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Original article

Serum syndecan-4 is a novel biomarker for patients with chronic heart failure

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KEYWORDS
Heart failure;
Ventricular remodeling;
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Summary
Background: Syndecan-4 is a transmembrane heparan sulfate-carrying glycoprotein that mediates signal transduction pathways activated by growth factors and cell surface receptors, thereby modulating tissue regeneration, angiogenesis, and focal adhesion. The aim of the present study was to determine the clinical use of serum syndecan-4 concentration for diagnosis of heart failure.
Methods: Concentration of serum syndecan-4 and other biomarkers of heart failure was measured in 45 patients with heart failure and 21 healthy subjects. Clinical and echocardiographic parameters of cardiac function were recorded.
Results: Serum syndecan-4 concentration significantly increased in proportion to the decrease in ejection fraction ($r = -0.599$, $p < 0.001$) and increase in the left ventricular (LV) mass index ($r = 0.315$, $p < 0.05$). Serum syndecan-4 concentration was significantly correlated with LV geometrical parameters (i.e. LV mass index, LV end-diastolic volume, and LV dimension), while B-type natriuretic peptide (BNP) was significantly correlated with pressure-related parameters [i.e. early transmitral flow velocity/early diastolic velocity of the mitral valve annulus (E/e'), right ventricular systolic pressure, and left atrial volume index]. Syndecan-4 concentration did not significantly correlate with plasma BNP, transforming growth factor-1, matrix metalloproteinase-2, and tenascin-C concentrations. Serum syndecan-4 concentration could predict cardiac death and re-hospitalization due to heart failure (area under curve, 0.706, $p < 0.05$).

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Conclusion: Serum syndecan-4 concentration shows promise as a novel diagnostic and prognostic biomarker for heart failure. Since syndecan-4 correlated with LV geometrical rather than hemodynamic parameters, serum syndecan-4 may represent a biomarker of LV remodeling in the failing heart.

Introduction

Chronic heart failure results from myocardial degradation and pathologic structural regeneration in a process known as cardiac remodeling. This multistage and multicellular repair process is mediated by a complex interplay between growth factors and cytokines. Progressive and end-stage heart failure is a culmination of this pathologic process. Many biomarkers have been proposed to diagnose heart failure and predict prognosis of the patient. However, the type of cardiac function that each biomarker represents remains uncertain.

Various studies have demonstrated that extracellular matrix (ECM) components, namely proteoglycans and fibrous proteins such as collagen, play an essential role in cardiac remodeling. Although the role of collagen in cardiac hypertrophy and heart failure has already been well characterized, comparatively little is known about the role of proteoglycans. Proteoglycans bind to long-chain polysaccharide glucosaminoglycans on the cell surface, and those consisting of transmembrane core proteins carrying heparan and chondroitin sulfate are called syndecans. Syndecans are thought to mediate cardiac remodeling by transmitting the cellular actions of a number of growth factors, including fibroblast growth factor, vascular endothelial growth factor, and transforming growth factor-beta (TGF-β) [1,2].

Syndecan-4 (ryudocan) is the most extensively studied isoform of the syndecan family. Syndecan-4 knockout mice show delayed wound repair and impaired angiogenesis [3]. In the skeletal muscle of syndecan-4 knockout mice, satellite cells cannot reconstitute damaged cells and cannot proliferate and differentiate into myotubes, suggesting that syndecan-4 also participates in muscle development and regeneration [4]. Furthermore, the plasma syndecan-4 level is elevated in patients with acute myocardial infarction with a peak at 2 weeks after infarction [5].

Although syndecan-4 plays a significant role in the cardiovascular system, the role of syndecan-4 in heart failure remains unclear. Thus, the present study investigated the clinical use of serum syndecan-4 concentration as a representative component of ECM in the diagnosis of heart failure. The aims of the study were: (1) to determine which echocardiographic parameters are represented by serum syndecan-4 concentration; (2) to determine whether serum syndecan-4 concentration predicts prognosis of patients with heart failure; and (3) to determine the difference between syndecan-4 as a potential biomarker for heart failure and those currently being used [i.e. B-type natriuretic peptide (BNP), TGF-β1, matrix metalloproteinase-2 (MMP2), and tenascin-C]. At present, BNP is considered the most powerful predictor of cardiac death and re-hospitalization for heart failure. TGF-β1 and MMP2 regulate ECM turnover, and tenascin-C is another proteoglycan that reportedly increases in the failing heart [6].

