Novel Method of Evaluating Liver Stiffness Using Transient Elastography to Evaluate Perioperative Status in Severe Heart Failure

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Background: The aim of the present study was to assess the efficacy of a non-invasive method, transient elastography (FibroScan), in measuring liver stiffness (LS), and whether LS can be used as a marker of cardiac – and hence perioperative – status.

Methods and Results: Perioperative LS was prospectively measured using a FibroScan in 30 patients (21 male; 42.2 ± 13.3 years old) who underwent left ventricular assist device (LVAD) implantation. LS was checked pre- and postoperatively, then analyzed in regard to perioperative status. Preoperative LS was 13.3 ± 13.0 kPa (normal, < 5.5 kPa), and was abnormal in 77% of patients. Four required bilateral VAD. LS in patients with bilateral VAD tended to be higher than in LVAD patients (25.1 ± 22.7 vs. 11.5 ± 10.5 kPa, $P = 0.051$). No patient with $LS \leq 7.0$ kPa required a right VAD. The incidence of major adverse events was lower in patients with $LS \leq 12.5$ kPa (25% vs. 80%, $P < 0.05$). There were also no mortalities among patients with $LS \leq 12.5$ kPa.

Conclusions: LS was correlated with preoperative severity in patients with severe heart failure and reflected liver congestion, and may be useful to predict the requirement of right VAD, as well as postoperative complications in patients with LVAD implantation. This novel modality may be a useful non-invasive assessment method for management of severe heart failure. (*Circ J* 2015; **79**: 391–397)

Key Words: Heart failure; Liver; Ventricular assist device

It is recognized that cardiac dysfunction may affect liver function, resulting in cardiac hepatopathy.^{1–5} Liver function abnormalities are frequently found in patients with severe heart failure who require mechanical support such as a left ventricular assist device (LVAD).^{6–11} Heart failure is a pathologic condition in which inadequate blood pumping reduces flow and leads to congestion of blood and fluids in other organs. Furthermore, increased pressure in the right side of the heart is followed by dilatation of the inferior vena cava and hepatic veins, which causes an enlarged and firm liver. Previous reports have highlighted the importance of either high central venous pressure (CVP) or reduced hepatic perfusion.^{8,12} Scant information is available, however, regarding the relationship between the heart and liver, although liver condition might reflect the severity of heart failure. Recently, a rapid, non-invasive, and reproducible approach was developed to assess liver fibrosis by measuring liver stiffness (LS) using transient elastography.^{13,14} This new modality is user friendly, and provides im-

mediate results and good reproducibility, and it has been used in many studies to demonstrate the correlation of LS with liver fibrosis.^{14,15} More recent investigations, however, have noted that LS is also affected by liver congestion¹⁶ and may be directly influenced by CVP.¹⁷ Unfortunately, no non-invasive tools are available to appropriately evaluate the severity of heart failure. In the present study, we focused on the impact of heart failure and changes in volume status on LS, and hypothesized that LS measured with transient elastography reflects cardiac status and can be used as a marker of perioperative status after LVAD implantation.

The purpose of this study was to assess the efficacy of non-invasive transient elastography during perioperative management of severe heart failure patients to measure variation in LS, and its relationship with clinical outcome and laboratory data. We also sought to clarify the relationship between LS and backward failure (liver congestion) in patients with severe heart failure, and assess the efficacy of transient elastography as a

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Table 1. Patient Demographics

Characteristics	Mean±SD or n
Age (years)	42.2±13.3
Body weight (kg)	57.4±14.0
Gender (M/F)	21/9
Etiology	
Dilated cardiomyopathy	20
Hypertrophic cardiomyopathy (dilated phase)	3
Ischemic cardiomyopathy	2
Secondary cardiomyopathy	5
LVAD	
HeartWare	10
HeartMate II	9
DuraHeart	4
EVAHEART	4
Others	3
INTERMACS profile	1: 3, 2: 16, 3:10, 4:1
Preoperative T-bil (mg/dl)	1.4±2.2
Preoperative AST (IU/L)	35±33
Preoperative ALT (IU/L)	49±94
Preoperative Cr (mg/dl)	1.4±0.9
Preoperative CRP (mg/dl)	2.3±3.3
Preoperative BNP (pg/ml)	844±806
Preoperative CVP (mmHg)	8.8±6.9
Preoperative sPAP (mmHg)	46.2±18.6
Preoperative PCWP (mmHg)	25.0±7.9
Echocardiography	
LVDd (mm)	71.7±12.5
LVEF (%)	21.7±7.4

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; Cr, creatinine; CRP, C-reactive protein; CVP, central venous pressure; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; LVDd, left ventricular diastolic dimension; LVEF, left ventricular ejection fraction; PCWP, pulmonary capillary wedge pressure; sPAP, systolic pulmonary arterial pressure; T-bil, total bilirubin.

method of evaluating severe heart failure.

