Evaluation of right ventricular function using liver stiffness in patients with left ventricular assist device†

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Abstract

OBJECTIVES: Although right ventricular failure (RVF) is a major concern after left ventricular assist device (LVAD) implantation, methodologies to evaluate RV function remain limited. Liver stiffness (LS), which is closely related to right-sided filling pressure and may indicate RVF severity, could be non-invasively and repeatedly assessed using transient elastography. Here we investigated the suitability of LS as a parameter of RV function in pre- and post-LVAD periods.

METHODS: The study included 55 patients with LVAD implantation as a bridge to transplantation between 2011 and 2015 whose LS was assessed using transient elastography.

RESULTS: Seventeen patients presented with RVF, defined as requiring inotropic support for >30 days, nitric oxygen inhalation for >5 days, and/or mechanical RV support following LVAD implantation. Survival of patients with RVF was significantly worse compared with that of patients without RVF. Multivariate logistic regression analysis identified preoperative LS, LV diastolic dimension, RV stroke work index, and dilated phase of hypertrophic cardiomyopathy aetiology as significant risk factors; the combination of these parameters could improve predictive power of post-LVAD RVF with areas under the curve of 0.89. Furthermore, LS was significantly decreased by LV unloading and significantly correlated with right-sided filling pressure.

CONCLUSIONS: In addition to dilated hypertrophic cardiomyopathy aetiology, reduced RV stroke work index and small LV dimension, we demonstrated that non-invasively measured LS was a predictor of post-LVAD RVF and can be used as a parameter for the evaluation and optimization of RV function in the perioperative period.

Keywords: Circulatory support devices • Heart failure • Liver • Abdominal organs

INTRODUCTION

Left ventricular assist device (LVAD) implantation has been established as a standard treatment for advanced heart failure (HF) and is associated with improved survival and quality of life of patients [1]. On the other hand, right ventricular failure (RVF) has been recognized as a complication in patients with LVAD implantation, and occurs with rates varying between 5% and 44% [2]. Because a variety of factors can be related to RV dysfunction, predicting RVF is difficult before and after LVAD implantation. Some authors emphasize that right-sided filling pressure measurements such as the central venous pressure (CVP)/pulmonary capillary wedge pressure (PCWP) ratio are important predictive factors of RVF after LVAD implantation, while others claim that liver function scores such as serum bilirubin levels or serum aspartate transaminase levels are useful to predict post-LVAD RVF [3, 4]. Generally, advanced HF has been reported to cause hepatic congestion or hepatic fibrosis via a chronic increase in CVP, upregulated proinflammatory cytokines, or oxidative stress [5–7]. In addition, because the liver is anatomically surrounded by a non-elastic capsule, liver congestion leads to increased liver stiffness (LS) suggesting that the degree of LS could be a marker of liver congestion or right-sided filling pressure [8]. LS can be assessed non-invasively by using transient elastography, which is recommended by the European Association for the Study of the Liver clinical practice guidelines for the evaluation of various chronic hepatic pathologies [9]. Because LS has been reported to be elevated in patients with advanced HF, especially RVF [10], LS may be a possible predictor of post-LVAD RVF and a useful indicator of perioperative RV function. In this study, we reviewed the clinical outcomes of...
patients who underwent LVAD implantation for advanced HF as bridge to transplantation, and investigated whether increased LS was associated with LVAD implantation.

MATERIALS AND METHODS

Cohort

The prospective database contained 82 implantable LVAD implantations that were performed for the treatment of end-stage HF in Osaka University Hospital between August 2011 and October 2015. In this study, we retrospectively analysed 55 patients, and excluded 15 patients whose liver stiffness was not assessed using transient elastography prior to LVAD implantation and 12 patients who required temporary LVAD because most of these critically ill patients required veno-arterial extracorporeal membrane oxygenation which influenced the LS.