Materials and methods

Patients

A local ethics committee and internal review board approved this study. All protocols conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Written informed consent was obtained from all patients.

This study enrolled 45 Japanese patients with chronic heart failure (31 men and 14 women), age 30—97 years (mean age 64.8 ± 15.9 years), who were admitted to Gunma University Hospital, Tomioka General Hospital, and Tsurugaya Hospital between June 2006 and February 2007 for the treatment of heart failure, in addition to 21 healthy subjects (12 men and 9 women, and age 25—81 with mean age 49.2 ± 12.5 years). The main demographic and clinical characteristics of the patients are summarized in Table 1. The prevalence of idiopathic dilated cardiomyopathy, hypertrophic cardiomyopathy, ischemic cardiomyopathy, and hypertensive cardiomyopathy was 22%, 13%, 20%, and 44%, respectively. The present study excluded patients with a history of neoplastic, hepatic, infectious, collagen, or peripheral atherosclerotic diseases or patients who underwent any surgical procedure in the preceding 6 months. None of the patients had signs of infection and collagen disease at the time of evaluation.

Patients were followed for 3 years and their clinical outcomes were recorded. The endpoint of follow-up was defined as cardiac death or re-hospitalization due to heart failure. Cardiac death during the re-hospitalization was counted as single event. Additionally, second or more re-hospitalizations were not counted as additional events but single event at the time of first re-hospitalization.

Blood sampling and measurement of syndecan-4

Plasma and serum samples were obtained from peripheral venous blood. Whole blood was withdrawn from an antecubital vein, placed in tubes containing sodium EDTA, and kept on ice. The plasma was separated by centrifugation for 30 min, and plasma and serum samples were stored at −80 °C until analysis. Serum syndecan-4 concentrations were measured by sandwich enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's protocol (IBL Co., Ltd., Fujioka, Japan). This ELISA system recognizes the secreted ectodomain of the syndecan-4 molecule in blood. Plasma BNP concentration was measured with an immunoradiometric assay (Shionoria BNP assay, Shionogi Pharmaceutical Co., Osaka, Japan). Plasma TGF-β1 concentration (R&D Systems, Minneapolis, MN, USA), serum MMP2 activity (GE Health Care Japan, Tokyo, Japan), and serum tenascin-C concentration (IBL Co., Ltd.) were measured by ELISA.

Table 1 Baseline characteristics of patients.

	Mean ± standard deviation or number of patients (% of patient population)
Age (years)	64.8 ± 15.9
Gender (male)	31 (69)
Hypertension	26 (58)
CHF admission in previous year	29 (64)
Etiology	
Dilated cardiomyopathy	10 (22)
Hypertrophic cardiomyopathy	6 (13)
Ischemic cardiomyopathy	9 (20)
Hypertensive cardiomyopathy	20 (44)
Medication	
β-Blocker	19 (42)
ARB and/or ACEI	36 (80)
Spironolactone	8 (18)
Loop diuretics	29 (64)
NYHA class	
I	16 (36)
II	18 (40)
III	5 (11)
IV	6 (13)
Plasma polypeptide hormones	
Plasma BNP (pg/mL)	509.7 ± 454.3
Echocardiogram	
LV end-diastolic dimension (mm)	53.6 ± 10.8
LV end-systolic dimension (mm)	41.5 ± 14.8
LV end-diastolic volume (mL)	109.7 ± 51.5
LV end-systolic volume (mL)	56.6 ± 44.3
EF (%)	48.4 ± 17.5
LV mass index (g/m^2)	142.9 ± 40.2
E/e'	13.9 ± 5.1
LA volume index (mL/m^2)	40.9 ± 15.8

ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; BNP, B-type natriuretic peptide; CHF, chronic heart failure; EF, ejection fraction; E/e', early transmitral flow velocity/early diastolic velocity of the mitral valve annulus; NYHA, New York Heart Association; LV, left ventricle; LA, left atrium.

Echocardiographic measurements

Two-dimensional imaging was performed according to the recommendations of the American Society of Echocardiography [7]. Pulsed Doppler was used to record transmitral flow in the apical four-chamber view [8]. Tissue Doppler velocities were acquired at the septal and lateral annular sites and averaged as previously described [9]. These measurements were performed using Aplio echocardiograph (Toshiba Medical Systems Co., Ltd., Tochigi, Japan). Studies were analyzed by an echocardiologist blinded to all clinical data.