Methods

Patient Selection

We prospectively investigated LS using transient elastography in 30 patients who underwent LVAD implantation at Osaka University Hospital between 2011 and 2013. Exclusion criteria included history of alcohol abuse, known chronic liver disease with an etiology other than heart failure, positivity for hepatitis C antibody or hepatitis B surface antigen reactivity, and obesity with a body mass index >35 kg/m². Prior to surgery, all patients underwent routine blood test, including liver function tests such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin (T-bil). Cardiac function tests were also performed including brain natriuretic peptide (BNP), as well as echocardiography with determination of left ventricular ejection fraction (LVEF) and ventricular size, cardiac catheterization with hemodynamic variables such as right atrial pressure as an indicator of CVP, systolic pulmonary pressure (sPAP), and pulmonary capillary wedge pressure (PCWP). Informed consent was obtained from all patients

A Patients with preoperative liver stiffness ≤ 7.0 kPa

B Patients with preoperative liver stiffness > 7.0 kPa

Figure 1. Changes in liver stiffness (LS) during the postoperative period in patients with (A) preoperative LS ≤ 7.0 kPa, and (B) preoperative LS > 7.0 kPa. (A) LS reached the maximum level on postoperative day (POD) 3 and was still high on POD 7, before returning to a normal level. (B) In contrast, LS gradually decreased during the postoperative period.

before surgery, and institutional review board approval for the study was also obtained. Baseline patient characteristics are listed in Table 1.

Determination of LS Using Transient Elastography

LS was determined using transient elastography (FibroScan; Echosens, Paris, France), as recently described in detail.¹⁸ The FibroScan consists of a 5-MHz US transducer probe mounted on the axis of a vibrator. Low-amplitude and low-frequency vibrations (50 Hz) induce an elastic shear wave that propagates through the underlying liver tissue at a velocity that is directly related to LS. In the present study the tip of the probe transducer was placed perpendicularly on the skin between the rib bones and the level of the right lobe of the liver with the patient lying in the dorsal decubitus position. The measurement depth was between 25 and 65 mm below the skin surface. In each evaluation, 10 measurements were performed with a success rate of at least 60% in each patient. The measurements are expressed in kPa, and the median of 10 acquisitions was used. Based on previous studies and a recent meta-analysis, a cut-off of <5.5 kPa was considered to indicate normal.¹³

Outcomes and Evaluation Factors

We used 2 different endpoints, requirement of additional right heart support, defined as need for a right ventricular assist device (RVAD), and a major adverse event (MAE), defined as mortality, postoperative bleeding, cerebrovascular event, and infection within 30 days postoperatively. This definition of

Figure 2. Correlations of preoperative liver stiffness with (A) preoperative central venous pressure (CVP; $r=0.515$, $n=30$, $P<0.01$); (B) CVP on postoperative day (POD) 3 ($r=0.416$, $n=30$, $P<0.05$); (C) preoperative b-type natriuretic peptide (BNP; $r=0.399$, $P<0.05$); and (D) preoperative C-reactive protein (CRP; $r=0.524$, $P<0.01$).

MAE was used because these are serious complications that occur after LVAD implantation. We assessed the relationship between LS and each endpoint, and various perioperative parameters were evaluated to identify possible risk factors for an MAE.

The preoperative factors examined were age, sex, body weight, etiology, INTERMACS profile, blood parameters (preoperative AST, ALT, T-bil, creatinine [Cr], C-reactive protein [CRP]), and other preoperative comorbidities. Body weight and blood test results were obtained within 3 days prior to operation. Hemodynamic parameters were obtained from the most recent results prior to surgery. These factors were analyzed to identify possible risk factors on univariate analysis. Postoperative LS was obtained on postoperative day (POD) 1, 3, 7, and 28, while postoperative CVP was obtained on POD 1 and 3, as well as POD 7 when possible. All data were obtained from a review of hospital records of patients who provided informed consent.

Operative Procedures

Implantation was performed either through a median sternotomy or as previously described.^{19,20} We prefer performing all of the related procedures without using cardioplegic arrest, unless the LV is seriously damaged by acute myocardial infarction or an LV thrombus is identified. If RVAD was needed due to difficulty with weaning from cardiopulmonary bypass, we

used extracorporeal membranous oxygenation (ECMO) established with right atrium and pulmonary artery cannulation. If right heart failure was so severe that the surgeon considered that weaning from the RVAD with ECMO was impossible within a few weeks after surgery, RVAD with an implantable device was utilized instead of ECMO.

