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Reliability of transient elastography as a noninvasive method for estimating central venous pressure in adult patients after a Fontan procedure☆

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ABSTRACT

Background: In adult patients, after a Fontan procedure, high central venous pressure (CVP) is a hemodynamic risk factor associated with poor prognosis. High liver stiffness (LS) on transient elastography (TE) is associated with high CVP in patients with heart failure without liver disease. Here, we investigated whether LS assessment using TE is a reliable method to noninvasively evaluate CVP in adult patients after a Fontan procedure, who can present varying degrees of liver fibrosis as a complication.

Methods: We measured LS using TE and CVP by cardiac catheterization in 24 adult patients who had undergone a Fontan procedure. The estimated CVP was calculated using the previously reported formula: $-5.8 + 6.7 \times \ln$ [LS]. We examined the correlation between LS and CVP, and degree of agreement between the estimated and measured CVPs. Patients were divided into two groups, with or without suspected liver cirrhosis, based on abdominal imaging studies.

Results: The median patient age was 35 years (interquartile range 25, 39). Overall, there was a strong correlation between LS and CVP ($\rho = 0.83$, $p < 0.001$). The estimated CVP based on LS and the CVP measured using cardiac catheterization were positively correlated; however, the estimated CVP tended to be higher than the measured CVP (mean difference 0.9 mmHg [95% limits of agreement: −2.8 to 4.6 mmHg]). These results were consistent across all groups.

Conclusions: In adult patients after a Fontan procedure, LS measured by TE showed a positive correlation with CVP by cardiac catheterization. TE can be useful as a noninvasive estimation of CVP.

1. Introduction

The Fontan procedure is the standard treatment for individuals with a functionally univentricular heart. The survival rate of patients after a Fontan procedure has improved over the last few decades, with most patients reaching adulthood [1]. However, various complications associated with the procedure may develop, including heart failure, arrhythmias, thromboembolism, protein-losing enteropathy, plastic bronchitis, renal dysfunction, and liver fibrosis. Therefore, identifying patients at a high risk of such complications is important for their management [2].

Due to the lack of a subpulmonary ventricle, a chronically high systemic venous pressure is maintained during Fontan circulation. Prolonged elevation of central venous pressure (CVP) can lead to organ damage due to congestion. A higher CVP has been reported as a risk factor for complications, such as protein-losing enteropathy and liver fibrosis, and is associated with worse prognosis after a Fontan procedure [3–6]. CVP can change after the procedure. Therefore, periodic CVP measurements are necessary to assess the risk of complications and prognosis in patients after a Fontan procedure. Cardiac catheterization is

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the gold standard for measuring CVP; however, it is invasive, time-consuming, and difficult to perform in daily practice. A noninvasive method for assessing CVP would contribute to the timely management of patients after a Fontan procedure.

Transient elastography (TE) is a noninvasive method that can rapidly measure liver stiffness (LS) by emitting a small pulse of energy (a shear wave) and calculating the speed of the wave as it travels through the liver. LS values are used as indicators of liver damage in liver diseases, such as non-alcoholic fatty liver disease/non-alcoholic hepatitis, because they increase with the progression of liver fibrosis and inflammation [7,8]; however, they can be influenced by liver congestion [9]. A positive correlation between LS and CVP has been reported in patients with heart failure without liver disease, and a formula for estimating CVP using LS ($CVP = -5.8 + 6.7 \times \ln[LS]$) was also derived [10]. However, the relationship between LS and CVP in adult patients after the Fontan procedure, who have a high prevalence of liver damage and congestion, has not yet been fully elucidated. Therefore, we investigated the correlation between LS and CVP and the reliability of a previously reported formula for estimating CVP using LS in adult patients who had undergone the Fontan procedure despite the high prevalence of various degrees of coexisting liver injury, including cirrhosis. In addition, the reliability of CVP estimation using LS was examined in patients with cirrhosis suspected on abdominal imaging studies post-Fontan procedure.

2. Patients and methods

2.1. Patients

We retrospectively evaluated 26 adult patients who underwent TE and cardiac catheterization after the Fontan procedure between 2016 and 2021. Two patients with invalid LS measurements were excluded. This study conformed to the principles outlined in the 1975 Declaration of Helsinki and was approved by the Institutional Review Board of Osaka University, including the waiver for informed consent.