Study end-points

The primary endpoint of the study was defined as heart transplantation, death, or LVAD removal. The secondary end-points included post-LVAD RVF, defined as requiring inotropic support for ≥30 days, nitric oxygen inhalation for ≥5 days, and/or mechanical RV support following LVAD implantation.

Treatments strategies and surgical techniques

In most of the patients, medication was optimized prior to the LVAD implantation (Table 1). Surgical strategies for severe HF that were refractory to medical treatment and the timing of LVAD implantation were determined through a prudent discussion within the institutional heart team. Device types were also determined by the institutional heart team based on the patients’ body shape and size at the time of surgery. As a result, 18 patients (33%) were implanted with HeartMate II (Thoratec Corporation, Pleasanton, CA, USA), 13 patients (24%) with DuraHeart (Terumo Corporation, Tokyo, Japan), 12 (22%) with HeartWare (HeartWare International Inc., Framingham, MA, USA), 6 (11%) with Jarvik 2000 (Jarvik Heart, Inc., New York, NY, USA) and 6 (11%) with EVAHEART (Sun Medical, Shiga, Japan). Concomitant temporary right ventricular assist device (RVAD) implantation using extracorporeal centrifugal pump was performed in 2 patients (4%), concomitant tricuspid annuloplasty in 15 (27%), aortic valve closure or re-implantation in 3 (6%), and mitral valve repair in 4 (7%).

Perioperative management of right ventricular failure

We used clinical parameters to assess RV dysfunction such as jugular vein diameters, hepatojugular reflex, ascites, peripheral oedema, and others. Also, RV dimension and motion or inferior vena cava diameter were regularly evaluated using echocardiography. Furthermore, we performed standard strategies for treatment of RVF after LVAD implantation as follows: (i) maintained optimal preload by preventing excess infusion or LVAD flow and aggressive diuretic therapy, ultrafiltration, and intra-aortic balloon pumping (IABP); (ii) reduced afterload routinely using NO inhalation and a pulmonary vascular dilator, such as milrinone or sildenafil; (iii) increased RV contraction by inotropic support and (iv) maintained optimal heart rate using a pacemaker [11].

Assessment of liver stiffness by transient liver elastography

Transient elastography using a Fibroscan device (Echosens, Paris, France) was performed to measure LS within 2 weeks prior to LVAD implantation, as previously described [8]. The probe of the transducer was placed vertically on the skin above the intercostal space at the level of the right liver lobe while the patient was in a supine position with the right arm fully abducted. All measurements were taken by the cardiologists or cardiovascular surgeon at our institution. LS was expressed as...
median interquartile range in kilopascals (kPa). A successful examination was defined as ≥10 successful readings with >60% success rate and an interquartile range to a median ratio of ≤0.25.

Transcatheter echocardiography

All cohorts were examined by standard transcatheter echocardiography within 7 days preoperatively with a 3.75-MHz transducer (Toshiba, Tokyo, Japan, and Hewlett-Packard Sonos) by expert echocardiographic examiners. Ejection fraction (EF), systolic and diastolic dimensions (SD and DD, respectively), and tricuspid regurgitation-pressure gradient were measured; and the degree of mitral regurgitation, tricuspid regurgitation, or aortic insufficiency was determined based on an effective regurgitant orifice area/volume/fraction, or vena contracta width, according to the guidelines published by the American and European Societies of Echocardiography [12].