Statistical Analysis

Data were analyzed using Statview 5.0 (SAS Institute, Cary, NC, USA) and JMP 7.0 (SAS Institute). Results are expressed as mean $\pm$ SD. Mann-Whitney U-test was used for comparison of continuous variables and Fisher's exact test was used to compare frequencies between the groups. Spearman's correlation coefficient by rank was calculated for linear correlation analysis between LS and the various parameters. Receiver operator characteristic (ROC) curves and the corresponding area under the curve (AUC) were used to obtain cut-offs for the outcomes. Logistic regression test was used for univariate and multivariate analysis. $P<0.1$ was used to select variables for the multivariate risk factor MAE analysis. $P<0.05$ was considered statistically significant.

Results

Clinical Outcome

Four patients required RVAD support and were classified as

Figure 3. Liver stiffness (LS) vs. presence of (A) major adverse events (MAE); and (C) need for right ventricular assist device (RVAD). (B,D) Use of LS cut-offs for (B) MAE and (D) need for RVAD. (A) LS was significantly higher in patients with MAE than in those without (22.4 ± 17.4 vs. 8.0 ± 5.0 kPa, $P < 0.05$). (B) Eighty percent of patients with LS > 12.5 kPa had MAE while only 25% of those with LS ≤ 12.5 kPa had them. (C) LS tended to be higher in patients who required RVAD as compared to those without (25.1 ± 22.7 vs. 11.5 ± 10.5 kPa, $P = 0.051$). (D) Among patients with LS > 7.0 kPa, 27% required RVAD, while none of the patients with LS ≤ 7.0 kPa required RVAD.

the RVAD group. There was no 30-day mortality in this cohort, with overall in-hospital mortality 10% ($n=3$). The cause of death was massive cerebral bleeding in 2 patients and multiple organ failure in 1. In addition, 2 patients underwent reoperation for bleeding and 1 patient had a deep sternal infection. Five patients had cerebral complications, including 3 with cerebral infarction, with subarachnoid hemorrhage, and 1 with cerebral bleeding. These 13 patients were classified as the MAE group. Ten patients had maximum T-bil > 5.0 mg/dl, and all of them recovered from the liver dysfunction.

Transient Elastography

Successful measurements were obtained in all patients. Mean preoperative LS in the entire group was 13.3 ± 13.0 kPa, and 23 patients (77%) of the entire cohort had abnormal preoperative LS (normal, < 5.5 kPa). We noted 2 types of perioperative change in regard to LS. On ROC analysis, LS = 7.0 kPa was identified as a cut-off for RVAD requirement. Therefore, we checked perioperative change of LS in 2 different groups. In patients with LS ≤ 7.0 kPa, LS was significantly increased on POD 3 and remained slightly elevated on POD 7 as compared to the preoperative level, while it returned to nearly normal on POD 28 (Figure 1A). In contrast, in patients with LS > 7.0 kPa, LS gradually decreased during the postoperative period and still remained higher than normal on POD 28 (Figure 1B). Preop-

erative CVP was also higher than that on POD 3. There were no significant differences regarding the amount of diuretics and requirement of hemodialysis between these 2 groups.

LS and Perioperative Factors

Preoperative CVP had a significant correlation with preoperative LS ($r=0.515$, $n=30$, $P < 0.01$; Figure 2A), and preoperative LS was also significantly correlated with CVP on POD 3 ($r=0.416$, $n=30$, $P < 0.05$; Figure 2B). The correlation between preoperative LS and LVEF was not significant. There were no significant relationships between preoperative LS and liver function parameters such as AST, ALT, and T-bil, whereas LS was correlated with preoperative BNP and CRP (Figures 2C,D).

LS and Outcome

LS was significantly greater in patients with MAE than in those without (22.4 ± 17.4 vs. 8.0 ± 5.0 kPa, $P < 0.05$; Figure 3A). On ROC analysis, the cut-off for LS was 12.5 kPa (AUC, 0.82). Among patients with LS > 12.5 kPa, 80% had MAE, while only 25% of those with LS ≤ 12.5 kPa had MAE. There were also no deaths among patients with LS ≤ 12.5 kPa (Figure 3B). Finally, preoperative LS between patients with and without MAE was significant on univariate analysis, and on multivariate analysis only preoperative LS was identified as a risk factor for MAE (Table 2).

