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ORIGINAL ARTICLE

Assessment of congestion and clinical outcomes in patients with chronic heart failure using shear wave elasticity

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Abstract

Aims The relief of congestion is essential for the prevention of worsening heart failure (HF) resulting in hospitalizations. Assessment of the degree of organ congestion in the chronic phase of HF is important for determining therapeutic strategies. The aim of this study was to evaluate the efficacy of shear wave (SW) elasticity for assessing congestion and clinical outcomes in patients with chronic HF.

Methods and results We prospectively enrolled 345 consecutive patients with chronic HF who underwent SW elastography at outpatient clinic. Patients were divided into two groups according to the median value of SW elasticity: low group (SW elasticity $<$6.4 kPa, n = 176) and high group (SW elasticity $\geq$6.4 kPa, n = 169). The endpoint was cardiovascular death or hospitalization for HF. During the median follow-up period of 19 months (range: 7–36 months), cardiovascular death or hospitalization for HF occurred in 4 patients of low group and 27 patients of high group. In high group, 8 patients died, and 19 patients were hospitalized for HF. In low group, 3 patients died, and 1 patient was hospitalized. Kaplan–Meier analysis showed that the event-free survival rate was worse in high group than in low group (log-rank test, P = 0.004). After adjusting for variables, high SW elasticity was independently related to cardiac events. In multivariate regression analysis, SW elasticity was correlated with left atrial volume index, early diastolic mitral inflow velocity to mitral annular velocity ratio, and inferior vena cava diameter.

Conclusions The SW elasticity reflected haemodynamic congestion in patients with chronic HF, which was related to cardiac events.

Keywords Congestion; Heart failure; Prognosis; Shear wave elasticity

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Introduction

The prevalence of heart failure (HF) increases progressively. HF is a common cause of hospitalizations in older patients, which are associated with morbidity, mortality, and high cost.[1] Thus, the reduction of hospitalizations is an important component for the management of HF.[2] The relief of congestion is essential for the prevention of worsening HF resulting in hospitalizations.[3] Therefore, the assessment of the degree of congestion in the chronic phase of HF is important for determining appropriate therapeutic strategies. However, congestion is difficult to assess, especially when signs and symptoms are mild. In recent years, multidisciplinary management has become increasingly important to quantify congestion at key stages of patient care.[4]

Shear wave (SW) elastography (SWE) is a novel ultrasound technique for assessing tissue characteristics based on SW velocity, which provides a quantitative estimate of tissue elasticity.[5–7] SW elasticity has been used to assess liver diseases in clinical practice.[8,9] In the field of heart diseases, a few studies have reported that SW elasticity is correlated with central venous pressure in the acute phase of HF.[10–12] Therefore, we expected that SW elasticity may be effective to assess the degree of organ congestion in the chronic phase of HF. We hypothesized that SW elasticity reflects persistent organ congestion and is related to cardiac events. This study

aimed to evaluate the efficacy of SW elasticity for assessing congestion and clinical outcomes in patients with chronic HF.

Methods

Study population

We prospectively enrolled 365 consecutive patients with chronic HF who underwent SWE at outpatient clinic of Okayama University Hospital from March 2018 to September 2020. The diagnosis of HF was made based on various findings, including medical history, symptoms, physical examinations, electrocardiogram, echocardiography, biomarker measurements, and chest X-ray, according to the guidelines of the European Society of Cardiology.[13] Electrocardiogram was used to detect abnormal findings, such as atrial fibrillation, myocardial infarction, and cardiomyopathy. Patients with a history of liver diseases such as fatty liver, hepatitis, cirrhosis, and/or hepatic tumours, and alcohol abuse (≥20 g/day) were excluded. Patients undergoing dialysis and those with congenital heart diseases were also excluded. All patients gave informed consent to undergo examination. The study was approved by the ethical committee of our institution.