Right heart catheter study

The right heart catheter study was performed within 4 weeks prior to surgery. Pressure data including pulmonary arterial pressure (PAP), PCWP, RV systolic pressure, RV end-diastolic pressure (RVEDP), or CVP were obtained using a Swan–Ganz catheter, while cardiac output (CO) was determined with the Fick method. In addition, SWI of the RV and pulmonary vascular resistance (PVR) were calculated offline as follows; RVSWI = (stroke volume index) × (mean PAP - RAP), PVR = (mean PAP - PCWP)/CO.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and compared using an unpaired Student t-test or Wilcoxon signed-rank test. Categorical variables were reported as percentages and compared using Chi-square and Pearson’s test. Correlations between continuous variables were tested with Pearson correlation coefficient (r). Logistic regression was subsequently performed against patients with RVF or the need for RVAD support, and those parameters that reached statistical significance were entered in a stepwise model to identify independent predictors of RVF or the need for RVAD support following LVAD implantation. Scatter plot analysis with regression was generated to determine the optimal cut-off value for the independent parameters to predict RVF or the need for RVAD support after LVAD implantation. Receiver operating characteristic (ROC) curves were constructed to calculate the areas under curve (AUC) for clinical risk prediction models. Kaplan–Meier survival curves were constructed to calculate survival and the two groups were compared using log-rank analysis. Values of P < 0.05 were considered significant. All data were analysed using JMP® 10.0.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Baseline characteristics and cardiac function of the cohort

Baseline characteristics and cardiac function of the cohort are presented in Table 1. The aetiology of the cardiomyopathy was diagnosed based on the patient’s medical and family history. The pathohistological diagnoses prior to LVAD implantation included idiopathic dilated cardiomyopathy (DCM) in 35 patients (64%), dilated phase of hypertrophic cardiomyopathy (d-HCM) in 14 (26%), secondary DCM in 3 (5%), adriamycin-induced cardiomyopathy in 2, DCM secondary to Becker muscular dystrophy in 1 and ischaemic cardiomyopathy in 3 (5%). Preoperatively, The Michigan RVF score [4] at the time of LVAD implantation was 4.2 ± 1.5, while the model for end-stage liver disease score was 13.8 ± 4.2 (calculated from the following: need for haemodialysis, total bilirubin level, serum creatinine level, and prothrombin time international normalized ratio). Preoperative LS was 12.7 ± 13.1 kPa. Preoperative echocardiographic findings and right heart catheter data are shown in Table 2.

Early and late outcome after left ventricular assist device implantation

All patients survived for at least 30 days after LVAD implantation. In-hospital mortality occurred in 2 patients (4%) due to cerebral
haemorrhage and severe RVF. On late follow-up, 3 patients had died of cerebral haemorrhage. During the mean postoperative follow-up period of 19.1 ± 12.5 months, 14 (26%) patients underwent heart transplantation with a mean waiting duration of 28 ± 13 months, while removal of LVAD was successfully performed in 1 (2%) patient with LV functional recovery at 9 months. In addition, 17 (31%) patients presented with RVF after LVAD implantation and 5 (9%) required mechanical RV support intra- or postoperatively. Actuarial postoperative survival of all the patients was 87.3% at 3 years, and in patients without RVF, actuarial survival was better than patients with RVF following LVAD implantation (96.3% vs 65.9% at 3 years, log rank <0.01) (Fig. 1).

Exploring predictive factors of right ventricular failure following left ventricular assist device implantation

Predictive factors for RVF after LVAD implantation were explored using logistic regression analysis. Univariate analysis identified d-HCM aetiology, preoperative LS, LVDD, LVEF, RVSWI and CVP/PCWP ratio as significant predictive factors; while multivariate analysis identified d-HCM aetiology, preoperative LS, LVDD and RVSWI as independent predictive factors for RVF following LVAD implantation (Table 3). Preoperative LVAD and CVP/PCWP ratio were not entered into the multivariate analysis because they did not contribute to improvement of the model's predictive value after a stepwise logistic regression analysis, and d-HCM aetiology, preoperative LS, LVDD and RVSWI incrementally improved the model's predictive value ($R^2 = 0.43$, Akaike's information criterion = 49.2, Bayesian information criterion = 57.8). A ROC curve was drawn to explore the optimal cut-off value of preoperative LS, LVDD, and RVSWI to predict RVF after LVAD implantation. As a result, AUC was 0.71 (sensitivity, 59%; specificity, 84%; $P < 0.01$) with a cut-off value of > 12.8 kPa for preoperative LS; 0.73 (sensitivity, 82%; specificity, 61%; $P < 0.01$) with a cut-off value of < 74 mm for LVDD; and 0.71 (sensitivity, 82%; specificity, 61%; $P < 0.01$) with a cut-off value of < 488 mm Hg·m/m² for RVSWI. Furthermore, a combination of these four factors improves the predictive power of RVF after LVAD implantation with an AUC of 0.89 (sensitivity, 100%; specificity, 64%; $P < 0.01$).