Table 2. Risk Factors for Major Adverse Events

	OR	95% CI	P-value
Univariate analysis			
Age (years)	1.047	0.983–1.114	0.1512
Gender (M/F)	1.231	0.238–6.359	0.8043
Body weight (kg)	1.017	0.895–1.156	0.7906
Liver stiffness (kPa)	1.156	1.018–1.313	0.0254
INTERMACS profile	0.913	0.311–2.685	0.8693
Preoperative T-bil (mg/dl)	0.953	0.637–1.425	0.8154
Preoperative AST (IU/L)	0.988	0.957–1.021	0.4751
Preoperative ALT (IU/L)	0.992	0.973–1.011	0.4156
Preoperative Cr (mg/dl)	1.813	0.657–5.011	0.2502
Preoperative CRP (mg/dl)	1.045	0.826–1.323	0.7123
Preoperative BNP (pg/ml)	1.000	0.999–1.001	0.8885
LVEF (%)	1.099	0.979–1.234	0.1084
Preoperative sPAP (mmHg)	1.058	0.972–1.153	0.1924
Preoperative PCWP (mmHg)	1.081	0.962–1.216	0.1899
Preoperative CVP (mmHg)	1.175	0.979–1.411	0.0832
Multivariate analysis			
Liver stiffness (kPa)	1.145	1.005–1.305	0.0402
Preoperative CVP (mmHg)	1.089	0.942–1.259	0.2508

Abbreviations as in Table 1.

As for the incidence of RVAD, LS tended to be higher in patients who required RVAD as compared to those without (25.1 ± 22.7 vs. 11.5 ± 10.5 kPa, $P=0.051$; **Figure 3C**). On ROC analysis, 7.0 kPa was the cut-off for LS (AUC, 0.87). Among patients with LS >7.0 kPa, 27% required RVAD, while none of the patients with LS ≤ 7.0 kPa required RVAD (**Figure 3D**). We also examined the relationship between CVP/PCWP and RVAD requirement. There was no significant difference between them.

Discussion

In the present study there was significant increase in LS in patients with severe heart failure and without known pre-existing liver disease, given that mean LS reached 13.3 kPa in those patients, which is substantially higher than normal. In particular, 15 (50%) of 30 patients had LS above the threshold normally used to diagnose substantial fibrosis, while 10 (33%) had LS at a level that usually indicates a diagnosis of cirrhosis. We also found that longitudinal changes in LS occurred in parallel with perioperative changes in volume status in patients with LS ≤ 7.0 kPa. In addition, as well as the correlations of LS with preoperative BNP and with CRP, there was also a correlation between LS and CVP prior to operation, as well as on POD 3. Finally, we showed that preoperative LS may be a possible predictor of right heart support during operation, as well as of postoperative outcome.

To the best of our knowledge, this is the first study to prospectively assess the performance of LS for predicting clinical outcome and complications in comparison with various hemodynamic parameters. The present findings may have an impact on postoperative management for severe heart failure patients, because this novel modality is non-invasive and user friendly, while it also provides immediate results and good reproducibility.^{13,14}

There are 2 possible reasons to explain high preoperative LS: the direct effect of CVP and the impact of chronic heart disease

on the liver. A previous study using an animal model showed that CVP directly controls LS in a reversible manner, and that LS is a linear function of intravenous pressure, reaching the upper detection limit of 75 kPa at an intravenous pressure of 36 cmH₂O.¹⁷ Generally, patients who require LVAD implantation have both right and left heart failure symptoms,²¹ thus most have relatively high CVP. Several reports have noted that heart failure plays a role in LS determinants.^{17,22,23} Cardiac hepatopathy is thought to be related to hepatic venous congestion, and all of the present patients had a long history of heart failure. Therefore, it is possible that their high LS simply reflected chronic hepatic injury due to cardiac dysfunction, and that LS may reflect acute volume status as well as the chronic effect of heart failure on the liver. Taniguchi et al reported a strong correlation between right atrium pressure and LS,²⁴ while in the present study there was a relatively slight correlation between them. This difference might be due to severity, given that all of the present patients had severe heart failure and other complications such as inflammation and chronic liver congestion, which are considered to affect LS.