Shear wave elastography

The SWE was performed on the liver using Aplio i900 with a 3.5 to 5.0 MHz convex probe (Canon Medical Systems, Otawara, Japan) at the time of outpatient clinic. SWE was obtained on the right lobe of the liver through the intercostal spaces at the end-expiratory period in the supine position.[14] Patients held their breath during the acquisition. The grey-scale image was optimized for the best acoustic window and gain setting. A sample box of 2.0 × 2.0 cm was placed on the grey-scale image at a depth of 1.0 to 1.5 cm from the liver capsule to avoid reverberation artefacts and intrahepatic vessels. A circular region of interest of 1.0 cm diameter was placed on the propagation map exhibiting parallel lines[15] (*Figure 1*). SWE was measured 10 times in each patient, and the average value of SW elasticity was calculated.[16]

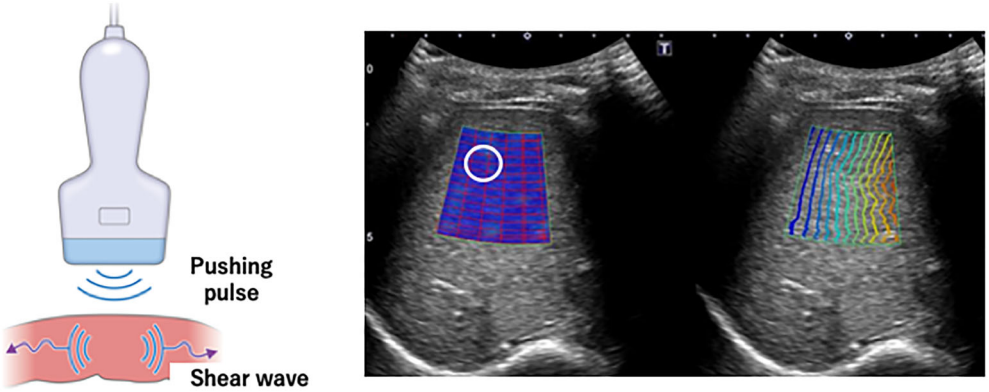
Clinical assessments

Transthoracic echocardiography was performed at the same time as SWE measurement by independent sonographers who did not know SWE data. Left ventricular (LV) end-diastolic diameter, LV end-systolic diameter, LV ejection fraction, LV mass index, left atrial (LA) volume index, early diastolic mitral inflow velocity to mitral annular velocity ratio (E/e′), tricuspid regurgitation pressure gradient, and inferior vena cava diameter were measured. LV ejection fraction was measured using the disc summation method. These measurements were performed according to the guidelines from the American Society of Echocardiography.[17] Liver function tests were measured, including aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ-glutamyl transpeptidase, total bilirubin, cholinesterase, albumin, and platelet levels. Haemoglobin and serum creatinine levels were measured, and plasma B-type natriuretic peptide levels were also measured using a fluorescence enzyme immunoassay.

Endpoint

The endpoint was cardiovascular death or hospitalization for HF. Patients were followed from the date of SWE measurement until the date of first documentation of cardiac events or the end of follow-up. Follow-up data were obtained from medical records.

Figure 1 Shear wave elastography. Shear wave elastography was performed on the right lobe of the liver through the intercostal spaces. The grey-scale image was optimized for the best acoustic window and gain setting, and a sample box of 2.0 × 2.0 cm was placed. A circular region of interest of 1.0 cm diameter was placed on the propagation map exhibiting parallel lines.



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Statistical analysis

Data are presented as mean ± standard deviation for continuous variables and as number and percentage for categorical variables. Continuous variables were compared between low SW elasticity group and high SW elasticity group, which divided according to the median value, using the *t* test for normally distributed variables and the Mann–Whitney *U* test for non-normally distributed variables. Categorical variables were compared using the χ^2 test. Event-free survival rate was estimated using the Kaplan–Meier analysis, with group differences compared using the log-rank test. Cox proportional hazard regression analysis was performed to identify independent factors related to cardiac events. Variables for analysis included age, high SW elasticity, LA volume index, and tricuspid regurgitation pressure gradient. Hazard ratios are shown with 95% confidence intervals. The data of SW elasticity and echocardiographic parameters showed a two-dimensional normal distribution. Pearson's correlation coefficient was calculated to identify the relationships of SW elasticity with echocardiographic parameters. Multivariate regression analysis was performed to identify independent factors related to SW elasticity. Variables for analysis included LV ejection fraction, LV mass index, LA volume index, E/e′, and inferior vena cava diameter. Statistical analysis was performed with statistical software (JMP version 14.0; SAS Institute Inc., Cary, NC, USA), and significance was defined as a *P* value of <0.05.