2.2. Transient elastography

LS was assessed by TE using FibroScan (Echosens, Paris, France) up to 4 days before cardiac catheterization. The patients raised the arm on the same side that the liver was situated to increase the intercostal space while lying flat. A 3.5-MHz probe was placed at the liver-side midaxillary line in the intercostal space. LS was measured 10 times during the end-expiratory phase, and the median value was calculated. LS values with an interquartile range/median ratio of >0.30 or a success rate of $<60\%$ were considered invalid. The estimated CVP was calculated using the previously reported formula: estimated $CVP = -5.8 + 6.7 \times \ln[LS]$ [10].

2.3. Hemodynamic assessments

Cardiac catheterization was performed according to standard protocols. Pressure measurements were referenced to the midaxillary line, with the patient in the supine position during the end-expiratory phase. Cardiac output was measured using the Fick method. The pressure measured at the inferior vena cava was regarded as the CVP.

2.4. Liver damage evaluation

The possibility of cirrhosis was assessed by abdominal computed tomography (CT) or magnetic resonance imaging (MRI) performed up to one year before or after the catheterization. Patients were divided into two groups: those suspected (H group) and not suspected (non-H group) of having cirrhosis. This was based on the radiologists' findings of irregular or nodular liver surfaces, caudate lobe hypertrophy, collateral circulation on CT, or increased T2-weighted and diffusion-weighted signal intensity with reduced T1-weighted signal intensity in the periphery of the liver on MRI [11].

2.5. Statistical methods

Continuous variables are presented as the median and interquartile range (IQR), and categorical data are presented as percentages. The Wilcoxon tests were used to compare continuous variables between groups, and chi-squared tests were used for categorical variables. For the correlation between two continuous variables, linear regression analysis and the Spearman's rank correlation coefficient (ρ) were used. Bland-Altman plots were used to show the agreement interval of the estimated and measured CVP by plotting their difference against the mean. Mean differences and 95% limits of agreement were estimated. Statistical significance was defined as a two-sided p-value of <0.05. Statistical analyses were performed using the JMP software (version 17.0; SAS Institute. Cary, NC, USA).

3. Results

3.1. Patient characteristics

Patient characteristics are shown in Table 1. The median age of the cohort was 35 years (IQR, 25,39). The first Fontan procedure was performed at a median age of 5 years (IQR, 4,10), with a 27-year period (IQR, 19,33) since the procedure. The main congenital heart defects were single ventricle in eight (33%), tricuspid atresia in seven (29%), pulmonary atresia with intact ventricular septum in two (8%), double outlet right ventricle in three (13%), Ebstein's anomaly in one (4%), and other ones in three (13%) patients. Of the 24 patients, fenestration flow or leakage from the Fontan pathway was found in four (17%), and veno-venous collaterals were identified in 11 (46%). There was no significant difference in CVP values because of the presence of fenestration or veno-venous collaterals. No significant correlation was found between LS values and laboratory parameters related to liver function or fibrosis.

3.2. Correlation between LS and CVP in overall cohort

Overall, there was a positive correlation between LS and CVP, as measured by cardiac catheterization (Fig. 1). The estimated CVP based on LS also showed a strong positive linear correlation with the measured CVP ($\rho = 0.83$, $p < 0.001$). Bland-Altman plots showed that most differences between the estimated and measured CVP were within the 95% agreement range (Fig. 2A). However, there was a significant mean difference of 0.9 mmHg (95% limits of agreement: -2.8 to 4.6 mmHg) between the estimated and measured CVP ($p = 0.04$), indicating a tendency for the estimated CVP to be higher than the measured CVP.

3.3. Characteristics of the patients with a higher estimated CVP than the measured CVP

Of the 24 patients, estimated CVP was higher than measured CVP in 17 (71%) patients and lower in seven (29%). Patients with a higher estimated CVP than the measured CVP were significantly older [35 (31–39) years versus 28 (21–36) years, $p = 0.04$], with a longer duration of Fontan circulation [31 (25–33) years versus 20 (1–27) years, $p = 0.01$] compared to those with a lower estimated CVP than the measured CVP. Laboratory and hemodynamic parameters were similar between the two groups (Supplemental table).

