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ORIGINAL ARTICLE

Hepatic Stiffness Using Shear Wave Elastography and the Related Factors for a Fontan Circulation

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Abstract Hepatic problems related to a Fontan circulation have been highlighted and elastography using ultrasound is a non-invasive tool that can measure the severity of hepatic stiffness. We investigated the hepatic stiffness using shear wave elastography (SWE) and related factors in patients with a Fontan circulation. This study enrolled 64 patients with a Fontan circulation who underwent cardiac catheterization and abdominal ultrasound from 2011 to 2015. The correlation between the laboratory tests, hemodynamic factors by cardiac catheterization, and SWE was evaluated. The patients were classified into non-cirrhotic level ($\geq$ 2.0 m/s) and cirrhotic level ($<$ 2.0 m/s) groups by the SWE value. The mean age was 17.6 years and the mean duration after the Fontan operation was 12.1 years. The mean value of SWE in patients (1.95 m/s) was higher than the normal ($<$ 1.3 m/s). The SWE was higher in patients without than those with a fenestration (2.03 vs. 1.75 m/s, $P = 0.003$). In a multiple regression analysis between SWE and other factors, the CVP, fenestration, and lipoprotein Apo B had a significant correlation. In a multivariate analysis of cirrhotic level group, the CVP was the only significant factor. The hepatic stiffness had significantly progressed in most patients with a Fontan circulation. A low CVP and Fontan circulation with a fenestration might reduce the progression of the hepatic stiffness.

Keywords Fontan operation · Hepatic stiffness · Elastography · Cardiac catheterization

Background

A decreased cardiac output and non-pulsatile passive flow to the pulmonary vascular bed cause a wide range of late morbidities including exercise intolerance, arrhythmias, thromboembolisms, heart failure, protein-losing enteropathy, and plastic bronchitis [1, 2]. One of the lesser known morbidities is hepatopathy. In 2010, late hepatic complications after the Fontan operation were reported [3]. In that article, it was observed that late hepatic dysfunction and cirrhotic changes are often observed in Fontan patients. Moreover, hepatic complications are correlated with the duration of the Fontan circulation [3]. However, the non-invasive diagnostic tools for hepatic changes have not been well established.

The gold standard for liver fibrosis assessment is biopsy. Recently, non-invasive methods have been used and elastography using ultrasound has been used as a screening tool in patients with alcoholic or viral hepatic diseases as well as patients with a Fontan circulation [4, 5]. In this study, we investigated the correlation between the hepatic stiffness measured by the acoustic radiation force impulse (ARFI) as point shear wave elastography and the laboratory results or hemodynamic factors assessed by cardiac catheterization in patients with a Fontan circulation.

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Methods

The subjects consisted of 64 patients who underwent liver ultrasound elastography and cardiac catheterization from January 2011 to February 2015. General laboratory tests, a hepatic function laboratory test, and a liver ultrasound were performed. The laboratory tests included a complete blood cell count (CBC), and the albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransaminase (ALT), prothrombin time (PT), activated prothrombin time (aPTT), gamma-glutamyl transpeptidase (γ-GTP), liver-related coagulation factors, N-terminal pro-brain natriuretic peptide (NT-proBNP), and protein C and protein S levels. During cardiac catheterization, central venous pressure (CVP), transpulmonary pressure gradient (TPG), ventricular end-diastolic pressure (VEDP), pulmonary vascular resistance (PVR), systemic blood flow, and oxygen saturation were measured. The radiologist performed ARFI using an ultrasound machine (Siemens Acuson S2000, Erlangen, Germany). All evaluations of the laboratory tests, liver ultrasound, and cardiac catheterization were performed within 1 week of admission.

In our study, we applied point shear wave elastography–ARFI quantification using a Siemens ultrasound machine. The ARFI quantification measured the propagation of acoustic waves in an attenuating medium. The propagation speed increased with the medial fibrosis severity. The radiologist measured the elastography in the fasting state the day before or after cardiac catheterization, and it was measured about five times on average. Scanning was performed by an intercostal approach in the right liver lobe, to avoid any cardiac motion (with the patient in the supine position), with minimal scanning pressure applied by the operator, while the patient was asked to stop breathing for a moment, in order to minimize the breathing motion.

According to a comparison study between the ARFI quantification and a biopsy study in pediatric patients with hepatic graft fibrosis, an ARFI velocity from 1.30 to 1.39 m/s predicted hepatic fibrosis [6] and an ARFI velocity from 1.8 to 2.25 m/s predicted liver cirrhosis [7–10]. Therefore, the patients were classified into non-cirrhotic level group and cirrhotic level group according to an ARFI velocity of 2.0 m/s. After that, the laboratory and hemodynamic data were compared between the two groups.