Exploring predictive factors of the need for right ventricular assist device following left ventricular assist device implantation

Predictive factors of the need for RVAD support after LVAD implantation were also explored by using logistic regression analysis. Univariate analysis identified d-HCM aetiology, preoperative LS, LVDD, LVEF and RVEDP as significant predictive factors; while multivariate analysis identified preoperative LS and LVEF as independent predictive factors of the need for RVAD support following LVAD implantation (Table 4). Preoperative LVDD, RVEDP and d-HCM aetiology were not entered into the multivariate analysis because they did not contribute to the improvement of the model's predictive value after a stepwise logistic regression analysis, and preoperative LS and LVEF incrementally improved the model's predictive value ($R^2 = 0.35$, Akaike's information criterion = 27.9, Bayesian information criterion = 33.2). A ROC curve was drawn to explore the optimal cut-off value of preoperative LS, LVDD, and RVSWI to predict RVF after LVAD implantation. As a result, AUC was 0.71 (sensitivity, 59%; specificity, 84%; $P < 0.01$) with a cut-off value of > 12.8 kPa for preoperative LS; 0.73 (sensitivity, 82%; specificity, 61%; $P < 0.01$) with a cut-off value of < 74 mm for LVDD; and 0.71 (sensitivity, 82%; specificity, 61%; $P < 0.01$) with a cut-off value of < 488 mm Hg·m/m² for RVSWI. Furthermore, a combination of these four factors improves the predictive power of RVF after LVAD implantation with an AUC of 0.89 (sensitivity, 100%; specificity, 64%; $P < 0.01$).

Table 3: Predictive factors of right ventricular failure following LVAD implantation

|                | Univariate | Multivariate |
|----------------|------------|--------------|
|                |            |              |
| Dilated phase  | <0.01      | 6.1          |
| HCM aetiology  |            | 1.001–44.7   |
| LVDD, mm       | <0.01      | 0.92         |
| LVEF, %        | >0.049     |              |
| Liver stiffness, | <=0.01     | 1.09         |
| kPa            |            | 1.006–1.16   |
| RVSWI, gm·m/m² | <=0.01     | 0.71         |
| beat           |            | 0.986–0.999  |
| CVP/PCWP ratio | <=0.049    |              |

LVAD: left ventricular assist device; HCM: hypertrophic cardiomyopathy; LVDD: LV diastolic dimension; LVEF: LV ejection fraction; RVSWI: right ventricular stroke work index; CVP/PCWP: central venous pressure/pulmonary capillary wedge pressure.

Table 4: Predictive factors of the need for RVAD support following LVAD implantation

|                | Univariate | Multivariate |
|----------------|------------|--------------|
|                |            |              |
| Dilated phase  | 0.01       |              |
| HCM aetiology  |            |              |
| LVDD, mm       | 0.01       | 1.11         |
| LVEF, %        | 0.02       | 1.003–1.26   |
| RVEDP, mmHg    | 0.03       | 1.08         |
| Liver stiffness, | <=0.01     | 1.02–1.15    |
| kPa            |            | 0.01         |

RVAD: right ventricular assist device; LVAD: left ventricular assist device; HCM: hypertrophic cardiomyopathy; LVDD: LV diastolic dimension; LVEF: LV ejection fraction; RVEDP: RV end-diastolic pressure.
cut-off value of preoperative LS and LVEF to predict the need for RVAD support after LVAD implantation. As a result, AUC was 0.85 (sensitivity, 80%; specificity, 72%; P < 0.01) with a cut-off value of 14.0 kPa for preoperative LS and 0.74 (sensitivity, 80%; specificity, 62%; P < 0.02) with a cut-off value of ≥22.0% for LVEF.

