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The relationship between aminoterminal propeptide of type III procollagen and heart rate variability parameters in heart failure patients: a potential serum marker to evaluate cardiac autonomic control and sudden cardiac death

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Abstract

Background: Cardiac extra-cellular matrix (ECM) fibrosis plays an important role in the pathophysiology of heart failure (HF). It may provide electrical heterogeneity and a substrate for arrhythmogenicity, which may cause sudden cardiac death (SCD).
Methods: Twenty-one patients with manifestations of HF and a left ventricular ejection fraction (LVEF) $\leq$50% were enrolled. The median age was 62 years and median LVEF was 33%. Time- and frequency-domain analysis of heart rate variability (HRV) on 24 h ambulatory electrocardiography recording was assessed. Serum markers of ECM turnover including type I and III aminoterminal propeptide of procollagen (PINP and PIIINP), matrix metalloproteinase-2 and -9 (MMP-2 and MMP-9), and tissue inhibitor of metalloproteinase-1 (TIMP-1) were analyzed.
Results: The serum PIIINP concentration was correlated significantly with standard deviation of all normal to normal R-R intervals (SDNN) ($r=-0.722$, $p=<0.001$), percentage of adjacent NN interval differences >50 ms (pNN50) ($r=-0.528$, $p=0.014$), percentage of adjacent NN interval differences >20 ms (pNN20) ($r=-0.545$, $p=0.002$), very low frequency (VLF) ($r=-0.490$, $p=0.024$), low frequency (LF) ($r=-0.491$, $p=0.024$), and high frequency (HF) ($r=-0.513$, $p=0.018$). PINP, MMP-2, -9, TIMP-1 were not correlated with time- and frequency-domain analysis of HRV.
Conclusions: PIIINP was significantly correlated with time- and frequency-domain analysis of HRV in HF patients. PIIINP is a potential serological marker to evaluate cardiac autonomic control and risk of SCD in HF patients.
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Keywords: collagen; extra-cellular matrix; heart failure; HRV.

Introduction

Heart failure (HF) is a progressive disorder characterized by high morbidity and mortality, despite state-of-art therapy (1). Even with the great improvements in medical therapy, the prognosis of patients with HF remains very poor, with nearly 20% of patients dying within 1 year and nearly 80% at 8 year mortality (2). Of the causes of death in these patients, sudden cardiac death (SCD) due to arrhythmic events is one of the major causes (3). In people diagnosed with HF, SCD occurs at 6–9 times the rate of the general population (2). The majority of lethal cardiac arrhythmia in SCD is most often due to ventricular tachycardia or fibrillation (4). In the prevention of SCD in HF patients, anti-arrhythmic drugs have not been shown to reduce mortality (3, 5, 6), and implantable cardioverter defibrillators are the only effective treatment for both primary and secondary prevention of SCD (3, 7, 8). However, due to the high cost and the potential risk of invasive procedures, the selection of the potential candidates is

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necessary. Heart rate variability (HRV) has been recognized as a useful non-invasive method to detect SCD in HF patients (9). Patients with HF had standard deviation (SD) of all normal-to-normal R-R intervals (SDNN) <65.3 ms had higher SCD rate and worse survival during 50 months of follow-up (10).

Recently, the serum markers of cardiac extra-cellular matrix (ECM) turnover provided prognostic value and had clinical implications in various cardiovascular disease, such as coronary artery disease (11), acute rejection of cardiac transplantation (12), or HF (13–17). Among them, serum type III aminoterminal propeptide of procollagen (PIIINP) was one of the most important and well-known markers (15, 16, 18). Cardiac ECM fibrosis may provide electrical heterogeneity and a substrate for arrhythmogenicity, which may cause SCD. Therefore, serum markers of ECM may have the potential to predict ventricular arrhythmia and SCD. However, to our knowledge, the relation between serological markers for cardiac ECM turnover and the risk of SCD in HF patients is still unclear.

This study was designed to evaluate the association between serological markers for cardiac ECM turnover and risk of SCD according to HRV parameters.