Results

Clinical characteristics

Of the 365 patients, 20 were excluded due to lost follow-up. The study consisted of the remaining 345 patients. The median value of SW elasticity was 6.4 kPa. Patients were divided into two groups according to the median value: low group (SW elasticity <6.4 kPa, $n = 176$) and high group (SW elasticity ≥ 6.4 kPa, $n = 169$). The mean SW elasticity was 5.3 ± 0.7 kPa in low group and 10.3 ± 6.9 kPa in high group. Comparisons of clinical characteristics between two groups are shown in *Table 1*. The mean age of all patients was 69 ± 13 years. Thirty-seven patients of high group and 19 patients of low group had New York Heart Association functional Class III or IV. Eighty-seven patients of high group and 49 patients of low group had previous HF hospitalization. New York Heart Association functional Class III or IV (22% vs. 11%, $P < 0.01$) and previous HF hospitalization (51% vs. 28%, $P < 0.01$) were observed more frequently in high group than in low group. Forty patients of high group and 26 patients of low group had atrial fibrillation. The prevalence of atrial fibrillation was higher in high group than in low group (24% vs. 15%, $P = 0.03$). The prevalence of ischaemic heart disease, cardiomyopathy, valvular disease, or hypertension was not different between two groups.

Clinical parameters

Comparisons of clinical parameters between two groups are shown in *Table 2*. LV end-diastolic diameter, LV end-systolic diameter, LV ejection fraction, or LV mass index was not different between two groups. LA volume index, E/e′, tricuspid regurgitation pressure gradient, and inferior vena cava diameter were higher in high group than in low group. Aspartate aminotransferase and γ-glutamyl transpeptidase levels were higher in high group than in low group. The mean values of almost liver function tests of all patients were within the normal range. Plasma B-type natriuretic peptide levels were not different between two groups.

Cardiac events

The median follow-up period was 19 months, and the latest period was 36 months. During the follow-up period, 31 patients had cardiac events, including 27 patients of high

Table 1 Clinical characteristics

Variables	All ($n = 345$)	Low group SW elasticity <6.4 kPa ($n = 176$)	High group SW elasticity ≥ 6.4 kPa ($n = 169$)	*P*
Age, years	69 ± 13	68 ± 15	71 ± 11	0.03
Male	179 (52%)	94 (53%)	85 (50%)	0.56
Body mass index, kg/m^2	22.2 ± 3.6	22.7 ± 3.3	21.8 ± 3.9	0.02
New York Heart Association functional Class III/IV	19 (11%)	19 (11%)	37 (22%)	<0.01
Previous HF hospitalization	136 (39%)	49 (28%)	87 (51%)	<0.01
Atrial fibrillation	66 (19%)	26 (15%)	40 (24%)	0.03
Hypertension	130 (38%)	65 (37%)	65 (38%)	0.77
Ischaemic heart disease	77 (22%)	40 (23%)	37 (22%)	0.85
Cardiomyopathy	136 (39%)	62 (35%)	74 (44%)	0.24
Valvular disease	75 (22%)	32 (18%)	43 (25%)	0.97

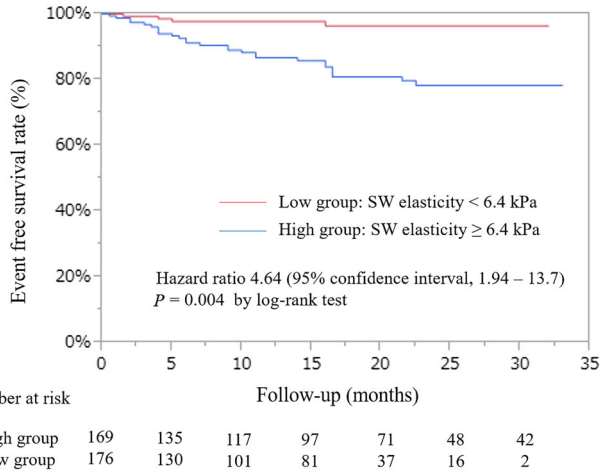
Data are presented as mean ± standard deviation or number (%) of patients. Continuous variables were compared using the *t* test. Categorical variables were compared using the χ^2 test.