Changes in liver stiffness before and after left ventricular assist device implantation

Serial changes in LS were assessed before and after LVAD implantation in 9 patients with post-LVAD RVF and in 17 patients without post-LVAD RVF in our cohort. LS was significantly decreased in 9 patients with post-LVAD RVF at 1 month and persisted 6 months after LVAD implantation (24.6 ± 26.1–11.8 ± 8.8 at 1 month, P < 0.04; and to 14.0 ± 19.5 kPa at 6 months, P = 0.08, respectively), whereas LS remained at a low level in patients without post-LVAD RVF before and after surgery (9.5 ± 6.6 kPa–8.2 ± 4.9 kPa at 1 month, P = 0.2; and to 7.6 ± 3.7 kPa at 6 months, P = 0.1, respectively) (Fig. 2).

Correlation between liver stiffness and cardiac or liver function

The correlation between LS and cardiac or liver function of the cohort is presented in Fig. 3. Preoperative LS was significantly correlated with the parameters of RV function, including RVDD (r = 0.58, P < 0.01) and CVP (r = 0.52, P < 0.01), while preoperative LS was also correlated with the parameters of LV function, including PCWP (r = 0.50, P < 0.01) (Fig. 3A and B). Furthermore, preoperative LS was significantly correlated with serum total bilirubin level (r = 0.45, P < 0.01) (Fig. 3C), but not aspartate transaminase, alanine transaminase level, or model for end-stage liver disease score (r = -0.16, P = 0.2; r = -0.24, P = 0.08; and r = 0.21, P = 0.1, respectively). Three patients had extremely higher LS than the other patients, which were indicated by dot circle in Fig. 3. All of them suffered from post-LVAD RVF, and 2 of them required RVAD support perioperatively.

**DISCUSSION**

This study documents the clinical outcomes of a series of 55 LVAD implantation for severe HF, in which LS was non-invasively assessed using transient elastography prior to LVAD implantation. In the 17 patients with RVF, survival was significantly worse than in the patients without RVF. In this cohort, we found that d-HCM aetiology, LVDD, RVSWI and preoperative LS were independent predictive factors of RVF following LVAD implantation; and the combination of these four parameters could improve the predictive power of post-LVAD RVF. Furthermore, LS successfully decreased after LVAD implantation, reflecting the effects of LV unloading and the consequent decrease in RV afterload. In addition, LS was significantly correlated with haemodynamic and hepatic parameters such as CVP, PCWP and serum total bilirubin level.

For patients with post-LVAD RVF, surgical strategies such as planned RVAD implantation or concomitant tricuspid valve surgery at the time of LVAD implantation were reported to have an effect on clinical outcome after LVAD implantation, suggesting that predicting post-LVAD RVF is important prior to LVAD implantation [13, 14]. Right-sided filling pressure has been recognized as a useful factor in predicting post-LVAD RVF [3], and can be measured during a right heart catheter pressure study. However, since right-sided filling pressure may be modified by preoperative medical treatment such as inotropic support or pulmonary vasodilators use, it may be important to obtain serial right-sided filling pressure before LVAD implantation. Moreover, since continuous monitoring of CVP with an indwelling line may cause catheter-related infection and sepsis, it is preferable to obtain an exact or serial right-sided filling pressure non-invasively and repeatedly before LVAD implantation.

Transient elastography has been an emerging methodology, in which the velocity of mechanical shear wave that is transmitted across the liver parenchyma is calculated using the Doppler technique to estimate liver stiffness non-invasively [15]. Increased LS would indicate a more advanced stage of liver congestion or fibrosis; therefore, serial assessments of LS are recommended to evaluate the stage of chronic liver disease according to the European Association for the Study of the Liver guidelines [9]. In addition, Hopper et al. [10] reported that LS was significantly elevated in the patients with right-sided HF, suggesting that LS may possibly evaluate RV function prior to LVAD implantation.