Materials and methods

Patients

We studied 21 patients with chronic HF secondary to left ventricular systolic dysfunction [left ventricular ejection fraction (LVEF) $\leq 50\%$ by echocardiography or Tc99m left ventriculography], who were regularly visiting the HF clinics at the National Taiwan University Hospital. In echocardiography, LVEF were measured via apical 4-chamber view (area-length method) in accordance with the recommendations of the American Society of Echocardiography (19). In all patients, a full clinical history was obtained, and examination was performed by a cardiologist (Y-H L or Y-L H). Baseline demographic data, functional status, cardiovascular risk factors and medication were also recorded. In the definition of the etiology of HF, patients with a history of prior myocardial infarction or coronary intervention, either coronary artery bypass graft surgery or percutaneous coronary intervention, were considered to have ischemic heart disease. Patients with a history of chest pain who had pathologic Q waves on the electrocardiogram and/or dyskinetic areas on the echocardiogram were also included in this group (20). The dilated cardiomyopathy group comprised patients with dilatation of the left ventricle when another distinct etiology had not been found, despite routine workup which included evaluation for the presence of ischemic heart disease (20). Patients with severe valvular disease were excluded.

The management of the HF patients was in accordance with the guidelines for HF management (3). A nurse specialist performed telephone counseling as described previously (21). Venous blood samples were collected into serum separation tubes following an overnight fast on the same day that a 24-h ambulatory ECG Holter recording was performed. After clotting and centrifugation, the serum was stored at –60°C until analysis (approx. 1 year). The study was approved by the Ethical Committee of the National Taiwan University Hospital and all subjects gave informed consent.

HRV analysis

All patients underwent 24 h ambulatory ECG Holter recording (MyECG E3-80, Mircostar Company, Taipei, Taiwan) 3 months after being in stable condition. The ECG signals were sampled at 250 Hz and stored electronically for off-line analysis. Abnormal complexes or noise were inspected visually and rejected by comparison to the adjacent QRS morphologic features. The annotated signals, which consisted of more than 80% of qualified normal sinus beats, were then used for analysis of HRV, including time-domain and frequency-domain analysis. The following time-domain parameters were computed. SDNN for the 24 h recording. The percentage of the number of paired adjacent NN intervals (pNNx) with absolute differences $>x$ ms during the entire recording. We obtained the pNN statistics of not only 50 ms, but also 20 ms which has been suggested to have better discriminative power between different physiological conditions (22).

Frequency-domain parameters were calculated using fast Fourier transform and the density of the spectrum in given bands were derived from the sum of the area within specific frequency ranges, as suggested by the North American Society of Pacing and Electrophysiology (23) very low frequency (VLF) (0.0033–0.04 Hz), low frequency (LF) (0.04–0.15 Hz), and high frequency (HF) (0.15–0.4 Hz).

Laboratory analysis

Brain natriuretic peptide (BNP) was measured with an enzyme immunoassay kit (BNP-32, Phoenix Pharmaceuticals, Belmont, CA, USA). The intra-assay variation was $<5\%$ and inter-assay variation was $<14\%$. The range of detection was 0–100,000 ng/L according to the manufacturer. Serum type I aminoterminal propeptide of procollagen (PINP) was determined using a rapid equilibrium radioimmunoassay kit (No. 67034, Orion Diagnostica, Espoo, Finland). Intra- and inter-assay variation was $<7\%$. The detection limit of this method was 2 μg/L according to the manufacturer. Serum PIIINP was determined by radioimmunoassay (No. 68570, Orion Diagnostica, Espoo, Finland). The detection limit of PIIINP was 0.3 μg/L and the intra- and inter-assay variation was $<5\%$ according to the manufacturer. Serum tissue inhibitor of metalloproteinase-1 (TIMP-1) was measured with an enzyme immunoassay kit (DTM100, R & D systems, Minneapolis, MN, USA). The intra- and inter-assay variation was $<5\%$ and the detection limit of this method was 0.08 ng/mL. Serum matrix metalloproteinase-2 (MMP-2) was measured using an enzyme immunoassay kit (DMP200, R&D systems). The intra- and inter-assay variation was $<6\%$ and $<8\%$ and the limit of detection was 0.16 ng/mL. Serum matrix metalloproteinase-9 (MMP-9) was measured with an enzyme immunoassay kit (DMP900, R&D systems). Intra- and inter-assay variation was $<3\%$ and $<8\%$, and the detection limit was 0.156 ng/mL.