Table 2 Clinical parameters

Variables	All (n = 345)	Low group SW elasticity <6.4 kPa (n = 176)	High group SW elasticity ≥6.4 kPa (n = 169)	P
Echocardiography				
LV end-diastolic diameter, mm	50 ± 9	50 ± 9	50 ± 9	0.69
LV end-systolic diameter, mm	37 ± 12	37 ± 12	37 ± 12	0.98
LV ejection fraction, %	52 ± 17	52 ± 17	51 ± 17	0.63
LV mass index, g/m^2	108 ± 36	108 ± 34	109 ± 38	0.66
LA volume index, ml/m^2	53 ± 41	45 ± 17	61 ± 54	<0.01
E/e′	15.7 ± 8.6	14.1 ± 7.2	17.3 ± 9.5	<0.01
Tricuspid regurgitation pressure gradient, mmHg	26 ± 11	24 ± 9	28 ± 12	<0.01
Inferior vena cava diameter, mm	12.6 ± 5.3	12 ± 4	14 ± 6	<0.01
Laboratory				
Aspartate aminotransferase, U/L	25 ± 14	23 ± 8	27 ± 16	<0.01
Alanine aminotransferase, U/L	20 ± 18	18 ± 12	20 ± 12	0.31
Alkaline phosphatase, U/L	240 ± 97	213 ± 71	244 ± 90	<0.01
γ-glutamyl transpeptidase, U/L	47 ± 54	39 ± 53	54 ± 54	0.02
Total bilirubin, mg/dL	0.8 ± 1.2	0.8 ± 1.6	0.9 ± 0.6	0.82
Cholinesterase, U/L	278 ± 82	292 ± 73	266 ± 87	0.01
Albumin, g/dL	3.9 ± 0.5	4.0 ± 0.5	3.9 ± 0.5	0.13
Platelet, ×10^3/μL	212 ± 77	225 ± 77	198 ± 75	<0.01
Haemoglobin, g/dL	12.6 ± 1.9	12.7 ± 1.8	12.5 ± 2.0	0.38
Creatinine, mg/dL	1.0 ± 0.8	0.9 ± 0.5	1.0 ± 1.3	0.20
B-type natriuretic peptide, pg/mL	336 ± 503	305 ± 542	365 ± 462	0.32

E/e′, early diastolic mitral inflow velocity to mitral annular velocity ratio; LA, left atrial; LV, left ventricular.
Data are presented as mean ± standard deviation. Continuous variables were compared using the t test for normally distributed variables and the Man–Whitney U test for non-normally distributed variables.

Figure 2 Event-free survival rate. Survival rate without cardiovascular death or hospitalization for heart failure. In 345 patients with chronic heart failure, cardiovascular death or hospitalization for heart failure occurred in 4 patients of low group and 27 patients of high group. SW, shear wave.



group and 4 patients of low group. In high group, 8 patients died due to cardiovascular disease, and 19 patients were hospitalized for HF. In low group, 3 patients died, and 1 patient was hospitalized. Kaplan–Meier analysis showed that the event-free survival rate was worse in high group than in low group (log-rank test, P = 0.004) (*Figure 2*). After adjusting for age, LA volume index, and tricuspid regurgitation pressure gradient, Cox proportional hazard regression analysis showed that high SW elasticity was independently related to cardiac events (hazard ratio: 2.70, 95% confidence interval 1.01–7.24, P = 0.04) (*Table 3*).