Statistical analysis

Values are expressed as the mean ± standard deviation. Statistical analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Serum syndecan-4 concentration of normal subjects and patients with heart failure was compared using Mann—Whitney test. Multiple and simple regression analyses were applied to determine the correlation among serum syndecan-4 concentration, clinical status, echocardiographic parameters, and other biomarkers associated with heart failure. Data of biomarkers were converted by logarithmic transformation and then statistical tests were performed. The optimal serum syndecan-4 concentration was evaluated by receiver operating characteristic (ROC) curve. The clinical outcomes were displayed with Kaplan—Meier event-free curve and compared with the use of log-rank test. A probability value <0.05 was considered statistically significant.

Results

Clinical characteristics and serum syndecan-4 concentration

Clinical characteristics of patients with heart failure are summarized in Table 1. Of the 45 patients with heart failure, 64% had a previous history of overt heart failure within the past year. The highest incidence of functional status based on the New York Heart Association (NYHA) classification was found for class II (40%), followed by classes I (36%), III (13%), and IV (11%). The mean left ventricular (LV) ejection fraction (EF) (48.4 ± 17.5%) was lower than that of healthy subjects (72.0 ± 5.3%, $p < 0.05$) and the LV mass index (142.9 ± 40.2 g/m^2) of patients with heart failure was significantly higher than that of healthy subjects (87.3 ± 9.2 g/m^2, $p < 0.05$).

Since the distribution pattern of serum biomarker concentration did not match with normal distribution, data were converted by logarithmic transformation and then statistical tests were performed. The mean plasma BNP concentration of patients with heart failure (509.7 ± 454.3 pg/mL) was significantly higher than that of healthy subjects (4.0 ± 2.7 pg/mL, $p < 0.05$). Similarly, serum syndecan-4 concentration was significantly higher in patients with heart failure than in healthy subjects (22.5 ± 12.3 ng/mL vs. 5.7 ± 3.3 ng/mL, $p < 0.01$; Fig. 1). Although healthy subjects were younger than patients, serum syndecan-4 concentration was not significantly different among different ages in healthy subjects (correlation coefficient of serum syndecan-4 concentration and age, 0.171; ns), suggesting that difference in serum syndecan-4 concentration between patients and healthy subjects is not due to age difference.

Relationship between serum level of biomarkers and echocardiographic parameters

We next determined which biomarkers represent the echocardiographic functional and architectural parameters. Table 2 shows the multiple correlation coefficient (R) of the predictive equation for each echocardiographic parameter and the partial regression coefficient (β) of each biomarker that is predictive of each echocardiographic parameter. Multiple regression analysis revealed unique correlation profiles of echocardiographic parameters between serum syndecan-4 and plasma BNP concentrations; only EF was correlated

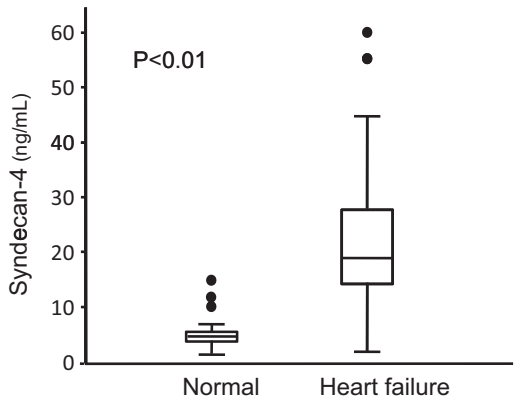

Figure 1 Serum syndecan-4 concentration in patients with heart failure and healthy subjects. The difference in Serum syndecan-4 concentration was compared between the two groups by Mann—Whitney test. Statistical significance was defined as 0.01.

with both of them. LV mass index, LV end-diastolic volume (LVEDV), and systolic left ventricular diameter (LVDs), parameters of LV geometry, were correlated only with serum syndecan-4 concentration, while early transmitral flow velocity/early diastolic velocity of the mitral valve annulus (E/e'), right ventricular systolic pressure (RVSP), and left atrial volume index, parameters for blood flow and pressure, were mainly correlated with plasma BNP concentration.