Statistical analysis

Continuous results were expressed as the median (25th, 75th percentile). Comparisons between groups for continuous data were performed using the Mann-Whitney U-test. Differences between proportions were assessed by the χ^2-test or Fisher's exact test. The Spearman non-parametric correlation test was used to analyze the association between serum markers of ECM turnover and HRV parameters. Using SDNN <65.3 ms as a cut-off threshold, receiver operating characteristic curve analysis was performed and the optimal cut-off point was obtained from the Youden index (24). The sensitivity, specificity, positive predictive rate, and negative predictive rate for the cut-off point were expressed as the 95% confidence

interval. Statistical analyses were performed with SPSS for Windows, version 10.0 (SPSS Inc., Chicago, IL, USA). A $p<0.05$ was considered statistically significant.

Results

Patient characteristics

A total of 21 (15 males and six females) patients were enrolled. The demographical and biochemical data and medication history are shown in Table 1. The measurement of LVEF was performed by Tc99m left ventriculography in six patients, and by echocardiogram in the other 15 patients.

Serum BNP and ECM turnover markers, HRV parameter and its correlations

The data for serum BNP and ECM turnover markers are shown in Table 2. The values of serum BNP and ECM turnover markers were not associated with LVEF, serum creatinine concentrations and medication usage. In addition, serum BNP concentrations were not correlated with serum PIIINP.

Table 1 Clinical data for the patients (n=21).

Patient characteristics	Data
Age, years	62 (52, 78)
Male/female	15 (71)/6 (29)
LVEF, %	33 (23, 41)
NYHA	
I	2 (10)
II	11 (52)
III	8 (38)
IV	0
Creatinine, μmol/L	92 (65, 103)
Body weight, kg	63 (52, 72)
Body height, cm	165 (154, 170)
Body mass index, kg/m^2	23 (22, 28)
Fasting glucose, mmol/L	6.4 (5.4, 7.8)
Triglyceride, mmol/L	1.6 (1.0, 2.6)
Cholesterol, mmol/L	5.3 (4.5, 5.7)
High-density lipoprotein, mmol/L	1.0 (0.9, 1.2)
Low-density lipoprotein, mmol/L	3.3 (2.4, 3.8)
Hemoglobin, g/L	129 (116, 144)
Uric acid, μmol/L	440 (357, 467)
Etiology of heart failure	
Ischemic heart disease	10 (48)
Dilated cardiomyopathy	11 (52)
Hypertension	6 (29)
Diabetes mellitus	8 (38)
Medication	
ACE-I/ARB	16 (76)
β-Blocker	10 (48)
Loop diuretics	12 (57)
Digoxin	12 (57)
Spironolactone	6 (29)

Data are expressed as the median (25th, 75th percentile) or number (percentage). NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 2 Serum markers of cardiac extra-cellular matrix turnover.

BNP, ng/L	1840 (1345, 2090)
PINP, μg/L	32 (22, 46)
PIIINP, μg/L	6.4 (4.6, 7.2)
TIMP, ng/mL	143 (108, 173)
MMP-2, ng/mL	241 (203, 271)
MMP-9, ng/mL	58 (32, 117)

Data are expressed as the median (25th, 75th percentile). BNP, brain natriuretic peptide; PINP, type I aminoterminal propeptide of procollagen; PIIINP, type III aminoterminal propeptide of procollagen; TIMP, tissue inhibitor of metalloproteinase; MMP, matrix metalloproteinase.

The HRV parameters are shown in Table 3. The use of spironolactone was significantly associated with pNN50 ($r=0.575$, $p=0.006$) and HF ($r=0.470$, $p=0.032$). The values of HRV parameters were not associated with LVEF, serum creatinine or use of other medications.

The correlations among serum markers of ECM turnover and values of HRV parameters are shown in Table 4. Serum PIIINP concentrations were significantly correlated with most HRV parameters, except that the LF/HF ratio. PINP, MMP-2, -9, TIMP-1 were not correlated with HRV parameters.

