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Liver fibrogenesis marker, 7S domain of collagen type IV in patients with acutely decompensated heart failure: Correlates, prognostic value and time course

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ABSTRACT

Background: Congestion in heart failure (HF) induces multiple organ injury, which may cause remodeling of extracellular matrix. We hypothesized that liver fibrogenesis marker, 7S domain of collagen type IV (P4NP 7S) was correlated with congestion and liver injury in HF.
Methods and results: We measured serum P4NP 7S in two cohorts. Cohort 1 included 70 patients undergoing catheterization. P4NP 7S was correlated with pulmonary capillary wedge pressure, right ventricular and atrial pressure ($r = 0.50$, $P < 0.001$, $r = 0.42$, $P < 0.001$, $r = 0.39$, $P = 0.001$, respectively) but not with cardiac index ($r = -0.05$. $P = 0.7$). Cohort 2 included 145 patients with acute HF, in whom we serially measured P4NP 7S at admission, discharge, early (1-month) and late (6-month) post-discharge period. γ-Glutamyltransferase and B-type natriuretic peptide were independently correlated with P4NP 7S at discharge. The cumulative 1-year incidence of death or HF hospitalization was much higher in the 3rd tertile of P4NP 7S than in the 1st and 2nd tertiles (50%, 25%, and 24%, Log-rank $P = 0.004$). P4NP 7S enhanced risk classification when added to conventional risk factors (net reclassification improvement = 0.47, $P = 0.02$). In patients without early readmission, P4NP 7S decreased during hospitalization and remained low for up to 6 months, whereas in patients with early readmission, P4NP 7S was persistently elevated during hospitalization, further increased at second admission, and remained high at 6 months.
Conclusion: P4NP 7S was correlated with hemodynamics. The results shed new light on the pathophysiology of HF.

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1. Introduction

Systemic venous congestion caused by impairment of cardiac pumping and decreased ability of ventricular filling is a hallmark of heart failure (HF) [1]. Fluid retention in HF can involve the lungs, kidneys and abdominal organs (i.e., liver and intestine), thereby unfavorably affecting multiple organs [2–5]. A substantial proportion of HF patients have systemic organ dysfunction as evidenced by impairment of renal function or elevation of simple liver function tests (LFTs) [6,7]. Recent reports demonstrated that markers of extra-cardiac organs have prognostic utility individually or as a composite scoring system representing hepatic and renal dysfunction such as the Model for END-Stage Liver Disease (MELD) score [8]. Despite extensive investigation, however, the pathophysiology of HF is poorly understood, particularly the association of congestion and organ injury.

Persistent injury of tissues and organs generally evokes remodeling of the extracellular matrix (ECM), with concurrent production and degradation of collagen fibers [9]. In this process, collagen fragments are released into the systemic circulation, and can be assayed in serum or plasma, thus serving as biomarkers reflecting ECM remodeling [10].

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The 7S domain of the collagen type IV N-terminal propeptide (P4NP 7S) is a fragment of collagen type IV, which is abundantly expressed in the basement membrane in the hepatic ECM [11]. Pathological, serological, and clinical evidence support P4NP 7S as a biomarker reflecting liver fibrosis in primary hepatic disease [12–15]. We hypothesized that turnover of collagen type IV may be associated with systemic congestion and organ injury in HF. Therefore, we investigated the correlates, prognostic significance and time course of serum P4NP 7S in patients with HF.

2. Methods

2.1. Study design and population

This study included two cohorts. In cohort 1, the relationships between P4NP 7S and hemodynamics were evaluated in 70 patients with HF. The patients had been admitted for assessment and management of HF, requiring right heart catheterization (RHC) for precise evaluation of hemodynamic status. Following RHC, left ventriculography and coronary angiography were performed in patients if they had normal renal function. P4NP 7S was measured on the same day of catheterization. In cohort 2, clinical correlates, prognostic significance, and change of P4NP 7S were evaluated in a consecutive series of prospectively enrolled patients hospitalized for acutely decompensated HF (ADHF). In these patients, biomarker analysis was performed at admission and immediately before discharge. Patients were followed up for at least 6 months. Post-discharge biomarker analyses were performed at the first ambulatory follow-up visits recommended within 90 days of discharge and at the 6-month visits. If patients were readmitted for worsening HF within 6 months of the initial discharge, P4NP 7S measurements were also performed on the second admission (Supplementary Fig. 1). The results of serial P4NP 7S measurements were stratified by readmission (readmission + stratum) or no readmission (readmission – stratum) for HF within 6 months. Patients were excluded if they had acute coronary syndrome, known active neoplasia, active hepatitis or liver cirrhosis, or overt inflammatory, metabolic, or bone disease, or were undergoing hemodialysis. The study was performed as a part of a translational biomarker analysis and was approved by the ethics committee of Osaka Red Cross Hospital. All study procedures were conducted in compliance with the ethical principles of the Declaration of Helsinki; all patients provided written informed consent.

2.2. Measurement of P4NP 7S

Blood samples were collected and centrifuged and the serum was transferred to a central laboratory for P4NP 7S measurement using a commercially available radioimmunoassay kit (Sceti Medical Labo). If necessary, samples were stored at ≤−30 °C until assayed following the established protocol used in the clinical setting. The normal cut-off value was ≤6 ng/mL; the low and high limits of detection were 1.25 and 80 ng/mL, respectively. The coefficient of variation was <5%.