3.4. CVP estimation using LS in patients with suspected cirrhosis

Of the 24 patients, nine (38%) were suspected to have cirrhosis based on CT or MRI findings (H group). As shown in Table 1, there were no significant differences in clinical characteristics and laboratory data between the H and non-H groups, except that more patients in the non-H

Table 1
Patient characteristics.

	Total	Non-H group	H group	p value
Number of patients	24	15	9	
Patient age, years	35 (25–39)	33 (24–39)	35 (27–38)	0.86
Duration of Fontan circulation	27 (19–33)	26 (17–33)	27 (25–31)	0.72
Sex, male	15 (63%)	8 (53%)	7 (78%)	0.39
Body mass index, kg/m^2	22 (19–23)	20 (19–24)	22 (21–23)	0.28
Type of main ventricle				
Left ventricle	15 (67%)	12 (80%)	3 (33%)	0.04
Type of Fontan connection				0.23
Extracardiac conduit	10 (42%)	7 (47%)	3 (33%)	
Lateral tunnel	6 (25%)	2 (13%)	4 (45%)	
Others	8 (33%)	6 (40%)	2 (22%)	
Laboratory				
Platelet, $\times 10^3$/μL	145 (103–191)	119 (102–172)	169 (139–204)	0.14
Total bilirubin, mg/dL	1.1 (0.6–1.8)	1.0 (0.6–1.6)	1.1 (0.6–2.1)	0.65
AST, IU/L	23 (20–28)	23 (20–28)	23 (22–31)	0.57
ALT, IU/L	21 (16–30)	21 (16–30)	21 (14–33)	0.95
γ glutamyl transpeptidase, IU/L	84 (61–175)	82 (60–189)	113 (64–164)	0.72
Creatinine, mg/dL	0.75 (0.65–0.89)	0.73 (0.67–0.87)	0.78 (0.61–1.04)	0.95
Albumin, g/dL	4.6 (4.3–4.8)	4.6 (4.3–4.8)	4.6 (4.0–4.9)	0.81
M2BPGi	0.36 (0.26–0.43)	0.38 (0.27–0.50)	0.34 (0.21–0.43)	0.52
Hyaluronic acid, ng/mL	26 (16–53)	28 (15–53)	26 (17–166)	0.73
Type IV collagen 7S, ng/mL	6.9 (5.2–8.3)	7.0 (5.9–8.2)	6.6 (5.1–9.7)	0.86
Brain natriuretic peptide, pg/mL	30 (9–50)	32 (14–42)	15 (8–63)	0.72
Transient elastography				
Liver stiffness, kPa	20 (14–29)	16 (12–21)	36 (23–46)	<0.01
Estimated CVP, mmHg	14 (12–17)	13 (11–15)	18 (15–20)	<0.01
Hemodynamic assessment				
Systolic arterial pressure, mmHg	105 (94–111)	106 (94–111)	100 (92–110)	0.51
Diastolic arterial pressure, mmHg	58 (52–67)	60 (56–70)	56 (49–65)	0.22
Arterial oxygen saturation, %	95 (94–96)	95 (94–96)	95 (93–96)	0.81
Heart rate, bpm	79 (66–80)	80 (68–80)	67 (62–87)	0.28
Measured CVP, mmHg	14 (11–16)	13 (11–14)	16 (13–18)	0.02
End diastolic pressure of main ventricle, mmHg	9 (8–11)	8 (7–9)	12 (9–14)	<0.01
Cardiac index, L/min/m^2	2.6 (2.0–3.4)	2.6 (1.9–3.4)	2.6 (2.2–3.5)	0.68

Values are shown as the median (interquartile range) or n (%).
AST = aspartate aminotransferase, ALT = alanine aminotransferase, M2BPGi = Mac-2 binding protein glycosylation isomer, CVP = central venous pressure.

group had a left ventricular-type systemic ventricle. The H group had significantly higher LS than the non-H group; consequently, the estimated CVP calculated using LS was also significantly higher in the H group than in the non-H group. The CVP measured by catheterization was also significantly higher in the H group than in the non-H group. The Bland-Altman plots demonstrated that the mean difference between the estimated and measured CVP was 0.7 mmHg (95% limits of agreement: −3.2 to 4.6 mmHg) in the non-H group and 1.1 mmHg (95% limits of agreement: −2.4 to 4.7 mmHg) in the H group (Fig. 2B and C). Although the differences were not significant ($p = 0.20$ for non-H group and $p = 0.10$ for H group, respectively), the estimated CVP tended to be higher than the measured CVP in both groups. The mean difference between the estimated and measured CVP was not significantly different between the groups ($p = 0.16$).