Simple regression analysis also demonstrated significant correlation of syndecan-4 with EF, LV mass index, LVEDV, and LVDs (Figs. 2 and 3 and Table 3). These data suggest that syndecan-4 represents a different aspect of cardiac function from BNP, MMP2, and TGF-β1.

Relationship among biomarkers

We next examined whether syndecan-4 correlates with other biomarkers. As shown in Table 4, serum syndecan-4 concentration did not significantly correlate with the concentrations of BNP, MMP2, TGF-β1, and tenascin-C.

Prognostic value of serum syndecan-4 concentration for cardiac events

During the 3-year follow-up, 10 patients were re-admitted to the hospital due to worsening of heart failure and 5 of them subsequently died of heart failure. The ROC curves of serum sybdecan-4 and plasma BNP concentration for the prediction of cardiac death or re-hospitalization due to heart failure are shown in Fig. 4. The area under the curve (AUC) of serum syndecan-4 concentration for the prediction of cardiac death or re-hospitalization due to heart failure was 0.706 (95% confidence interval: 0.537—0.875, $p < 0.05$), while that of plasma BNP concentration was 0.763 (95% confidence interval: 0.601—0.912, $p < 0.01$). AUCs of TGF-β, MMP2, and tenascin-C for the prediction of cardiac death or re-hospitalization due to heart failure were 0.418, 0.639, and 0.618, respectively, and these values were not significant.

Since the value for $(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2$ was minimal when the serum syndecan-4 concentration was 18.4 ng/mL, we defined this concentration as the optimal cut-off point discriminating cardiac events for further analysis. Fig. 5 shows event-free curve for high- and low-serum syndecan-4 concentration by Kaplan—Meier analysis. Patients with serum syndecan-4 concentration >18.4 ng/mL had a significantly lower event-free rate ($p < 0.01$, log-rank test).

Table 2 Biomarkers for prediction of echocardiographic parameters in multiple regression analysis.

Objective variable	Multiple correlation coefficient (R)	p	Explanatory variables							
			Syndecan-4		BNP		MMP2		TGF-β1	
			Partial regression coefficient (β)	p	β	p	β	p	β	p
EF	0.708	0.001	−0.382	0.003	−0.481	0.001				
LV mass index	0.313	0.041	0.313	0.041						
LVEDV	0.384	0.013	0.384	0.013						
LVDs	0.548	0.001	0.548	0.001						
e'	0.331	0.022							0.331	0.022
E/e'	0.450	0.001			0.450	0.001				
RVSP	0.602	0.001			0.602	0.001				
LA volume index	0.614	0.004			0.424	0.004	0.316	0.029		

BNP, B-type natriuretic peptide; EF, ejection fraction; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVDs, systolic left ventricular diameter; RVSP, right ventricular systolic pressure; LA, left atrial; E/e', early transmitral flow velocity/early diastolic velocity of the mitral valve annulus; MMP2, matrix metalloproteinase-2; TGF-β1, transforming growth factor-beta 1. Data of biomarkers were converted by logarithmic transformation.

Biomarkers (explanatory variables) used to predict each echocardiographic parameter (objective variables) were determined by multiple regression analysis. Multiple correlation coefficient (R) of each predictive formula and partial regression coefficient (β) of biomarkers that are predictive of echocardiographic parameters are shown. Tenascin-C was not significantly correlated with each echocardiographic parameter in multiple regression analysis.