2.3. Assessment of liver dysfunction by using MELD-XI score

We calculated MELD-XI score, a modification of MELD score by formula developed by Heuman et al.: 5.11 × (ln total bilirubin [T-Bil]) + 11.76 × (ln creatinine) + 9.44 [16]. Its potential utility as a prognostic marker reflecting hepato-renal impairment in HF has been reported previously [17].

2.4. Hemodynamic assessment

During RHC, pulmonary artery pressure, pulmonary capillary wedge pressure (PCWP), right ventricular pressure, right atrial pressure, and cardiac index were obtained using a triple-lumen Swan–Ganz catheter. Selective coronary angiography was performed with left heart catheterization after aortic pressure recording. Left ventricular (LV) pressure recording and left ventriculography were performed with a pigtail catheter to measure the LV pressure, LV volume and LV ejection fraction (EF).

2.5. Cohort 2 endpoints

Primary outcomes in cohort 2 were all-cause death and HF hospitalization, which was defined as hospitalization for worsening HF and requiring intravenous drug therapy. Follow-up began on the day of discharge.

2.6. Statistical analysis

Continuous variables were expressed as the means ± SD or medians and interquartile range (IQR). The significances in differences between-group in continuous variables were assessed by Student's *t*-test or by the Mann–Whitney *U* test, as appropriate. Those in categorical variables were by chi-squared tests. Differences in continuous variables among the three groups were assessed by one-way analysis of variance (ANOVA) or Kruskal–Wallis test; Dunn's multiple comparison test was performed as post-hoc comparisons, if necessary. In cohort 1, correlation of clinical and hemodynamic parameters with P4NP 7S were tested with Spearman's correlation coefficient. In cohort 2, baseline characteristics at discharge were divided into tertiles of P4NP 7S. Factors independently correlated with P4NP 7S values were identified by multivariate linear regression models after log transformation of P4NP 7S. Cumulative incidence of clinical events across P4NP 7S tertiles were estimated by the Kaplan–Meier method, and differences among the groups were assessed with the log-rank test. The risk of 2nd and 3rd tertiles P4NP 7S relative to the 1st tertile P4NP 7S were estimated by Cox proportional hazard model and expressed as hazard ratio (HR) and 95% confidence interval (CI). The discrimination capabilities of the models with or without biomarker of interest were evaluated from the receiver-operating characteristic (ROC) analysis by calculating incremental area under curve (AUC) before and after adding biomarkers to the reference model [18]. The following variables were incorporated into the reference model: age; EF < 40%; estimated glomerular filtration rate (eGFR); sodium < 140 mmol/L; hemoglobin and B-type natriuretic peptide (BNP). Values of biomarker were log-transformed before analysis. When we analyzed the incremental value of MELD-XI score, we excluded eGFR from reference model to avoid duplicate inclusion of renal parameters into the model. The incremental prognostic utility of LFTs, MELD-XI score and P4NP 7S on top of the reference model for risk reclassification was assessed by using the continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) [19].

All statistical analyses were performed with JMP 10.0.0 (SAS Institute Inc., Cary, NC, USA), GraphPad Prism 6.05 (GraphPad Software, Inc. La Jolla, CA, USA) and statistical software R (version 3.3.1). *P*-values < 0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics of cohort 1 patients

The baseline characteristics of patients in cohort 1 are summarized in Supplementary Table 1. Nearly half of patients had hypertension, and 60% or more of patients were taking an angiotensin-converting-enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) and β-blocker. Cardiac and hemodynamic evaluations revealed that median BNP was 412 pg/mL, and the average PCWP was 14 mmHg, cardiac index was 2.2 L/min/m^2, and EF was 38%. The median P4NP 7S value was 5.7 (IQR 4.7–6.9) ng/mL.

3.2. Correlation of P4NP 7S with laboratory and hemodynamic parameters in cohort 1 patients

Among laboratory measurements, P4NP 7S was positively correlated with aspartate aminotransferase (AST), γ-glutamyltransferase (γ-GTP) and BNP (Table 1). Regarding hemodynamics, P4NP 7S was significantly correlated with PCWP as well as all right-side pressures including pulmonary artery pressure, right ventricular pressure, and right atrial pressure (Table 1). No significant correlation was observed between P4NP 7S and cardiac index. In the 44 patients (63%) undergoing left-side catheterization, P4NP 7S was not correlated with aortic pressure, LV volume, or LV EF.

3.3. Baseline characteristics of cohort 2 patients

Baseline characteristics of patients in cohort 2 are summarized in Supplementary Table 2. The median hospital stay was 16 (11−21) days and nine (6%) patients died during the hospitalization. 42% of patients had reduced LV systolic dysfunction and a similar percentage were taking β-blockers and ACEIs or ARBs on admission, which increased to nearly 60% at discharge. Among laboratory measurements, hemoglobin levels increased while BNP and LFT values such as T-Bil, AST, alanine transaminase (ALT) and γ-GTP decreased significantly during hospitalization. The median P4NP level at admission was 6.8 (IQR; 5.6–8.0) ng/mL, and it significantly decreased to 5.9 (IQR; 4.8–7.1) ng/mL at discharge (Supplementary Table 2). Patients with abnormally high level of P4NP 7S was 97 (67%) at admission and 63 (46%) at discharge.

3.4. Relationships of clinical characteristics and P4NP 7S on admission in cohort 2 patients

P4NP 7S on admission was not correlated with systolic blood pressure (Supplementary Fig. 2A) or presence of leg edema at presentation

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