IGF-1 level is closely related to left ventricular dysfunction. Cardiac IGF-1 formation was previously found

to be increased in patients with increased left ventricular wall stress and athletes with physiological hypertrophy (9,21). Moreover, the myocardial IGF-1 level is increased in an experimental myocardial infarction model (22,23). Furthermore, IGF-1 mRNA expression is increased by graded mechanical stress in the rat heart Langendorff model, which is not affected by circulating IGF-1 (24). These studies support the presence of a local tissue IGF-1 system in the heart. However, it remains unclear whether left ventricular dysfunction leads to an increased level of pericardial IGF-1 or vice versa, although many studies have reported that IGF-1 has a protective effect on the heart (2-4,25-27). Further studies are needed.

Table 2. Degrees of IGF-1 and IGF-1 Receptor Staining in the Myocardial Biopsy Tissues Obtained From Patients With Impaired and Normal Left Ventricular Function

	Age	Gender	Diagnosis	LVEF (%)	IGF-1	IGF-1 Receptor
Case 1	54	M	DCM	35	3+	3+
Case 2	71	M	DCM	31	2+	3+
Case 3	71	F	DCM	36	2+	3+
Case 4	34	M	DCM	26	2+	2+
Case 5	34	F	VT	53	1+	2+
Case 6	73	M	ECG abnormality	71	1+	2+
Case 7	15	F	ECG abnormality	68	1+	1+
Case 8	71	F	VT	57	1+	1+

1+ = mildly stained; 2+ = moderately stained; 3+ = strongly stained.
 DCM = dilated cardiomyopathy; ECG = electrocardiogram; IGF-1 = insulin-like growth factor-1; LVEF = left ventricular ejection fraction; VT = ventricular tachycardia.

Decreased plasma IGF-1 level in heart failure. The plasma BNP level is well known to reflect the severity of heart failure (28). In the present study, the plasma total IGF-1 level was inversely correlated with the plasma BNP level, whereas the pericardial total and free IGF-1 levels were positively correlated with it. Moreover, the pericardial BNP level was positively correlated with the plasma BNP level. Thus, the IGF-1 level shows a disparity between the plasma and pericardial fluid. The mechanism of the decrease in the plasma IGF-1 level still remains unclear. The plasma total IGF-1 level is known to gradually increase after birth, and then gradually decrease with age in adults. In fact, our results showed that the plasma total IGF-1 level was inversely correlated with age. Previous clinical studies have shown that the plasma total IGF-1 level is decreased in patients with advanced heart failure (29,30) and that the plasma IGF-1 level is inversely related to the risk of

congestive heart failure in elderly people without previous myocardial infarction (31). In the present study, the plasma total IGF-1 level was positively correlated with the serum cholinesterase level, which reflects the ability of protein synthesis in the liver. We believe that the decrease in the plasma total IGF-1 level in patients with advanced heart failure results from the decreased protein synthetic activity caused by congestive liver dysfunction. In fact, impaired hepatic function attributable to biventricular cardiac failure and hepatic stasis was reported to cause reduced synthesis and release of IGF-1 (32). It should be stressed that the plasma BNP level was confirmed to predict LVEF and NYHA functional class, and was generally a stronger predictor than pericardial IGF-1 (Figs. 2 and 3).

Study limitations. Although the composition of the pericardial fluid was reported to be influenced by the myocardial interstitial fluid (16), we do not have any direct evidence of a correlation between the IGF-1 levels in the pericardial and interstitial fluids. The enhanced expressions of IGF-1 and IGF-1 receptor proteins in endomyocardial biopsy samples obtained from the failing heart may explain the increased level of IGF-1 in the pericardial fluid. The present study only included patients who underwent CABG under general anesthesia. No data were obtained from subjects with a normal heart because it is ethically impossible to sample pericardial fluid from normal subjects. Therefore, it is difficult to compare the levels of substances in the pericardial fluid between patients with CAD and healthy subjects. We also were unable to obtain permission for biopsy samples from the ethics committee of our institute. Therefore, we examined the expressions of IGF-1 and IGF-1 receptor proteins immunohistochemically in endomyocardial biopsy samples obtained from other patients with normal or impaired left ventricular function.

In conclusion, the pericardial total and free IGF-1 levels were both increased in patients with left ventricular dysfunction and advanced heart failure. In contrast, the plasma total IGF-1 level was inversely correlated with the plasma BNP level. These results indicate that the local cardiac IGF-1 system is up-regulated with progression of left ventricular dysfunction and heart failure.

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