Cardiac catheterization was performed while conscious, and the pressure and oxygen saturation were measured in a stable state using a multipurpose catheter. The oxygen consumption used in the calculation of the vascular resistance and systemic blood flow is reported in the literature [7]. Cardiac catheterization was performed by a pediatric cardiologist with more than 5 years of experience.

For the statistical analysis, SPSS 19.0 software (SPSS Inc., Chicago, IL, USA) for Windows was used. The descriptive data are presented as numbers with percentage, the mean with SD, or the median with the range, as appropriate. Differences between groups were assessed using χ^2 test for qualitative data, and independent t tests were applied for quantitative data to detect any differences between the groups. In case the group had less than 30 cases, non-parametric analysis was used. The correlation between two quantitative datasets was assessed using Pearson's correlation, and a binary multiple logistic regression analysis was used to assess the association among the elastography and factors from the laboratory or cardiac catheterization data. A binary logistic regression analysis was used to find the risk factor for cirrhotic group.

This study was approved by the institutional research board in Sejong General Hospital.

Results

There were a total of 64 patients. Their mean age was 17.6 years and there were 34 males. Their mean age at the time of the Fontan operation was 5.4 years and the mean time duration from the Fontan operation to cardiac catheterization was 12.1 years (Table 1). With respect to the type of Fontan operation, an atriopulmonary type was performed in 1 patient, lateral tunnel in 8, Kawashima type in 6, and extracardiac conduit (ECC) type in 49. Regarding the type of systemic ventricle, a right ventricle type was observed in 31 patients, left ventricle type in 26, and both a left ventricle and a right ventricle type in 7. Eighteen (28.1%) patients had a patent fenestration during cardiac catheterization (Table 1).

The results of most of the laboratory tests were within the normal range. However, γ-GTP and NT-proBNP levels were mildly elevated (Table 2). With respect to the liver function test, the macroglobulin level was slightly elevated and most of the parameters were within the normal range (Table 2). Regarding the hemodynamic data assessed by cardiac catheterization, the mean arterial oxygen saturation level was 94.3%, CVP 14.1 mmHg, TPG 3.8, VEDP 10.3 mmHg, PVR 1.35 Wu m^2, and systemic blood flow 2.97 L/min/m^2 (Table 1).

Liver ultrasound revealed that five patients had ascites and another five hepatic nodules. The mean velocity of ARFI was 1.95 m/s and it was in the borderline cirrhotic range. The ARFI measurement was performed for a mean of 4.6 times in different liver areas, ranging from 3 to 7 times. Regarding the baseline characteristics, the ARFI value did not exhibit a significant correlation with patient's age, age at the time of the Fontan operation, or the time period from the Fontan operation to ultrasound. When

Table 1 Baseline characteristics

Total No. of patients	64
Mean age (years)	17.6 ± 5.3 (9.0–37.2)
Sex (male: female)	34: 30
Mean age at the time of the Fontan operation (years)	5.4 ± 5.5 (1.3–29.3)
Mean time duration from the Fontan operation to cardiac catheterization (years)	12.1 ± 4.0 (2.8–20.9)
Type of Fontan operation	
Atriopulmonary type	1
Lateral tunnel type	8
Kawashima operation	6
Extracardiac conduit type	49
16 mm	3
18 mm	15
19 mm	1
20 mm	21
22 mm	7
24 mm	2
Type of systemic ventricle	
RV type	31
LV type	26
Both	7
Patent fenestration	18/64 (28.1%)
Arterial oxygen saturation (%) (mean ± SD)	94.3 ± 2.6
Central venous pressure (mmHg) (mean ± SD)	14.1 ± 3.1
Transpulmonary pressure gradient (mmHg) (mean ± SD)	3.8 ± 1.9
Ventricular end-diastolic pressure (mmHg) (mean ± SD)	10.3 ± 3.2
Pulmonary vascular resistance (Wu m^2) (mean ± SD)	1.35 ± 0.83
Systemic blood flow (L/min/m^2) (mean ± SD)	2.97 ± 1.25

SD standard deviation

comparing sex, Fontan type, and systemic ventricle type, there was no difference in the mean ARFI value (Table 3). However, the mean ARFI value in the patients with a fenestration was lower than that in those without (*P* value 0.008) (Fig. 1).

In the laboratory tests, the ARFI value had a significant correlation with only γ-GTP (Table 4). The correlation coefficient for γ-GTP was 0.304, and γ-GTP had a positive correlation with the ARFI value (Fig. 2). With respect to the laboratory tests that were related to the hepatic function, the ARFI value had a significant correlation with the lipoprotein Apo B and coagulation factor IX. The lipoprotein Apo B was more obviously positively correlated with elastography (correlation coefficient 0.374) (Table 4). With respect to the hemodynamic data assessed by cardiac catheterization, the ARFI value had a significant correlation with CVP and VEDP (Table 4; Fig. 2). In a multiple regression analysis, it was observed that the lipoprotein Apo B, CVP, and fenestration were correlated with hepatic stiffness (Table 5).