In Table 5, patients with higher PIIINP concentrations (>mean level; group 2) had significantly lower SDNN, pNN50, pNN20, VLF, LF and HF values than patients with lower PIIINP (<mean level; group 1).

Using SDNN <65.3 ms as a predictor, receiver operating characteristic curve showed an area under curve of 0.894 for PIIINP. By using PIIINP 6.07 μg/L as a cut-off point, the sensitivity, specificity, positive predictive rate, negative predictive rate, and accuracy were 100% (51%, 100%), 67% (39%, 87%), 55% (25%, 82%), 100% (66%, 100%), and 76%, respectively (Figure 1).

Discussion

In the present study, we found the relationship between serum PIIINP concentrations and HRV parameters to be

Table 3 Heart rate variability parameter.

Time-domain	
SDNN, ms	75 (60, 98)
pNN50, ms	1.2 (0.3, 4.0)
pNN20, ms	13.8 (2.6, 21.5)
Frequency-domain	
VLF, ms^2	600 (254, 868)
LF, ms^2	124 (27, 209)
HF, ms^2	54 (17, 112)
LF/HF ratio	1.7 (0.9, 2.7)

Data are expressed as the median (25th, 75th percentile). SDNN, standard deviation of all normal to normal R-R intervals; pNN50, percentage of adjacent NN interval differences >50 ms; pNN20, percentage of adjacent NN interval differences >20 ms; VLF, very low frequency; LF, low frequency; HF, high frequency; LF/HF ratio, low frequency/high frequency ratio.

Table 4 Correlation between serum markers of cardiac extra-cellular matrix turnover and heart rate variability parameter.

	PINP	PIIINP	TIMP	MMP-2	MMP-9
SDNN					
R	–0.214	–0.722	–0.204	–0.396	0.066
p	0.351	<0.001	0.375	0.075	0.775
pNN50					
R	–0.190	–0.528	–0.249	–0.389	0.093
p	0.410	0.014	0.277	0.082	0.689
pNN20					
R	–0.112	–0.545	–0.208	–0.412	0.099
p	0.630	0.002	0.366	0.064	0.670
VLF					
R	–0.178	–0.490	–0.338	–0.294	0.087
p	0.440	0.024	0.134	0.197	0.708
LF					
R	–0.227	–0.491	–0.229	–0.357	0.134
p	0.225	0.024	0.319	0.112	0.563
HF					
R	–0.192	–0.513	–0.235	–0.344	0.047
p	0.404	0.018	0.305	0.127	0.841
LF/HF ratio					
R	–0.106	0.103	–0.109	–0.149	0.205
p	0.646	0.658	0.638	0.51	0.372

BNP, brain natriuretic peptide; PINP, type I aminoterminal propeptide of procollagen; PIIINP, type III aminoterminal propeptide of procollagen; TIMP, tissue inhibitor of metalloproteinase; MMP, matrix metalloproteinase; SDNN, standard deviation of all normal to normal R-R intervals; pNN50, percentage of adjacent NN interval differences >50 ms; pNN20, percentage of adjacent NN interval differences >20 ms; VLF, very low frequency; LF, low frequency; HF, high frequency; LF/HF ratio, low frequency/high frequency ratio.

indicators of cardiac autonomic control and SCD in HF patients. To our knowledge, this is the first study demonstrating such an association and indicating PIIINP as having a potential role in monitoring cardiac autonomic tone in HF patients. In the present study, patients with increased serum PIIINP concentrations had decreased SDNN, pNN50, pNN20, VLF, LF, and HF which implied impaired cardiac autonomic control. The demographical and biochemical data and LVEF were comparable between the two groups. Therefore, the difference in HRV parameters may not be due to differences in cardiac systolic function or function status in HF patients.

