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Prognostic impact of intestinal wall thickening in hospitalized patients with heart failure

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ABSTRACT

Background: Intestine-cardiovascular relationship has been increasingly recognized as a key factor in patients with heart disease. We aimed to identify the relationships among intestinal wall edema, cardiac function, and adverse clinical events in hospitalized heart failure (HF) patients.
Methods and results: Abdominal computed tomographic images of 168 hospitalized HF patients were retrospectively investigated for identification of average colon wall thickness (CWT) from the ascending to sigmoid colon. Relationships between average CWT and echocardiographic parameters, blood sampling data, and primary outcomes including readmission for deteriorated HF and all-cause mortality were evaluated. Among the echocardiographic parameters, lower left ventricular diastolic function was correlated with higher average CWT. In multivariate analysis, higher logarithmic C-reactive protein level, lower estimated glomerular filtration rate, lower peripheral blood lymphocyte count, higher E/E′ ratio, and extremely higher/lower defecation frequency were independently correlated with higher average CWT. Multivariate Cox-hazard analysis demonstrated that higher average CWT was independently related to higher incidence of primary outcomes.
Conclusion: In hospitalized HF patients, increased CWT was associated with lower cardiac performance, and predicted poorer long-term clinical outcomes.

1. Introduction

Interactions between the intestine and the cardiovascular system are increasingly recognized as playing an important role in cardiovascular disease. Dynamic changes in gut-microbiota composition, known as dysbiosis, can trigger systemic inflammation, which is known to be a key determinant of the pathophysiological progression of cardiovascular disease. Recently, possible pathways linking dietary phosphatidylcholine, intestinal microbiota, and adverse atherosclerotic events were suggested [1,2]. Furthermore, there is also an increasing evidence of gut-cardiovascular interaction in heart failure (HF) patients [3].

A thickened colon wall, suggestive of colon wall edema, and increased intestinal permeability have been clinically demonstrated in patients with chronic HF compared to those of healthy controls [4,5]. Reduced intestinal blood flow is postulated to contribute to juxtamucosal bacterial overgrowth in patients with HF, possibly leading to gut-microbiotal dysbiosis. This reduced intestinal blood flow has also been linked to gastrointestinal symptoms, cardiac cachexia, and advanced HF complications [6]. However, no reports have studied the association between the morphological features of the intestine, cardiac function, and long-term outcomes in patients with HF.

In the present study, we aimed to clarify whether intestinal wall thickness would be increased in HF patients with lower cardiac performance and related to poorer long-term prognosis.

2. Methods

2.1. Study population

The present study is a single-center, retrospective, and observational study. From January 1, 2012 to April 1, 2013, patients referred to the Kitasato University Hospital with a primary diagnosis of acute decompensated HF were screened from the HF database at our institute. To be included, all patients had to have echocardiography and abdominal computed tomography performed. Patients with a history of gastrointestinal disease including gastrointestinal cancer, enteritis, infectious colitis, ischemic colitis, inflammatory bowel disease, food hypersensitivity, and ileus were excluded. The diagnosis of acute decompensated HF was based on the presence of two major criteria or one major criterion and two minor criteria from the Framingham classification. The use of conventional HF treatments, including beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, diuretics, digitalis, and spironolactone, when appropriate, were introduced according to current HF guidelines [7,8]. The present study was approved by our local institutional review board. Informed consent was obtained from all patients prior to their participation.

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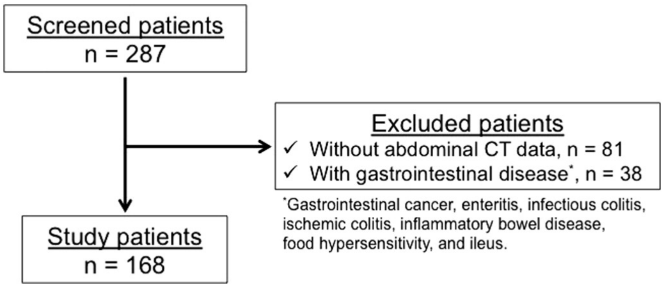

Fig. 1. Study overview. CT = computed tomography.

2.2. Clinical measurements

Patients' demographic data, physical examination, electrocardiography, blood-laboratory tests, echocardiography, and abdominal computed tomography imaging results at discharge were obtained from chart reviews. Defecation frequency was obtained from clinical charts and presented as mean frequency per week (/week) during the in-hospital period. Transthoracic echocardiographic parameters were assessed in the standard fashion in accordance with the current American Society of Echocardiography guidelines [9]. Left ventricular end-diastolic/end-systolic dimension, left ventricular posterior thickness, and left atrial diameter were measured by M-mode, and left ventricular ejection fraction was assessed by 2-dimensional echocardiography using the modified Simpson's biplane method. The severity of mitral and tricuspid regurgitation was graded according to the regurgitant jet area on a color Doppler image. The transmitral inflow velocity was obtained by pulsed Doppler imaging while positioning the sample volume between the tips of the mitral leaflets. The diastolic annular velocity at the medial annulus was also measured using pulse and tissue Doppler imaging. The left ventricular stroke volume was calculated according to the following formula: stroke volume (mL) = Pi × {(left ventricular outflow tract dimension) / 2}^{2} × (time-velocity integral using pulse Doppler imaging on left ventricular outflow tract) [10]. Left ventricular diastolic dysfunction was graded according to the recommendations of the American Society of Echocardiography and the European Association of Echocardiography [11].