In the classification of non-cirrhotic level and cirrhotic level, there were 24 patients in the cirrhotic level group. The mean velocity in the non-cirrhotic level group was 1.66 m/s and that in the cirrhotic level group was 2.44 m/s (*P* value 0.000). There was no difference in the baseline characteristics between the two groups (Table 6). In laboratory tests, the cirrhotic level group had higher levels of AST, ALT, and γ-GTP even though they were within the normal range. In laboratory tests related to the hepatic function, the cirrhotic level group had a higher level of AFP (*P* value 0.003). However, the AFP level was within the normal range. In the hemodynamic data, the cirrhotic level group had a significantly higher level of CVP (15.1 vs 13.4 mmHg, *P* value 0.041). There was no difference in the arterial oxygen saturation, TPG, VEDP, PVR, or systemic blood flow between the two groups. With respect to the frequency of ascites or hepatic nodules, there was no difference between the two groups. In the analysis of cirrhotic level group, multivariate analysis showed that high CVP was the only significant risk factor suggesting severe hepatic stiffness and its odds ratio was 1.216 (Table 7).

Table 2 Results of the laboratory tests

	Mean	SD	Reference range
WBC (/L)	5578.4	1531.3	4000–10,000
Platelet (×1000,/L)	186.3	61.8	150–400
Albumin (g/dl)	4.62	0.58	3.5–5.2
Total bilirubin (mg/dl)	0.97	0.55	0.2–1.2
AST (U/L)	25.7	9.7	< 32
ALT (U/L)	21.2	9.7	< 33
Prothrombin time (INR)	1.19	0.21	0.8–1.2
Activated PTT (seconds)	32.3	6.4	22.6–36.1
γ-GTP (U/L)	59.2	39.9	5.0–36.0
NT-pro BNP (pg/ml)	137.1	208.0	0–125
α2-Macroglobulin (mg/dl)	286.0	64.6	130–250
Lipoprotein Apo A1 (mg/dl)	124.4	19.4	108–225
Lipoprotein Apo B (mg/dl)	64.9	19.3	60–117
α-Fetoprotein (ng/ml)	2.97	2.47	0–5.8
Haptoglobin (mg/dl)	52.0	37.0	30–200
Coagulation factor II (%)	83.7	14.5	65–125
Coagulation factor V (%)	51.0	20.2	66–126
Coagulation factor VII (%)	71.8	21.5	70–130
Coagulation factor IX (%)	88.8	22.8	60–150
Coagulation factor X (%)	74.2	18.1	70–120
Protein C (%)	90.4	26.3	70–130
Protein S (%)	79.5	20.1	55–126

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *NT-proBNP* N-terminal pro-b-type natriuretic peptide, *PT* prothrombin time, *γ-GTP* gamma-glutamyl transpeptidase, *WBC* white blood cell

Table 3 Mean values of shear wave elastography according to the baseline characteristics

	Shear wave elastography	*P* value
Sex (male/female)	1.96 ± 0.39/1.94 ± 0.53	0.545
Fontan type		0.354
Extracardiac conduit	1.94 ± 0.40	
Lateral tunnel	2.05 ± 0.75	
Atriopulmonary	1.22 ± 0.00	
Kawashima	2.06 ± 0.47	
Systemic ventricle		0.768
Right ventricle	1.99 ± 0.47	
Left ventricle	1.94 ± 0.50	
Both ventricles	1.80 ± 0.29	
Fenestration (yes/no)	2.02 ± 0.49/1.74 ± 0.30	0.008

Discussion

Fontan Circulation

Fontan operation was first performed in 1968 [11]. In a 'Fontan circulation,' there is no subpulmonic ventricle to propel blood into the pulmonary arteries since the systemic veins are directly connected to the pulmonary arteries [12]. In contrast to a biventricular circulation, in a Fontan circulation a high systemic venous pressure and non-pulsatile pulmonary flow are inevitable. The preload to the single ventricle is limited and appears to be the most important determinant of the cardiac output. The preload to the ventricle is determined by the transpulmonary flow and the transpulmonary flow is determined by the transpulmonary gradient and transpulmonary resistance. Therefore, a good circulatory output and thus a good long-term outcome in Fontan patients require a low pulmonary vascular resistance [13].