4. Discussion

Our study had three major findings regarding adult patients who had undergone the Fontan procedure. First, there was a good correlation between LS measured using TE and CVP measured using cardiac catheterization. Second, the CVP estimated from LS using the previously mentioned equation had a good agreement with the measured CVP (but 0.9 mmHg higher on average). Third, the results were consistent even in patients with suspected cirrhosis on abdominal imaging, who had undergone the Fontan procedure.

4.1. Correlation between LS and CVP

LS measured using TE has been used to assess liver damage in various diseases as an indicator of liver inflammation and fibrosis [7,8]. Several

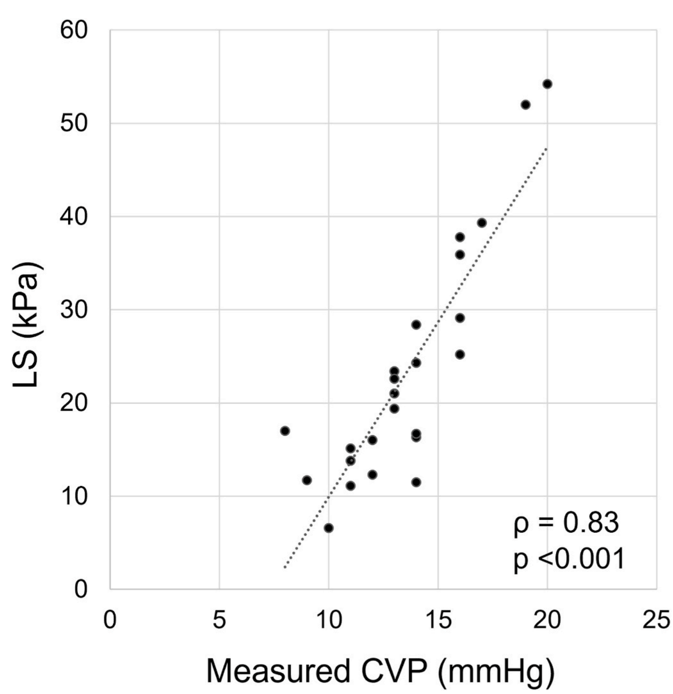

Fig. 1. The correlation between LS and measured CVP in all patients. There is a positive correlation between LS and CVP measured by cardiac catheterization ($\rho = 0.83$, $p < 0.001$). CVP = central venous pressure, LS = liver stiffness, ρ = Spearman's rank correlation coefficient.