Relationships of shear wave elasticity with echocardiographic parameters

Pearson's correlation coefficient showed that SW elasticity was positively correlated with LV mass index, LA volume

Table 3 Factors related to cardiac events

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% confidence interval)	*P*	Hazard ratio (95% confidence interval)	*P*
Age >60 years	6.03 (1.35–112)	0.01	2.46 (0.32–18.6)	0.38
SW elasticity ≥6.4 kPa	4.64 (1.94–13.7)	<0.01	2.70 (1.01–7.24)	0.04
LA volume index ≥34 mL/m^2	7.45 (2.64–31.1)	<0.01	4.56 (0.60–34.6)	<0.01
Tricuspid regurgitation pressure gradient ≥35 mmHg	4.51 (2.19–9.17)	<0.01	2.97 (1.39–6.33)	0.14

LA, left atrial; SW, shear wave.
Variables for multivariate analysis included age, SW elasticity, LA volume index, and tricuspid regurgitation pressure gradient.

Table 4 Relationships of SW elasticity with echocardiographic parameters

Variables	SW elasticity				
	Univariate analysis		Multivariate analysis		
	r	*P*	Beta	95% confidence interval	*P*
LV end-diastolic diameter	0.05	0.30			
LV end-systolic diameter	0.01	0.85			
LV ejection fraction	−0.11	<0.01	−0.06	(−0.06, 0.02)	0.32
LV mass index	0.12	0.03	−0.13	(−0.04, −0.01)	0.03
LA volume index	0.45	<0.01	0.28	(0.02, 0.05)	<0.01
E/e′	0.28	<0.01	0.18	(0.04, 0.18)	<0.01
Tricuspid regurgitation pressure gradient	0.07	0.19			
Inferior vena cava diameter	0.45	<0.01	0.30	(0.19, 0.41)	<0.01

E/e′, early diastolic mitral inflow velocity to mitral annular velocity ratio; LA, left atrial; LV, left ventricular; SW, shear wave.

index, E/e′, and inferior vena cava diameter and was negatively correlated with LV ejection fraction. In multivariate regression analysis, LA volume index, E/e′, and inferior vena cava diameter were remained as independent factors correlated with SW elasticity (*Table 4*).

Discussion

The major findings of the present study are as follows: (i) SW elasticity was correlated with echocardiographic parameters such as LA volume index, E/e′, and inferior vena cava diameter, which reflect congestion; and (ii) SW elasticity was a predictor of cardiac events in patients with chronic HF. To the best of our knowledge, this is the first study to show the efficacy of SW elasticity for assessing congestion and cardiac events in the chronic phase of HF.

Congestion in heart failure

In patients with HF, hospitalization is a prognostic predictor for increased mortality.[2] HF is characterized by a series of decompensation and progressive decline of condition, until cardiac death due to pump failure occurs. Once HF decompensation requiring hospitalizations develops, the patient's prognosis is worsening. Thus, apart from survival, the prevention of hospitalizations for HF is an increasing priority for clinicians. The main mechanism leading to hospital admission is congestion.[3] One previous study reported that residual pulmonary congestion assessed by radiographic scoring at discharge was associated with poor prognosis.[18] Therefore, the relief of organ congestion is essential to reduce hospitalizations that is required for the management in the chronic phase of HF.

Congestion is a phenomenon with several phenotypes underlying different and interconnected factors.[19] To control congestion in patients with HF, the assessments of intravascular and interstitial fluid compartments are needed. Intravascular and interstitial fluid compartments are interacting and redistributing, and interstitial fluid compartment supports the maintenance of intravascular volume overload.[20] Thus, it is important to assess organ congestion which reflects intravascular and interstitial congestion.

Regarding cardiohepatic interaction, liver dysfunction due to congestion affects the prognosis in patients with HF.[21–23] Liver function tests are used to assess the degree of hepatic congestion, but the abnormalities are often not observed unless HF is advanced.[24] In the liver, 70% of the blood supply is dependent on the portal system, and 30% is delivered by the hepatic artery. Because blood is supplied from both systems, liver function tests abnormalities are less likely to occur.[25] Especially in the chronic phase of HF, it is difficult to assess hepatic congestion by liver function tests. Actually, in the present study, the mean values of almost liver function tests of all patients such as aspartate aminotransferase and

alanine aminotransferase were not elevated. Thus, clinical tools for evaluating subclinical and clinical organ congestion are needed for the management of HF therapies.