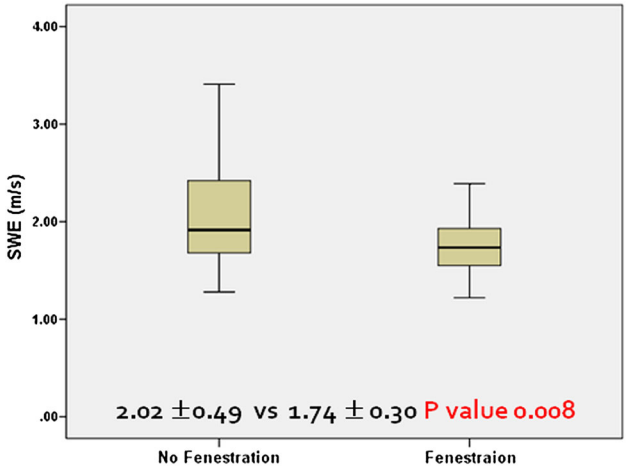

Fig. 1 Shear wave elastography with or without a fenestration. *P* value was 0.008

Liver Problems in Patients with a Fontan Circulation

In individuals with a normal heart anatomy and function, the hepatic blood flow consists of a portal vein and hepatic arterial flow. The portal blood flow is dependent on the mesenteric circulation and is related to the pressure gradient between the portal and hepatic venous pressures. The hepatic artery is responsible for the autoregulation of the hepatic blood flow [14]. Therefore, increased CVP and decreased portal flow could be buffered by an increased hepatic arterial flow. In a Fontan circulation, an elevated central venous pressure induces a decrease in the portal vein flow. As patients' age and hemodynamic changes become more pronounced, it is very possible that the capability of the hepatic arterial buffer response to compensate for a diminished portal vein flow is exceeded, contributing to hepatic injury [15].

Additionally, liver injury may be common in the natural and surgical history of patients undergoing single-ventricle palliative surgery [15]. The initial clinical presentation may be marked by cardiovascular collapse, congestive heart

Table 4 Correlation between shear wave elastography and results of the laboratory tests and cardiac catheterization data

	Pearson's correlation	*P* value
WBC (/L)	−0.12	0.924
Platelet (×1000/L)	−0.02	0.990
Albumin (g/dl)	−0.087	0.494
Total bilirubin (mg/dl)	−0.214	0.090
AST (U/L)	0.155	0.221
ALT (U/L)	0.196	0.121
Prothrombin time (INR)	−0.137	0.279
Activated PTT (seconds)	−0.223	0.076
γ-GTP (U/L)	0.304	0.027
NT-proBNP (pg/ml)	0.083	0.594
α2-Macroglobulin (mg/dl)	0.460	0.073
Lipoprotein Apo A1 (mg/dl)	−0.028	0.843
Lipoprotein Apo B (mg/dl)	0.374	0.007
α-Fetoprotein (ng/ml)	0.169	0.278
Haptoglobin (mg/dl)	0.165	0.242
Coagulation factor II (%)	0.095	0.506
Coagulation factor V (%)	0.242	0.086
Coagulation factor VII (%)	0.157	0.271
Coagulation factor IX (%)	0.298	0.0340
Coagulation factor X (%)	0.118	0.410
Protein C (%)	−0.048	0.735
Protein S (%)	0.245	0.083
Arterial oxygen saturation (%)	−0.052	0.683
Central venous pressure (mmHg)	0.344	0.005
Transpulmonary pressure gradient (mmHg)	0.07	0.953
Ventricular end-diastolic pressure (mmHg)	0.332	0.007
Pulmonary vascular resistance (Wu m^2)	0.027	0.832
Systemic blood flow (L/min/m^2)	−0.040	0.753

ALT alanine aminotransferase, *AST* Aspartate aminotransferase, *NT-proBNP* N-terminal pro-b-type natriuretic peptide, *PT* prothrombin time *γ-GTP* gamma-glutamyl transpeptidase, *WBC* white blood cell

failure, and marked hypoxemia in an infant with a single ventricle. Further, the perioperative periods of aortopulmonary shunts, Glenn shunts, or completion of the Fontan circulation are also well documented as causing ischemic liver insults [15, 16]. Chronic venous congestion characterizes the late Fontan circulation, and this combined with a low cardiac output, particularly during periods of cardiovascular stress, is likely to induce hypoxic stress and acute chronic injury that may trigger inflammation, subsequent fibrosis, and potential cirrhosis [15].

Recently, the presence of hepatic nodules in the Fontan liver has been described [17], and 5 patients (7.8%) in our study group had one or multiple nodules. They typically reside in the outer margins of the liver and are observed in Fontan patients with higher venous pressures. It is believed that they represent arterialization of the hepatic blood supply, an adverse adaptation associated with portal venous deprivation of the liver parenchyma [15]. Although these nodules are benign and pathologically identifiable as focal nodular hyperplasia, the initial characterization and follow-up treatment is challenging but vitally important because the main differential is hepatocellular carcinoma, which is currently being increasingly reported [18].