In the development and progression of systolic HF, LV remodeling is a critical pathophysiological process. Cardiac ECM turnover is an essential process in LV remodeling and interstitial fibrosis (14). Interstitial fibrosis may provide electrical heterogeneity and a substrate for arrhythmogenicity. That may potentially contribute to the occurrence of ventricular tachycardia or fibrillation and subsequent SCD. In recent studies, altered expression of several markers of ECM turnover involving collagen synthesis or degradation in failing myocardium previously has been reported (13, 14, 25). In addition, serum markers of ECM turnover provided prognostic value (13–17). Among them, serum PIIINP was one of the most important markers. In patients with HF, serum PIIINP was widely used not only to evaluate cardiac function (15) and exercise capacity (26), but to predict prognosis (16, 18), and response to medication (18). However, the relationship between serological markers for cardiac ECM turnover and HRV parameters or the risk of SCD in HF patients is still unclear. Therefore, we designed this study and found that PIIINP is associated with HRV parameters. Although the number of patients was small, this study provides evidence for performance of future larger outcome study using PIIINP as a predictive marker.

In our study, PIIINP, but not PINP, was associated with HRV parameters. Both collagen types I and III were present in cardiac tissue. Although type I collagen is predominant in myocardium, type III collagen is more specific for cardiac tissue (18, 27). In the study of Alla et al., serum PIIINP, but not PINP, changed in patients with congestive HF (27). Also, the evidence for PIIINP in the prediction of prognosis of HF is much more abundant than PINP. Furthermore, serum PIIINP concentrations decrease greater than PINP after use of spironolactone (18). Therefore, PIIINP seems to be a better marker than PINP in HF patients. However, one study involving post-myocardial infarction patients revealed a paradoxical association between serum PIIINP and the occurrence of ventricular tachycardia (17). In that study, patients with higher PINP values had a higher incidence of ventricular arrhythmia, but those with higher PIIINP had a lower incidence of ventricular arrhythmia. Different patient settings, disease severity and cause of disease may be possible explanations. The patients included in that study were post-myocardial infarction and had a median serum PIIINP of 4.3 μg/L and a median BNP of 64 ng/L. In our study, 52% of patients had HF of non-ischemic origin, and a median serum PIIINP concentration of 6.4 μg/L and a median BNP

Table 5 Characteristics of the two groups.

	Group 1 (n = 10)	Group 2 (n = 11)	p-value
PIIINP, μg/L	3.6 (4.6, 5.4)	7.2 (6.5, 8.7)	<0.001
BNP, ng/L	1570 (1240, 2113)	1900 (1780, 2130)	0.275
Age, years	70 (49, 80)	59 (52, 68)	0.314
Gender	7 (70)	8 (73)	1.000
LVEF	36 (23, 44)	32 (21, 40)	0.341
NYHA functional classification	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	0.605
Creatinine, μmol/L	72 (59, 101)	92 (69, 107)	0.349
Body mass index	23 (20, 29)	23 (22, 27)	0.756
Etiology of heart failure			
Ischemic heart disease	4 (40)	7 (64)	0.395
Dilated cardiomyopathy	6 (60)	4 (36)	
Hypertension	1 (10)	5 (45)	0.149
Diabetes mellitus	3 (30)	5 (45)	0.659
Medication			
ACE-I/ARB	8 (80)	8 (73)	1.000
β-Blocker	3 (30)	7 (64)	0.198
Loop diuretics	3 (30)	9 (82)	0.030
Digoxin	5 (50)	7 (64)	0.670
Spironolactone	4 (40)	2 (18)	0.361
HRV parameter			
SDNN	93 (76, 105)	62 (36, 73)	0.003
pNN50	4.0 (0.7, 6.2)	0.6 (0.1, 1.4)	0.006
pNN20	22 (12, 32)	5.6 (0.9, 13.8)	0.004
VLF	768 (547, 1174)	383 (74, 658)	0.020
LF	209 (102, 247)	33 (15, 162)	0.005
HF	98 (29, 200)	30 (10, 61)	0.016
LF/HF ratio	1.8 (0.8, 2.6)	1.7 (1.0, 2.8)	0.973

Data are expressed as the median (25th, 75th percentile) or number (percentage). PIIINP, type III aminoterminal propeptide of procollagen; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; SDNN, standard deviation of all normal RR intervals; pNN50, percentage of adjacent NN interval differences >50 ms; pNN20, percentage of adjacent NN interval differences >20 ms; VLF, very low frequency; LF, low frequency; HF, high frequency; LF/HF ratio, low frequency/high frequency ratio.