Shear wave elasticity

SWE provides information regarding tissue elasticity, which is calculated by SW speed.[5–7] SW is generated by inducing a push pulse of ultrasound wave, which deforms a part of the tissue. SW within the tissue is detected by tracking pulse. SWE has been recognized as a clinical method for assessing liver diseases. Several studies have reported that SW elasticity is significantly increased in cirrhosis.[8,9] However, in the field of heart diseases, the usefulness of SWE has not been fully investigated. A few recent studies have reported that SW elasticity is correlated with central venous pressure in patients with acute decompensated HF, which is associated with adverse outcomes.[10–12,26–28] Because appropriate HF therapeutic interventions are required to prevent worsening HF, the assessment of organ congestion is important in the chronic phase of HF as well as in the acute phase of HF. Therefore, the present study investigated the efficacy of SWE on the assessment of congestion in patients with chronic HF.

Congestion develops gradually. Elevated LV filling pressure occurs in patients with HF despite the absence of congestion such as dyspnoea, jugular venous distention, or oedema.[29] This subclinical congestion progresses to clinical congestion, leading to increased venous pressure. In the present study, SW elasticity was correlated with E/e′, which estimates elevated LV filling pressure.[29] Additionally, similar to the previous study in the acute phase of HF,[12] SW elasticity was correlated with dilated inferior vena cava diameter, which is associated with increased venous pressure. Furthermore, SW elasticity was correlated with LA volume index. Many pathophysiologic mechanisms drive LA enlargement. The persistence of elevated LV filling pressure is also a mechanism of LA enlargement.[29,30] Our finding can indicate that SW elasticity reflects the influence of long-standing congestion in patients with HF. Based on these results, the present study suggests that SW elasticity has the potential to assess the degree of organ congestion in patients with HF.

In the present study, SW elasticity was related to cardiovascular death or hospitalization for HF. High SW elasticity of $\geq$6.4 kPa had cardiac events more frequently. This finding suggests that SW elasticity is effective to predict the prognosis, including the severity of HF, in the chronic phase of HF. One previous study presented the value of 8.8 kPa in relation to adverse outcomes.[27] The study included patients with acute decompensated HF, whereas our study population included those with chronic HF. The difference in the value of SW elasticity seems to be due to the HF condition. In the chronic phase of HF, the value of SW elasticity of 6.4 kPa is considered to be appropriate.

Although plasma B-type natriuretic peptide levels are dependent on congestion,[31] the present study showed that plasma B-type natriuretic peptide levels were not different between high SW elasticity group and low SW elasticity group. For the reason, we consider that SW elasticity assesses organ congestion influenced by intravascular congestion as well as interstitial congestion. SW elasticity may be a useful tool for sensitively assessing congestion beyond biomarkers, such as plasma B-type natriuretic peptide levels. Further studies are needed to evaluate the clinical significance of SW elasticity.

Clinical implications

The SWE is a simple, objective, and non-invasive modality. The present study showed that SW elasticity reflected the influence of organ congestion in the chronic phase of HF. SW elasticity was notably correlated with LA volume index, which is enlarged by long-standing elevated LA pressure. SW elasticity can provide information regarding persistent organ congestion for long-term. Furthermore, SW elasticity of $<$6.4 kPa showed better clinical outcomes in the present study. This value of SW elasticity may be effective as the target for HF therapies in the chronic phase of HF to prevent worsening HF.

Study limitations

There are some limitations in the present study. First, the number of patients was relatively small for assessing clinical outcomes in patients with HF. This study was conducted in a single centre. Larger studies are needed to confirm our findings. Second, liver biopsy was not performed. The relationship between SW elasticity and histological findings was not assessed. Finally, this study excluded patients with liver diseases, but this might have been insufficient.

Conclusions

The SW elasticity was correlated with echocardiographic parameters of congestion, such as LA volume index, E/e′, and inferior vena cava diameter, in patients with chronic HF. SW elasticity was related to cardiovascular death or hospitalization for HF. Our results suggest that SW elasticity can assess the degree of organ congestion, which predicts cardiac events.

Conflict of interest

The authors declare that they have no conflict of interest.

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