Elastography

For the evaluation of hepatic fibrosis, elastography, an ultrasound method for surveying the stiffness of a cylindrical hepatic sample, has advantages of rapidity, ease of use, and reliability. However, the use of elastography in Fontan-associated liver disease is problematic because any cause of altered hepatic stiffness would have an impact on

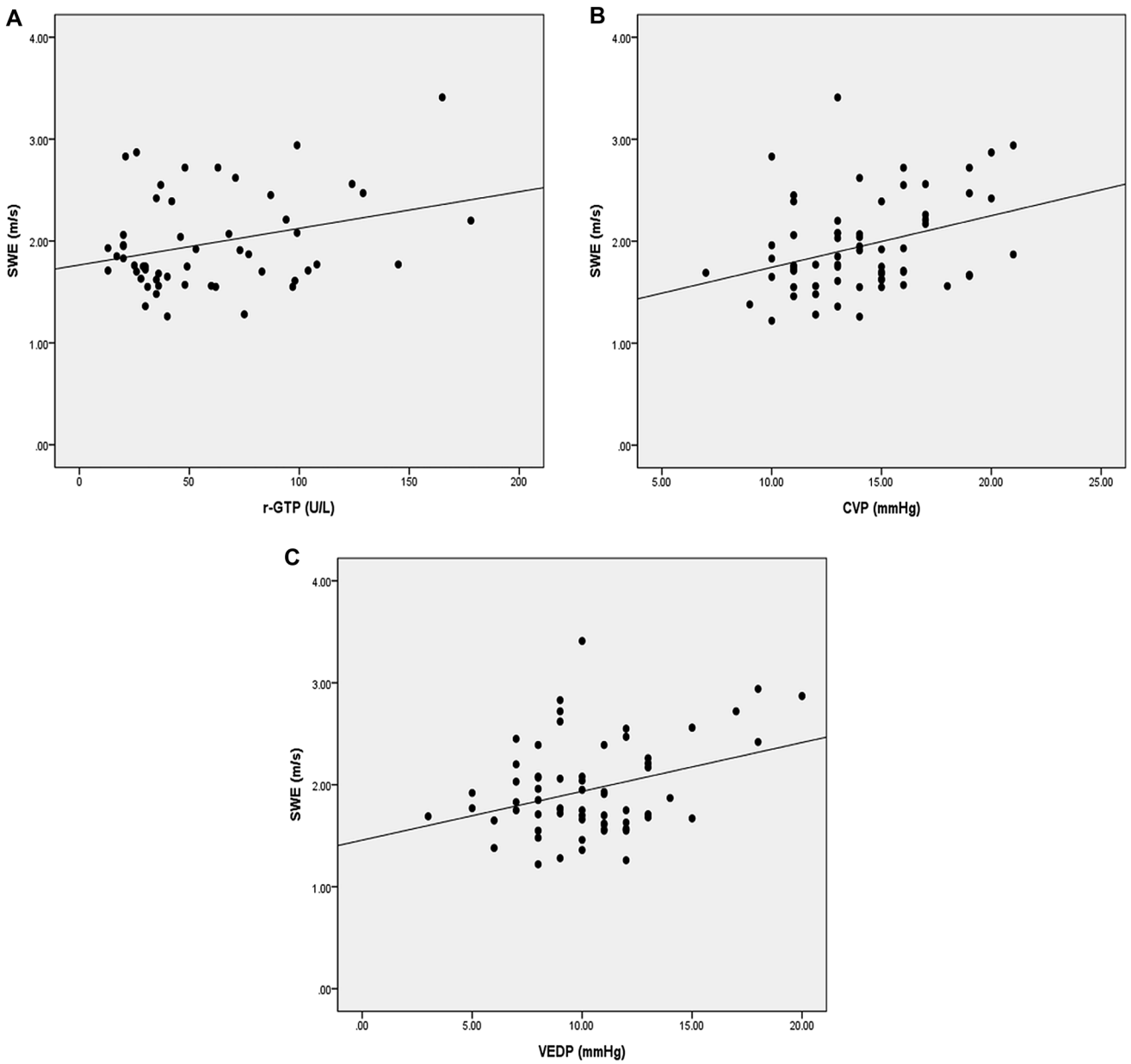

Fig. 2 With respect to the laboratory data, (**a**) γ-GTP had an obvious positive correlation with shear wave elastography (correlation coefficient 0.304). With respect to the hemodynamic data assessed by cardiac catheterization, the central venous pressure (**b**) and ventricular end-diastolic pressure (**c**) had an obvious positive correlation with shear wave elastography

the results [19]. Although the "gold standard" and best tool for diagnosing liver disease is biopsy, it has significant drawbacks ranging from the risk of the procedure to the potential for a sampling error and difficulty in the interpretation of the results. A comprehensive meta-analysis of 40 studies examining transient elastography concluded that elastography theoretically has a good sensitivity and specificity for cirrhosis, even though there is no validation of the stiffness cut-offs for the various stages [20]. The elastography methods using ultrasound waves are classified as strain and shear wave elastography. "Point" shear wave

Table 5 Multiple regression analysis

Variables	β ± SE	Partial R^2	*P* value
γ-GTP	0.002 ± 0.001	0.0449	0.148
Lipoprotein Apo B	0.008 ± 0.003	0.1451	0.008
CVP	0.042 ± 0.020	0.0894	0.039
Fenestration	−0.263 ± 0.127	0.0846	0.045