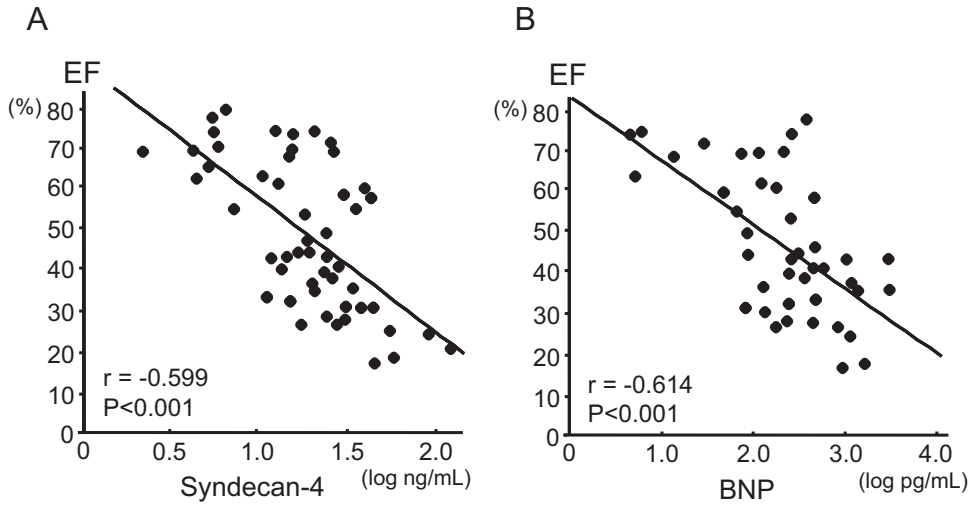

Figure 2 Correlation of serum syndecan-4 and B-type natriuretic peptide (BNP) concentrations with ejection fraction (EF). Pearson's correlation coefficient of the concentration of serum syndecan-4 (A) and plasma BNP (B) with EF was calculated. Since the distribution pattern of serum biomarker concentration did not match with normal distribution, data were converted by logarithmic transformation and then statistical tests were performed.

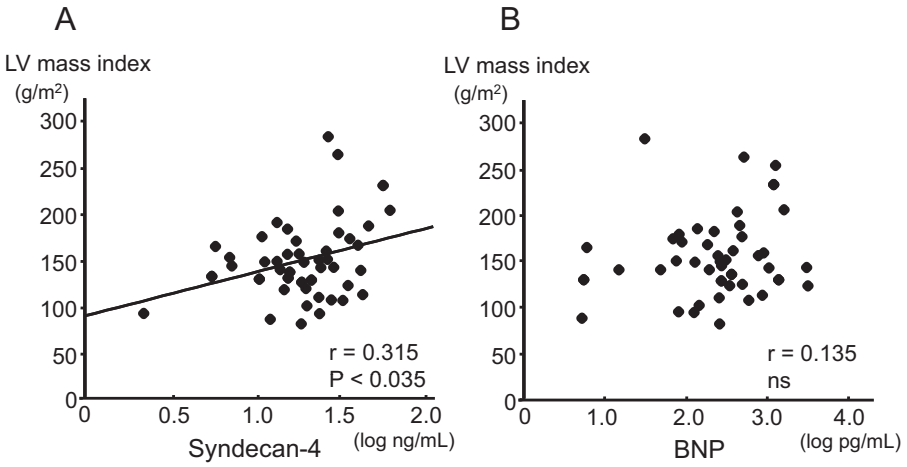

Figure 3 Correlation of serum syndecan-4 and plasma B-type natriuretic peptide (BNP) concentrations with left ventricular (LV) mass index. Pearson's correlation coefficient of the concentration of serum syndecan-4 (A) and plasma BNP (B) with the LV mass index was also calculated after logarithmic transformation. ns, not significant.

Table 3 Correlation between biomarkers and echocardiographic parameters in simple regression analysis.

	Syndecan-4	BNP	MMP2	TGF-β1	Tenascin-C
EF	−0.599*	−0.614*	−0.224	0.018	−0.301*
LV mass index	0.315*	0.135	−0.084	0.187	0.102
LVEDV	0.380*	0.277	0.101	−0.109	−0.064
LVDs	0.583*	0.354*	0.127	−0.155	0.124
e'	−0.268*	−0.035	−0.113	0.380*	0.189
E/e'	−0.132	−0.441*	0.191	−0.303*	0.083
RVSP	0.056	0.618*	0.381*	−0.118	0.392
LA volume index	0.111	0.538*	0.479*	−0.225	0.206

BNP, B-type natriuretic peptide; EF, ejection fraction; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVDs, systolic left ventricular diameter; RVSP, right ventricular systolic pressure; LA, left atrial; E/e', early transmitral flow velocity/early diastolic velocity of the mitral valve annulus; MMP2, matrix metalloproteinase-2; TGF-β1, transforming growth factor-beta 1.
* $p < 0.05$.

Table 4 Correlation among biomarkers in simple regression analysis.

	BNP	MMP2	TGF-β1	Tenascin-C
Syndecan-4	0.258	0.018	0.07	0.205
BNP		0.294*	−0.054	0.652*
MMP2			−0.539*	−0.033
TGF-β1				0.365*

BNP, B-type natriuretic peptide; MMP2, matrix metalloproteinase-2; TGF-β1, transforming growth factor-beta 1.
* $p < 0.05$.