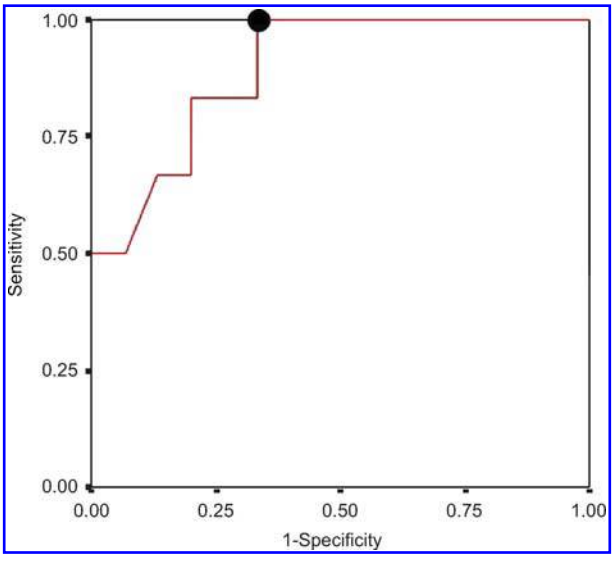

Figure 1 Receiver operating characteristic curves for the ability of PIIINP to detect SDNN <65.3 ms.
Area under the curve is 0.894. Using a PIIINP cut-off threshold of 6.07 μg/L (black dot), the sensitivity and specificity were 100% and 67%, respectively. The optimal cut-off point is calculated by the Youden index.

of 1840 ng/L. The mode of myocardial remodeling and type I/III ratio in remodeling may be different in patients in these two studies.

The relationship between PIIINP and HRV may also be associated with renin-angiotensin-aldosterone (RAAS) signaling. RAAS activation is an important pathophysiological condition in HF, involving autonomic imbalance and interstitial fibrosis (28). Aldosterone blockade improves cardiac vagal control (29). In recent clinical studies, administration of spironolactone, an aldosterone antagonist, improved cardiac autonomic control as measured by HRV (30, 31), deceased ventricular arrhythmia (32), reduced serum PIIINP (30) and improved survival (18, 33). However, the impact of RAAS activation on the association of PIIINP and HRV is not clear and needs further investigation.

This study had limitations. First, this study is cross-sectional in design, and the number of patients is relatively small. It cannot provide definitive evidence, but is suitable to stimulate further research into this area. Second, the concentrations of serum markers of ECM turnover, such as PIIINP, were not associated with LVEF, serum creatinine concentrations and medication use. The differences in the findings in the current study and previous studies may due to the small number of patients in this study. However, unlike

creatinine, spironolactone use, or HF status (such as NYHA functional classification), the association between serum PIIINP and LVEF were not consistent. In previous studies, serum PIIINP was associated with serum creatinine and the NYHA functional classification (34), but not with LVEF (18, 34, 35). It appears that the relationship between PIIINP and cardiac systolic function needs to be further validated. Third, the method of LVEF measurement is not uniform in our study and may add bias and decrease the power to detect the association among LVEF and other parameters. However, Tc99m left ventriculography is highly correlated with echocardiography, even in patients with regional wall motion abnormalities (36).

Fourth, this is not an outcome study, and we used HRV as SCD outcome predictors. Further, large scale outcome studies are needed to demonstrate the prognostic value of PIIINP. Fifth, no histological evidence was available to demonstrate the relation between tissue formation of type III collagen and serum fibrosis markers. In addition, histological data provided more information about the mechanism between serum PIIINP, tissue fibrosis, inhomogenities of local nerve innervations and arrhythmogenicity. However, it is not ethical to perform endomyocardial biopsy in these patients without other clinical indications.

Conclusions

PIIINP was significantly correlated with time- and frequency-domain analysis of HRV in HF patients. Increased serum PIIINP is associated with more severe impairment of cardiac autonomic control. Serum PIIINP concentrations are a potential serological marker to evaluate cardiac autonomic control and risk of SCD in HF patients.

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Conflict of interest statement

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