CVP central venous pressure, *γ-GTP* gamma-glutamyl transpeptidase, *SE* standard errors

Table 6 Comparative analysis between the non-cirrhotic and cirrhotic groups

	Non-cirrhotic level group ($N = 40$)	Cirrhotic level group ($N = 24$)	P value
SWE (m/s)	1.66 ± 0.19	2.44 ± 0.35	<0.001
Age (mean ± SD, months)	213.5 ± 71.6	205.9 ± 48.3	0.649
Sex (male/female)	20/20	14/10	0.609
Mean age at the time of the Fontan operation (months)	73.8 ± 78.1	51.1 ± 33.4	0.113
Mean time duration (from the Fontan operation to cardiac catheterization) (months)	139.7 ± 50.8	154.8 ± 43.8	0.23
Type of Fontan operation (ECC/LT/AP/Kawashima)	32/4/1/3	17/4/0/3	0.637
Type of systemic ventricle (RV/LV/Both)	18/17/5	13/9/2	0.744
Patent fenestration	14/40	4/24	0.155
WBC(/L)	5660.3 ± 1472.0	5442.1 ± 1648.7	0.585
Platelet (×1000/L)	191.4 ± 70.0	177.9 ± 45.2	0.403
Albumin (g/dl)	4.65 ± 0.59	4.59 ± 0.57	0.692
Total bilirubin (mg/dl)	1.07 ± 0.59	0.81 ± 0.45	0.076
AST (U/L)	23.7 ± 6.3	29.1 ± 13.1	0.022
ALT (U/L)	18.9 ± 6.6	24.9 ± 12.7	0.033
Prothrombin time (INR)	1.22 ± 0.25	1.14 ± 0.14	0.141
Activated PTT (seconds)	33.3 ± 7.1	30.6 ± 4.7	0.107
γ-GTP (U/L)	49.6 ± 32.2	76.4 ± 47.1	0.029
NT-proBNP (pg/ml)	119.4 ± 152.3	171.2 ± 290.8	0.44
α2-Macroglobulin (mg/dl)	262.9 ± 38.1	315.8 ± 81.6	0.153
Lipoprotein Apo A1 (mg/dl)	124.6 ± 18.3	124.1 ± 21.8	0.936
Lipoprotein Apo B (mg/dl)	61.4 ± 16.9	70.7 ± 22.1	0.124
α-fetoprotein (ng/ml)	2.49 ± 2.54	3.85 ± 2.11	0.003
Haptoglobin (mg/dl)	49.3 ± 36.3	56.6 ± 38.8	0.499
Coagulation factor II (%)	82.2 ± 15.0	86.2 ± 13.7	0.337
Coagulation factor V (%)	47.5 ± 17.8	56.7 ± 22.9	0.116
Coagulation factor VII (%)	69.0 ± 22.5	76.5 ± 19.3	0.228
Coagulation factor IX (%)	85.6 ± 19.8	94.2 ± 26.9	0.194
Coagulation factor X (%)	72.0 ± 16.7	78.0 ± 20.0	0.255
Oxygen saturation (%)	94.3 ± 2.7	94.3 ± 2.7	0.866
Central venous pressure (mmHg)	13.4 ± 2.9	15.1 ± 3.2	0.041
Transpulmonary pressure gradient (mmHg)	3.75 ± 2.02	3.79 ± 1.82	0.592
Ventricular end-diastolic pressure (mmHg)	9.7 ± 2.6	11.3 ± 3.8	0.204
Pulmonary vascular resistance (Wu m^2)	1.33 ± 0.78	1.38 ± 0.92	0.994
Systemic blood flow (L/min)	2.98 ± 1.34	2.96 ± 1.11	0.617
Ascites	3/40	2/24	0.626
Nodules on the liver	4/40	1/24	0.374

ALT alanine aminotransferase, *AP* atriopulmonary, *AST* Aspartate aminotransferase, *ECC* extracardiac conduit, *LT* lateral tunnel, *LV* left ventricle, *NT-proBNP* N-terminal pro-b-type natriuretic peptide, *PT* prothrombin time, *γ-GTP* gamma-glutamyl transpeptidase, *RV* right ventricle, *SE* standard deviation, *SWE* shear wave elastography, *WBC* white blood cell

elastography, acoustic radiation force impulse quantification, and real-time SWE (ARFI) are the shear wave elastography techniques that have evolved [21]. In a meta-analysis, ARFI elastography had a higher rate of reliable measurements and a similar predictive value to transient elastography. In our study, ARFI was used and measured repeatedly from 3 to 7 times.