Perioperative change is another important finding, in that LS showed a shift in volume status during the postoperative period. We found 2 patterns of preoperative LS change. In patients with approximately normal LS, LS increased to a maximum on POD 3, then gradually decreased and reached the preoperative level after 1 month. This change occurred in parallel with the usual postoperative change in fluid status. Following the operation, fluid level reached maximum during the first few days, followed by a depletion phase due to diuretics. Therefore, LS may be useful to evaluate volume status in a non-invasive manner. In patients with high LS, LS had a gradual decrease, although it remained higher than normal after 1 month, which likely reflected perioperative status severity and liver dysfunction. Among patients with preoperative LS >7.0 kPa, most had very high LS >10 or 20 kPa, which is higher than the maximum LS in patients with preoperative LS ≤ 7.0 kPa. We assume that this continuous decline in patients with preoperative LS

>7.0kPa reflects continuous unloading of liver congestion. We think that LS may be more useful in patients without liver dysfunction due to heart failure.

We also found a significant correlation between LS and preoperative CVP, as well as with POD 3 CVP. This result is similar to that in previous reports showing that LS is directly influenced by CVP.¹⁴ Although previous reports noted a specific correlation between CVP and LS,^{17,24} it might not be suitable to compare results from patients with a relatively lower disease level with that of the present cohort.

Interestingly, even though LS did not have a significant correlation with PAP, PCWP, or LVEF, which is similar to other results, there was a significant correlation between LS and POD 3 CVP. A possible explanation is that LS may reflect right heart function.²² Following LVAD implantation, cardiac return generally increases, while right ventricle load also increases. Given that LS is also determined by already established liver fibrosis secondary to chronic hepatic congestion,²⁵ higher LS indicates long-term liver damage due to right heart failure. This chronic change, as well as the direct influence by CVP, may be determinants of LS. We also found a significant relationship between preoperative LS and BNP, which is in contrast to Millonig et al,¹⁷ but agrees with Hopper et al.²² This discrepancy may be related to the low number of subjects in each study. Although it is possible that LS is directly correlated with heart failure, further study is needed to clarify the direct relationship with BNP.

The present investigation provides several important findings. LS may be effective for prediction of surgical outcome. Transient elastography is a rapid and non-invasive means of assessing LS, and can be readily incorporated into clinical evaluation of patients with heart failure to assist with their management. We found that LS might also be useful to predict the need for additional right heart support such as RVAD in patients undergoing LVAD implantation. Notably, all patients with RVAD had high LS, thus care must be taken when treating patients with elevated LS. Furthermore, LS might be useful to predict requirement of TAP. A previous study found a significant relationship between liver function and severity of tricuspid regurgitation, in that severe regurgitation causes severe hepatic congestion.²⁶ Also, LS might be a possible risk factor for postoperative outcome, which is compatible with a previous study that showed that intensive care patients with LS in the upper quartile had increased short-term mortality.²⁷ In addition, several reports have described the relationship between liver dysfunction and outcome.²⁻⁴ Also, LS may be a predictor of recovery from liver dysfunction. In the present study, however, we were not able to investigate that possibility, because all of the present patients recovered from liver dysfunction. The prognostic importance of LS may be a reflection of poor hemodynamic status and underlying secondary hepatic injury. Based on these findings, LS might be useful as a screening test for clinical outcome in patients scheduled for LVAD surgery. Some reports have described the importance of CVP/PCWP as a predictor of RVAD in patients undergoing LVAD implantation.²⁸ In the present study, we did not find a relationship between CVP/PCWP and RVAD requirement, which may have been due to the small number of patients who required RVAD.

Study Limitations

There were several limitations in this study. No liver biopsy results were available, which would have allowed a better description of the relationship between LS and histologic findings. Therefore, we were unable to correlate LS with the un-

derlying histological severity of liver fibrosis. The invasive procedure needed to obtain such results, however, was considered inappropriate and therefore unethical. Furthermore, the characteristics of the present cohort limited interpretation of the findings. Patients requiring LVAD implantation are categorized as critically ill. To prove the usefulness of LS in general heart failure patients, an investigation of such a cohort is needed. It is also important to keep in mind that LS is influenced by several specific conditions, such as hepatitis,¹³ inflammation,²⁹ and cholestasis.³⁰ Therefore, even though we excluded patients with hepatitis and obvious previous liver disease, the present results must be interpreted with caution in regard to those conditions. Finally, the sample size was not large enough for definitive conclusions to be drawn. Although further multicenter studies with larger groups of patients are necessary to confirm the present results, the present findings highlight the novel concept that LS can be useful for management of severe heart failure patients.

Conclusions

LS was correlated with preoperative severity in patients with severe heart failure, and may be useful to predict the requirement of additional right heart support or postoperative complications in patients undergoing LVAD implantation, while its change reflected liver congestion. This novel modality may be useful for non-invasive assessment of patients with severe heart failure.

Disclosures

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