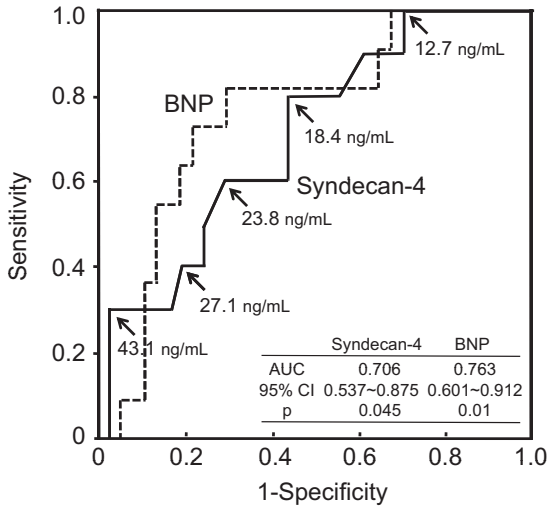

Figure 4 Predictive ability of serum syndecan-4 and plasma B-type natriuretic peptide (BNP) concentration for heart failure events. The receiver operating characteristic curve was created to predict death and re-hospitalization caused by worsening of heart failure based on serum syndecan-4 and plasma BNP concentration. AUC, area under the curve.

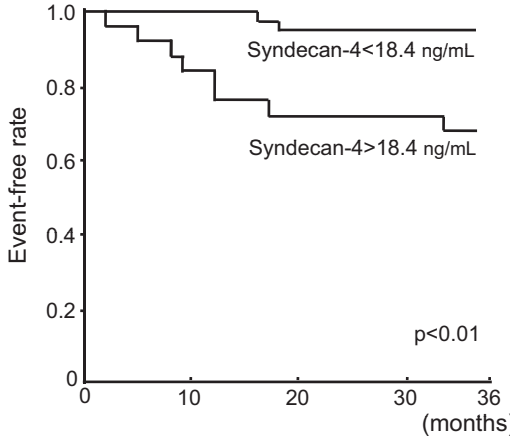

Figure 5 Kaplan—Meier event-free curves for serum syndecan-4 concentrations. Event-free rate from death and re-hospitalization caused by worsening of heart failure was compared between high- and low-serum syndecan-4 concentrations by Kaplan—Meier analysis. Cut-off level of serum syndecan-4 concentration (18.4 ng/mL) was determined by the receiver operating curve. Statistical significance of separation between 2 groups was achieved by log-rank test at 36 months.

Discussion

This study demonstrated that serum syndecan-4 concentration was significantly increased in patients with heart failure. In addition, serum syndecan-4 concentration inversely correlated with EF and positively correlated with geometrical parameters of LV hypertrophy and enlargement, including LV mass index, LVEDV, and LVDs. The increase in serum syndecan-4 concentration was a predictor of cardiac death and re-hospitalization due to heart failure. This is the first report to demonstrate elevated serum syndecan-4 concentration in patients with heart failure.

Heart failure results from complex architectural, cellular, and molecular changes involving necrosis, apoptosis, and repair processes. Several humoral factors have been used to monitor cardiac performance in the context of heart failure. Many biomarkers are now applied to estimate the cardiac function in the failing heart [10]. At present, the most representative cardiac biomarker for heart failure is considered to be BNP, which exerts a natriuretic effect as well as an anti-fibrotic effect [11]. BNP is secreted mainly from the ventricle in response to myocardial stretch, i.e. the elevation of the LV filling pressure [12]. BNP subsequently reduces hemodynamic overload in the failing heart and inhibits fibrosis-mediated cardiac remodeling. Measuring the plasma BNP level is useful to diagnose true heart failure in patients with dyspnea during their visit to the emergency room [13]. It also can predict in-hospital and postdischarge survival in heart failure patients [14].