Laboratory Findings

In spite of hepatic fibrosis, the hepatic function was well preserved, as reflected by the liver enzymes, bilirubin, albumin, and prothrombin time. Our results corroborated the results of a previous study and most laboratory values were within the normal range. However, the γ-GTP and

Table 7 Analysis for risk factors of cirrhotic groups by SWE

Covariate	Univariate			Multivariate		
	Odd ratio	95% CI	*P* value	Odd ratio	95% CI	*P* value
Age	0.912	0.822–1.013	0.087			
Sex (male/female)	0.778	0.291–2.080	0.617			
Mean age at the time of the Fontan operation (months)	0.993	0.984–1.002	0.142			
Mean time duration (from the Fontan operation to cardiac catheterization) (months)	0.998	0.988–1.008	0.722			
Type of Fontan operation	0.960	0.215–4.280	0.957			
Type of systemic ventricle	1.417	0.498–4.034	0.514			
Central venous pressure (mmHg)	1.202	1.010–1.432	0.039	1.216	1.011–1.463	0.038
Transpulmonary pressure gradient (mmHg)	1.182	0.903–1.546	0.223			
Ventricle end-diastolic pressure (mmHg)	1.116	0.948–1.315	0.188			
Pulmonary vascular resistance (Wu m^2)	1.165	0.638–2.127	0.618			
Systemic blood flow (L/min/m^2)	1.203	0.801–1.806	0.374			
Fenestration	0.535	0.176–1.624	0.269			
Oxygen saturation (%)	0.831	0.675–1.023	0.080			

CI confidence interval

NT-proBNP values were mildly elevated. In the hemodynamic data, most patients had high oxygen saturation (94.3%) and low CVP (14.1 mmHg) and PVR (1.35 wu m^2) (Table 1). Therefore, our subjects had a good Fontan status and the characteristics of such a group may have an impact on the correlation with the elastography value. In most previous studies [3, 7], the degree of hepatic complications was well correlated with the time period after the Fontan completion. However, our data differed from the previously reported data, which could be because our patients had a good Fontan condition and the time period after Fontan completion did not vary.

Lipoprotein Apo B is an important component of the lipoproteins that are involved in the development of atherosclerosis and cardiovascular disease. It was noted that lipoprotein Apo B had a strong correlation to the LDL cholesterol and risk of cardiovascular disease. In our study, γ-GTP and lipoprotein Apo B had a positive correlation to elastography. We did not reveal the underlying mechanism for the correlation between the lipoprotein Apo B and hepatic stiffness even though the lipoprotein Apo B might have been involved in the hepatic fatty change. For γ-GTP, the cirrhotic group exhibited a significantly more elevated value than the non-cirrhotic group.

The analysis of the hemodynamic data and hepatic stiffness was the unique feature of our study. The CVP and VEDP values were well correlated with the hepatic stiffness, and the cirrhotic group had a higher CVP. Additionally, the patients with a Fontan circulation and fenestration had a lower elastography value. Based on the results of the hemodynamic data, we could conclude that the amount of hepatic congestion affected the severity of hepatic stiffness. The PVR or cardiac output did not show any correlation with elastography. These results might have been obtained because our subjects had a good Fontan circulation. In the hemodynamic data, the mean PVR was 1.35 Wu m^2 and systemic blood flow was 2.97 L/min/m^2 (Table 1).

Our study had several limitations as it was a retrospective study and it included a small number of patients. The usefulness of elastography using ultrasound in patients with a Fontan circulation was not confirmed by liver biopsy, and it was only confirmed in pediatric patients with other liver diseases [6, 7]. Therefore, the classification of the cirrhotic level and non-cirrhotic level groups and the comparison between the two groups may be meaningless. Moreover, we have only less experience with shear wave elastography (ARFI quantification) in patients with a Fontan circulation. Also, cardiac catheterization and shear wave elastography were performed by multiple clinicians.

In spite of the various limitations, our study revealed the following findings. Conclusively, a progression of hepatic stiffness in most patients with Fontan circulation could be identified by SWE (ARFI). Because the serum γ-GTP and lipoprotein Apo B had a significant correlation with SWE, measurement of these parameters would be a useful indicator for hepatic stiffness. According to the hemodynamic data, hepatic congestion was an important factor in hepatic stiffness. Patients with a low CVP and fenestrated Fontan circulation might have reduced progression of hepatic stiffness.

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Compliance with Ethical Standards

Conflict of interest All authors except Seong-Ho Kim declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent for this retrospective study was waived from the institutional research board of our hospital.