Computed tomography scans were performed on a multiscan spiral computed tomography system (SOMATOM Definition FLASH, Biograph6, Symbia T, Siemens, Germany; Light Speed VCT, Optima660ProFD, GE Healthcare, USA), with a slice thickness of 2.5 mm. Abdominal computed tomography imaging was obtained with plain films or contrast studies, depending on availability. Images were retrospectively analyzed by one experienced radiologist, and reviewed by another one who was blinded to patient clinical information. Colon wall thickness (CWT) was measured carefully at the inner luminal and outer mesenteric aspects on transaxial projections of the bowel in the area of well-distended colon whenever possible [12,13], and presented as an average. Average CWT was calculated from the averages of each three points among the terminal ileum, ascending colon, transverse colon, descending colon, and sigmoid colon. The normal CWT on computed tomography was reported as if it was <3 mm [13,14].

2.3. Outcomes

The end of follow-up was considered to be December 31, 2015, or the date of death. The primary outcome was defined as the first occurrence of readmission for deteriorated HF or all-cause mortality. Information regarding the primary outcomes was obtained through direct telephone interviews with the patient or his/her physician, or information from chart reviews.

2.4. Statistical analysis

To elucidate the association between average CWT and other clinical variables, we compared clinical variables among patient subgroups divided according to quartiles of average CWT. Continuous variables were expressed as means ± standard deviations and categorical variables as percentages. Comparison of continuous variables among groups was performed using one-way analysis of variance, and categorical variables were compared using the chi-square or Fisher's exact tests, as appropriate. The clinical variables associated with average CWT at a level of $p \le 0.10$ in univariate analyses were included in the multiple regression analysis with backward stepwise selection to explore the association between clinical variables and average CWT. Kaplan-Meier survival curves were drawn, stratified by quartile of average CWT, and compared using the log-rank test. The associations between clinical variables and primary outcomes were evaluated using a Cox proportional hazards regression model, and were expressed as hazard ratios with 95% confidence intervals. The clinical variables associated with primary outcomes at a level of $p \le 0.10$ in univariate analyses and quartiles of average CWT were included in the first Cox regression model (model 1). In addition, the logarithm of C-reactive protein, estimated glomerular filtration rate, peripheral lymphocyte count, left ventricular ejection fraction, and E/E′ ratio were added to the first model as the second regression model (model 2). Differences were considered statistically significant at $p < 0.05$. All statistical analysis was performed using JMP 10.0 software for Windows (SAS Institute, Cary, North Carolina, USA).

3. Results

3.1. Patient characteristics

Fig. 1 shows an overview of the recruitment process used in this study. A total of 287 consecutive hospitalized patients diagnosed with acute decompensated HF were screened. We excluded 81 (28%) patients whose abdominal computed tomography data were unavailable, and 38 (13%) patients with gastrointestinal disease. Finally, the participants included in the statistical analyses totaled 168 (59%). The purposes for the enforcement of abdominal computed tomography are listed in Table 1. Intestinal wall thickness became increasingly larger near the terminal colon (terminal ileum: 2.8 ± 0.9 mm, ascending colon: 3.5 ± 1.2 mm, transverse colon: 3.4 ± 1.1 mm, descending colon: 3.7 ± 1.2 mm, and sigmoid colon: 4.5 ± 1.2 mm).

Patient demographic and clinical characteristics divided into subgroups according to quartiles of average CWT (CWT-Q1 to Q4) are presented in Table 2. Among the demographic data, higher age, presence of ischemic etiology, and presence of prior HF hospitalization were found in the higher quartile group of average CWT. Tolvaptan was more frequently used in the higher quartile group of average CWT, while usage of other medications was not significantly different among subgroups. A higher presence of HF symptom of New York Heart Association functional class ≥3 was found in the higher quartile group of average CWT. Among laboratory data, higher serum B-type natriuretic peptide levels, lower serum albumin, lower estimated glomerular filtration rate, and lower peripheral lymphocyte count were found in the higher quartile group of average CWT. Among echocardiographic data, no significant difference in left ventricular ejection fraction, higher E/E′ ratio, higher presence of left ventricular diastolic dysfunction grade ≥2, and higher presence of tricuspid regurgitation grade ≥3 were found in the higher quartile group of average CWT.

3.2. Echocardiographic parameters

We evaluated the association between echocardiographic parameters and average CWT as shown in Fig. 2. In the parameters of left ventricular systolic function, there was no significant difference in average CWT among the quartiles of left ventricular ejection fraction or left ventricular end-diastolic dimension. In contrast, higher average CWT was found in the higher quartile of E/E′ ratio, and in higher-grade subgroups of left ventricular diastolic dysfunction.

3.3. Relationship to colon wall thickness

Although there is no significant linear correlation between average CWT and defecation frequency, patients with the lowest (DF-Q1: 0–4.0/week) and the highest (DF-Q4: 8.0–38/week) quartile defecation frequency had higher average CWT than those with middle (DF-Q2: 4.1–6.0/week, Q3: 6.1–7.9/week) (average CWT: 3.9 ± 1.0 mm in DF-Q1, 3.3 ± 0.8 mm in DF-Q2, 3.4 ± 0.8 mm in DF-Q3, and 4.1 ± 1.1 mm in DF-Q4, respectively; $p = 0.001$).

Table 1
The purposes for the enforcement of abdominal computed tomography.

Purpose	*n* (%)
Screening of malignant disease	48 (29)
Surveillance for infectious focus	44 (26)
Synchronization of the scintigraphy	28 (17)
Surveillance for vascular thrombosis	15 (9)
Surveillance for peripheral vascular disease	12 (7)
Surveillance for unidentified abdominal symptom	11 (6)
Others	10 (6)

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