Syndecan-4 has been reported to promote wound healing and angiogenesis in granulation tissue after skin injury [3]. In the rat experimental infarction model, mRNA levels and protein amount of syndecan-4 were increased in the noninfarcted LV tissue one week after myocardial infarction, suggesting that syndecan-4 has the potential to promote the hypertrophic response in the noninfarcted myocardium [15]. Kojima et al. reported an elevated serum syndecan-4 level with a peak value at 2 weeks after myocardial infarction [5], which corresponds to the repair phase. They also demonstrated abundant production of syndecan-4 protein in the repair region, but not the undamaged or fibrous scar region after myocardial infarction [5]. Thus, syndecan-4 may represent an aspect of heart failure different from BNP. In fact, our data show a significant correlation of serum syndecan-4 concentration with LV geometrical parameters (LV mass index, LVEDV, and LVDs), while BNP was significantly correlated with pressure-related parameters (E/e', RVSP, and LA volume, a barometer of LV filling pressure) [16]. Since EF is the ratio between stroke volume (a pressure-related physiological measurement) and EDV (a geometrical mea-

surement), it is not surprising that both syndecan-4 and BNP were correlated with EF. Moreover, no correlation was found between syndecan-4 and BNP and other biomarkers, suggesting that syndecan-4 is a novel independent biomarker from BNP, MMP2, TGF-β1, and tenascin-C. Our data thus suggest that serum syndecan-4 concentration may represent a biomarker specifically for LV geometrical remodeling rather than hemodynamic changes in the failing heart.

We next examined whether serum syndecan-4 concentration has predictive power of cardiac events. During the 3-year follow-up, 10 patients (22%) were re-admitted to the hospital, and 5 of them (11%) died of heart failure. The AUC for the prediction of cardiac death and re-hospitalization due to heart failure, based on serum syndecan-4 concentration at the first hospitalization (0.706, $p < 0.05$), was second to that based on plasma BNP concentration (0.763, $p < 0.01$). However, since the 95% confidence interval of serum syndecan-4 (0.537—0.875) overlapped with that of plasma BNP (0.601—0.912), predictive power of cardiac events of these biomarkers was not statistically different. AUCs based on concentrations of TGF-β1, MMP2, and tenascin-C did not significantly predict death and re-hospitalization due to heart failure. In addition, Kaplan—Meier analysis demonstrated that patients with serum syndecan-4 concentration >18.4 ng/mL had a significantly lower cardiac event-free rate.

Tenascin-C is a ubiquitously expressed heparan sulfate proteoglycan that is structurally related to syndecan-4. A recent study has reported that tenascin-C is increased in patients with heart failure and idiopathic dilated cardiomyopathy [17]. Tenascin-C and syndecan-4 are transiently up-regulated during tissue repair and wound healing in various tissues. Thus, this study also measured serum tenascin-C concentration in the patient population. However, tenascin-C concentration had a weak inverse correlation only with EF (Table 3) and there was no significant correlation between levels of these two proteoglycans (Table 4). Among syndecan-4, TGF-β1, MMP2, and tenascin-C, which are involved in ECM turnover, only syndecan-4 could predict cardiac events, suggesting a key role of syndecan-4 in cardiac remodeling in the context of ECM metabolism.

Approximately 50% of patients with heart failure have preserved EF [18]. The plasma BNP level is reportedly higher in those patients with reduced EF than with preserved EF [19]. We also found significantly higher plasma BNP concentration in patients with EF of less than 55% (688.0 ± 358.7 pg/mL) than with EF more than 55% (164.2 ± 147.9 pg/mL, $p < 0.05$). In contrast, serum syndecan-4 concentration in each group was not significantly different between patients with reduced and preserved EF (25.9 ± 12.8 ng/mL vs. 20.7 ± 12.9 ng/mL, ns); serum concentrations of TGF-β1, MMP2, and tenascin-C were also not significantly different between these two types of heart failure. These data suggest no differences in ECM metabolism in patients with reduced or preserved EF heart failure.

Study limitations

Although our study indicated a significant correlation between serum syndecan-4 concentration, other humoral factors, and echocardiographic parameters, the relatively small patient population limits the statistical power for detecting the relationships between other parameters. Thus, further investigation with a larger patient population would be of benefit. In addition, investigation of the source of syndecan-4 production would greatly advance our understanding of the pathophysiology of heart failure and remodeling.

Conclusions

Serum syndecan-4 concentration is increased in patients with chronic heart failure, inversely correlated with EF, and positively correlated with LV geometric parameters. Furthermore, serum syndecan-4 concentration could predict cardiac death and re-hospitalization due to heart failure. Given that it is a co-receptor of growth factor receptors for fibroblast growth factor-2, hepatocyte growth factor, and platelet derived growth factor, syndecan-4 may be useful as a biomarker for diagnosis of the LV remodeling process in patients with heart failure.

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