References

1. Hsu DT (2015) The Fontan operation: the long-term outlook. Curr Opin Pediatr 27(5):569–575
2. Rychik J, Goldberg DJ (2014) Late consequences of the Fontan operation. Circulation 130(17):1525–1528
3. Baek JS, Bae EJ, Ko JS, Kim GB, Kwon BS, Lee SY, Noh CI, Park EA, Lee W (2010) Late hepatic complications after Fontan operation; non-invasive markers of hepatic fibrosis and risk factors. Heart 96(21):1750–1755
4. Castera L, Pinzani M, Bosch J (2012) Non invasive evaluation of portal hypertension using transient elastography. J Hepatol 56(3):696–703
5. Friedrich-Rust M, Koch C, Rentzsch A, Sarrazin C, Schwarz P, Herrmann E, Lindinger A, Sarrazin U, Poynard T, Schafers HJ, Zeuzem S, Abdul-Khaliq H (2008) Noninvasive assessment of liver fibrosis in patients with Fontan circulation using transient elastography and biochemical fibrosis markers. J Thorac Cardiovasc Surg 135(3):560–567
6. Tomita H, Hoshino K, Fuchimoto Y, Ebinuma H, Ohkuma K, Tanami Y, Du W, Masugi Y, Shimojima N, Fujino A, Kano M, Fujimura T, Ishihama H, Shimizu T, Tanabe M, Saito H, Sakamoto M, Hibi T, Kitagawa Y, Kuroda T (2013) Acoustic radiation force impulse imaging for assessing graft fibrosis after pediatric living donor liver transplantation: a pilot study. Liver Transpl 19(11):1202–1213
7. Andersen SB, Ewertsen C, Carlsen JF, Henriksen BM, Nielsen MB (2016) Ultrasound elastography is useful for evaluation of liver fibrosis in children: a systematic review. J Pediatr Gastroenterol Nutr 63(4):389–399
8. Fierbinteanu-Braticevici C, Andronescu D, Usvat R, Cretoiu D, Baicus C, Marinoschi G (2009) Acoustic radiation force imaging sonoelastography for noninvasive staging of liver fibrosis. World J Gastroenterol 15(44):5525–5532
9. Lupsor M, Badea R, Stefanescu H, Sparchez Z, Branda H, Serban A, Maniu A (2009) Performance of a new elastographic method (ARFI technology) compared to unidimensional transient elastography in the noninvasive assessment of chronic hepatitis C. Preliminary results. Gastrointestin Liver Dis 18(3):303–310
10. Rizzo L, Calvaruso V, Cacopardo B, Alessi N, Attanasio M, Petta S, Fatuzzo F, Montineri A, Mazzola A, L'Abbate L, Nunnari G, Bronte F, Di Marco V, Craxi A, Camma C (2011) Comparison of transient elastography and acoustic radiation force impulse for non-invasive staging of liver fibrosis in patients with chronic hepatitis C. Am J Gastroenterol 106(12):2112–2120
11. Fontan F, Baudet E (1971) Surgical repair of tricuspid atresia. Thorax 26(3):240–248
12. Gewillig M, Brown SC (2016) The Fontan circulation after 45 years: update in physiology. Heart 102(14):1081–1086
13. Gewillig M, Brown SC, Eyskens B, Heying R, Ganame J, Budts W, La Gerche A, Gorenflo M (2010) The Fontan circulation: who controls cardiac output? Interact Cardiovasc Thorac Surg 10(3):428–433
14. Eipel C, Abshagen K, Vollmar B (2010) Regulation of hepatic blood flow: the hepatic arterial buffer response revisited. World J Gastroenterol 16(48):6046–6057
15. Rychik J, Veldtman G, Rand E, Russo P, Rome JJ, Krok K, Goldberg DJ, Cahill AM, Wells RG (2012) The precarious state of the liver after a Fontan operation: summary of a multidisciplinary symposium. Pediatr Cardiol 33(7):1001–1012
16. Kiesewetter CH, Sheron N, Vettukattill JJ, Hacking N, Stedman B, Millward-Sadler H, Haw M, Cope R, Salmon AP, Sivaprakasam MC, Kendall T, Keeton BR, Iredale JP, Veldtman GR (2007) Hepatic changes in the failing Fontan circulation. Heart 93(5):579–584
17. Bryant T, Ahmad Z, Millward-Sadler H, Burney K, Stedman B, Kendall T, Vettukattil J, Haw M, Salmon AP, Cope R, Hacking N, Breen D, Sheron N, Veldtman GR (2011) Arterialised hepatic nodules in the Fontan circulation: hepatico-cardiac interactions. Int J Cardiol 151(3):268–272
18. Josephus Jitta D, Wagenaar LJ, Mulder BJ, Guichelaar M, Bouman D, van Melle JP (2016) Three cases of hepatocellular carcinoma in Fontan patients: review of the literature and suggestions for hepatic screening. Int J Cardiol 206:21–26
19. Wong VW, Chan HL (2010) Transient elastography. J Gastroenterol Hepatol 25(11):1726–1731
20. Tsochatzis EA, Gurusamy KS, Ntaoula S, Cholongitas E, Davidson BR, Burroughs AK (2011) Elastography for the diagnosis of severity of fibrosis in chronic liver disease: a meta-analysis of diagnostic accuracy. J Hepatol 54(4):650–659
21. Sporea I, Gilja OH, Bota S, Sirli R, Popescu A (2013) Liver elastography—an update. Med Ultrason 15(4):304–314