学 位 論 文 の 要 旨

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学 位 論 文 名	Gallbladder Wall Thickness-Based Assessment of Organ Congestion in Patients with Heart Failure
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論 文 内 容 の 要 旨

INTRODUCTUION

In heart failure (HF) occurring due to the compensatory failure of the cardiac pump function, blood flow remains upstream of the ventricles, consequently causing high filling pressure (i.e., congestion) and impairing organ function. As a result, pulmonary congestion and pulmonary edema occur when the blood flow remains upstream of the left ventricle (left-sided HF) from an increase in the left atrial pressure, whereas congestion of the organs in the abdominal cavity occurs when the blood flow remains upstream of the right ventricle (right-sided HF). Left-sided HF is usually associated with high left ventricular (LV) filling pressure and has been well assessed using echocardiography as a noninvasive method. In fact, the increasing severity of diastolic dysfunction has been associated with an increasing risk of cardiovascular events and death. Organ congestion due to right-sided HF is also a common manifestation, and its prognostic value has been well recognized and reported. Residual congestion commonly occurs despite providing adequate medical treatment, resulting in poor survival outcomes. Organ congestion can now be evaluated using extracardiac ultrasound, which is considered a novel technique. In particular, liver stiffness on elastography at admission and discharge has been found to reflect prognosis in patients with HF.

In addition to the previously mentioned conditions, diffuse GB wall thickening has been found to be related to elevated portal or systemic venous pressures, such as cirrhosis and HF. Although the thickness of GB wall depends on the degree of GB distention, 3 mm is regarded as the upper limit of normal. Given these findings, we hypothesized that GB wall thickness could be an indicator of congestion and the severity of HF. This study aimed to identify the

relationships between GB wall thickness and HF, demonstrating the prognostic impact of GB wall thickness in patients with HF.

MATERIALS AND METHODS

This prospective study included 116 patients with pre-HF or HF and 11 healthy participants, and was conducted at Masuda Red Cross Hospital between July 2018 and June 2019. HF was defined as a clinical syndrome of signs and/or symptoms caused by a structural and/or functional cardiac abnormality, which is corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion. Pre-HF (Stage B) was diagnosed in patients without current or prior signs and/or symptoms of HF but with evidence of structural heart disease, abnormal cardiac function, or elevated natriuretic peptide levels. HF (Stage C) was diagnosed in patients with current or prior signs and/or symptoms of HF, which are caused by a structural and/or functional cardiac abnormality. Advanced HF (Stage D) was diagnosed in patients based on the following characteristics: (1) severe signs and/or symptoms of HF at rest; (2) recurrent hospitalizations despite guideline-directed management; (3) refractory or intolerant to guideline-directed management; and (4) requiring advanced therapies, such as consideration for transplant, mechanical circulatory support, or palliative care. Among the 116 patients, 30 with measurement of GB wall thickness in the postprandial state, a history and/or signs of GB disease on ultrasonography, or acute decompensated HF were all excluded. The studied patients were outpatients with stable condition and inpatients at the time of discharge. Of the included patients, none had a history or signs of liver disease, previous diagnosis of chronic liver disease, hepatic ultrasound data indicating liver surface nodularity (a sign of severe fibrosis or ascites), anti-hepatitis C antibody positivity, or hepatitis B surface antigen reactivity. Healthy participants had no history or signs of cardiac, liver, or GB disease.

A total of 11 healthy participants were compared with 86 patients with pre-HF or HF for GB wall thickness. The relationship between GB wall thickness measured via ultrasonography and the clinical characteristics [echocardiography, laboratory tests, and composite congestion score (CCS)] were investigated among the 86 patients with pre-HF or HF (Stage B, 22 patients; Stage C, 60 patients; and Stage D, 4 patients). All data were collected on the same day, and the GB wall thickness in patients with Stages B, C, and D HF were compared. Furthermore, 64 patients with Stage C or D HF were followed up for hospitalization for HF from the date of GB wall thickness measurement until August 2019.

The study protocol conforms to the principles outlined in the Declaration of Helsinki and was approved by the Masuda Red Cross Hospital Ethics Committee (approval number 49). Informed consent was obtained from all participants prior to the study.

RESULTS AND DISCUSSION

The remaining 86 patients had significantly higher GB wall thickness than the healthy participants [2.0 (1.7–2.4) vs. 1.3 (1.1–1.6) mm, $p<0.001$]. GB wall thickness was significantly correlated with brain natriuretic peptide (BNP; $r=0.386$, $p<0.001$), left atrial volume index (LAVI; $r=0.452$, $p<0.001$), and tricuspid annular plane systolic excursion (TAPSE; $r=-0.311$, $p=0.006$). GB wall thickness also exhibited a stepwise increasing relationship with increasing HF stage [Stage B, 22 patients: 1.8 (1.7–2.1) mm; Stage C, 60 patients: 2.0 (1.8–2.5) mm; and Stage D, 4 patients: 4.0 (3.5–4.5) mm]. In Stage C or D patients, 11 hospitalizations for HF were observed during a median follow-up of 303 (125–394) days. Furthermore, the high thickness group (≥3 mm) had a significantly higher rate of hospitalization events for HF than the low thickness group ($p=0.007$).

There were four major findings in this study. First, GB wall thickness significantly increased in the HF group compared with that in the control group. Second, BNP, LAVI and TAPSE, which is used as a marker for organ congestion and assessment of RV systolic function on echocardiography, significantly correlated with GB wall thickness in patients with HF. Third, GB wall thickness was positively correlated with HF stage. Lastly, the high GB wall thickness group had a significantly higher incidence of hospitalization events for HF. To the best of our knowledge, this is the first clinical study to measure GB wall thickness and address its relationship with the cardiovascular system of patients with HF. This method may have the unique advantage of easily providing additional information on organ congestion and estimating the stage in patients with HF. Assessment of organ congestion via extracardiac ultrasound may also facilitate understanding of the interaction between the heart and other organs, as observed between the heart and kidney in cardiorenal syndrome.

As limitation, first, the sample size was small with relatively few events, posing a potential risk of model overfit. Second, we were not able to compare GB wall thickness at admission and discharge. Third, there was also no comparison of GB wall thickness and central venous pressure, measured by right heart catheterization. Fourth, GB wall thickness was measured after the echocardiogram was already performed by the same sonographers. Therefore, it is possible that the measurements of the GB wall thickness were affected. Lastly, it should be noted that in this study, GB wall thickness was measured using a sector scan, which is different from a convex scan, the usual method of measuring GB wall thickness on ultrasonography.

CONCLUSION

Despite these limitations, we conclude that GB wall thickness can be used to assess organ congestion and estimate the stage in patients with HF.