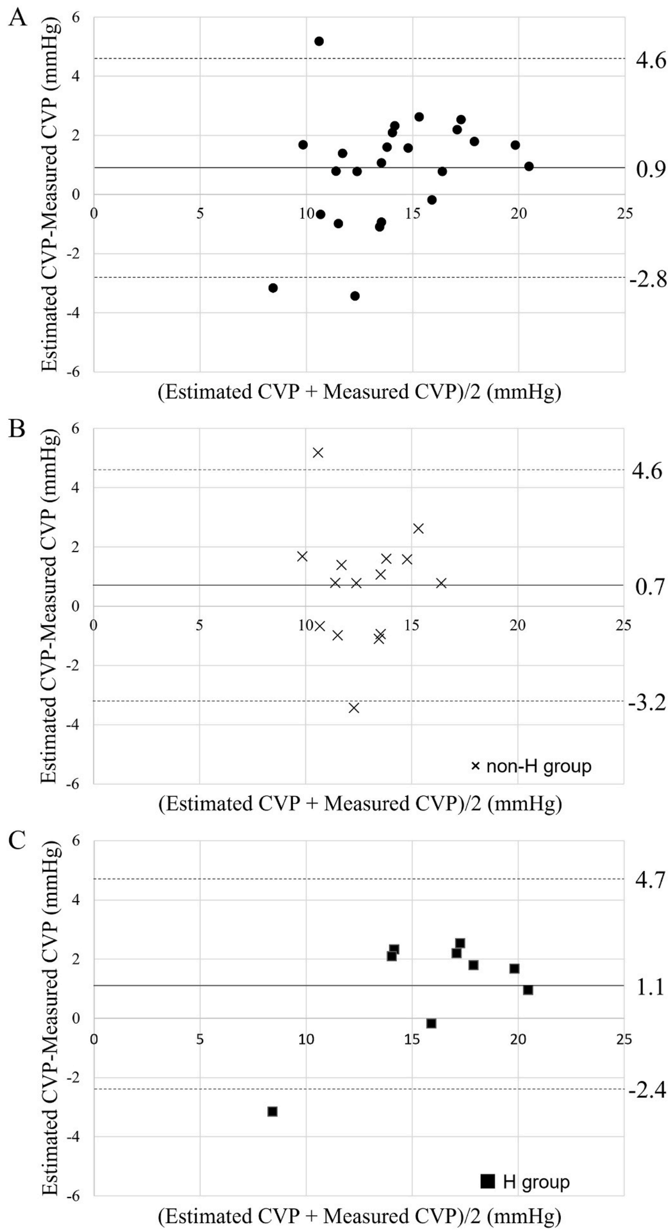

Fig. 2. Bland-Altman plot of the estimated and measured CVP in the (A) overall cohort, (B) non-H group, and (C) H group. The difference between the estimated and measured CVP is plotted against their mean values. The solid line shows the average of the difference, and the dotted line shows 95% limits of agreement.
CVP = central venous pressure.

studies have investigated liver damage after the Fontan procedure using TE [12–19]. Some of these studies have further examined the relationship between CVP and LS; however, the results have not been consistent [14,17–19]. The timing of the LS and CVP measurements varied widely across studies, which may have contributed to the inconsistent results. Wu et al. performed TE up to 5 days before catheterization in 45 patients with Fontan circulation and reported a good correlation between LS and CVP [14], which is in accordance with our results. Although their study included many pediatric patients with a relatively short postoperative period (median duration: 9.9 years), we demonstrated consistent results in adult patients with a long postoperative period (median duration, 27 years) who were at a high risk of complications after the Fontan procedure.

4.2. CVP estimation based on LS

In addition, this is the first clinical study to investigate the reliability of LS-based CVP estimation in patients after a Fontan procedure. The formula reported in a previous study for patients with heart failure and no congenital heart disease (except two patients with atrial septal defects) was the basis for the formula we used for estimating CVP using LS [10]. Patients with a history or signs of liver disease on hepatic ultrasound were excluded from the study [10]. In our study of adult patients who had undergone the Fontan procedure, we included nine (38%) patients who were suspected of having cirrhosis based on CT or MRI findings. Regardless of the presence or absence of suspected cirrhosis, differences between the CVP estimated using LS and CVP measured by catheterization were mostly within the 95% limits of agreement and were considered to be in good agreement. However, the estimated CVP tends to be higher than the measured CVP. Liver damage gradually progresses after the Fontan procedure [20]. The coexistence of liver congestion and various degrees of liver fibrosis may have caused the LS-based CVP values to exceed the measured CVP values. Combining TE with a modality that can quantify liver fibrosis and/or some clinical indices related to liver fibrosis severity may provide a more accurate estimation of CVP after the Fontan procedure; however, further studies are warranted.

Various risk factors for late mortality after the Fontan procedure have been reported [3]. Several studies have shown that high CVP is associated with poor prognosis [5,21,22]. TE is a noninvasive method that can be easily performed in daily practice. We believe that a noninvasive estimation of CVP based on LS using TE can help identify high-risk patients after a Fontan procedure.

4.3. Study limitations

Our study had some limitations. First, this was a single-center study that included a relatively small number of subjects. Second, although the mean difference between the estimated and measured CVP was not significantly different between the H and non-H groups, liver biopsies were not always performed, and the non-H group may have included patients with cirrhosis. Third, this was a cross-sectional study, and the accuracy of CVP estimation using LS during serial follow-ups requires further investigation.

5. Conclusion

In adult patients after a Fontan procedure, LS measured by TE showed a good correlation with CVP measured by cardiac catheterization, and the estimated CVP based on LS was in good agreement with the measured CVP, regardless of the degree of liver damage. Noninvasive estimation of CVP using TE can contribute to patient management after Fontan surgery.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcchd.2023.100469.

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