This study explored the predictive factors of RVF or the need for RVAD following LVAD implantation. In this cohort, patients who had RVF or needed RVAD support following LVAD implantation were characterized by significantly higher LS. Although significantly higher preoperative LS was demonstrated recently in non-survivors after LVAD implantation, the relationship between LS and RVF was not investigated and it was not clarified whether preoperative LS could predict post-LVAD RVF [16, 17]. Because LS is immediately influenced by changes in CVP, serial assessments of LS would contribute to perioperative optimization of right-sided filling pressure without a pulmonary catheter study. Interestingly, the cases with higher LS than expected from preoperative CVP tended to undergo RVF or RVAD implantation after LVAD implantation, which implies that LS may indicate not only CVP but also other factors such as chronicity of RVF or RV compliance as described in a previous report [10] (Fig. 3A). In fact, in patients with greater LS, there may be a more negative effect by an increase in preload rather than a positive effect by a decrease in afterload on the RV by LVAD support, suggesting that RV with impaired compliance may increase RV filling pressure easily by elevating preload by LVAD flow. Because liver function including serum total bilirubin level is useful marker of RV function in the patients with severe HF, we investigated the relationship between serum total bilirubin level and other cardiac factors and found that serum total bilirubin level was significantly

![Liver stiffness vs time](https://example.com/liver_stiffness.png)

**Figure 2:** Serial changes in LS before and after LVAD implantation. LS: liver stiffness; RVF: right ventricular failure; Post: a month after surgery; Late: 3–6 months after surgery; N.S indicates not significant (vs preoperative). *indicates P < 0.05 (vs preoperative).
correlated with right atrial pressure \( r = 0.32, P = 0.02 \), but not significantly correlated with other cardiac parameters. Importantly, because LS can possibly be enhanced by the existence of chronic hepatic disease [18] or severe pulmonary hypertension due to LV dysfunction, LS must be evaluated carefully as not to overestimate systemic volume, and serial changes in LS should be evaluated. On the other hand, in this cohort, LV unloading successfully decreased RV filling pressure and LS, although LS was still higher in patients with post-LVAD RVF than those without. This suggests that LS may accurately reflect RV haemodynamics, and that this parameter can be used to manage haemodynamics not only right after LVAD implantation, but also long term. In fact, in some patients with bi-VAD support, RVAD flow was appropriately adjusted with reference of real-time changes in LS, and the effects of medical therapy was judged by the decrease in this parameter in daily practice. Moreover, late-onset RVF, or developing aortic insufficiency, has been associated with morbidity or mortality after LVAD implantation, which would worsen the cardiac loading condition [19, 20]. Routine assessment of LS after LVAD implantation may enable the earlier detection of changes in cardiac loading condition, suggesting that this technology may also work as a useful tool to manage patients before and after LVAD implantation.

This study is limited by its retrospective nature and small sample size. LS is technically difficult to measure correctly in patients with a history or signs of liver disease, severe obesity, narrow intercostal space, or substantial ascites. Furthermore, right-sided filling pressure may decrease in patients with veno-arterial extracorporeal membrane oxygenation support prior to LVAD implantation, which would not reflect RV function accurately. In addition, we used various types of LVAD, which may affect RV function after LVAD implantation. However, this study drew a novel and reasonable conclusion by statistical analysis of the data retrieved from thorough laboratory investigations and intensive institutional follow-up.

In conclusion, in addition to d-HCM aetiology, reduced RVSWI or small LV dimension, we demonstrated that non-invasively measured LS was an important predictor of post-LVAD RVF and can be used as a parameter for evaluation and optimization of RV function in the perioperative period.

**Conflict of interest**: none declared.

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