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ORIGINAL RESEARCH

# Increases in Hepatokine Selenoprotein P Levels Are Associated With Hepatic Hypoperfusion and Predict Adverse Prognosis in Patients With Heart Failure

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**BACKGROUND:** Although multiorgan networks are involved in the pathophysiology of heart failure (HF), interactions of the heart and the liver have not been fully understood. Hepatokines, which are synthesized and secreted from the liver, have regulatory functions in peripheral tissues. Here, we aimed to clarify the clinical impact of the hepatokine selenoprotein P in patients with HF.

**METHODS AND RESULTS:** This is a prospective observational study that enrolled 296 participants consisting of 253 hospitalized patients with HF and 43 control subjects. First, we investigated selenoprotein P levels and found that its levels were significantly higher in patients with HF than in the controls. Next, patients with HF were categorized into 4 groups according to the presence of liver congestion using shear wave elastography and liver hypoperfusion by peak systolic velocity of the celiac artery, which were both assessed by abdominal ultrasonography. Selenoprotein P levels were significantly elevated in patients with HF with liver hypoperfusion compared with those without but were not different between the patients with and without liver congestion. Selenoprotein P levels were negatively correlated with peak systolic velocity of the celiac artery, whereas no correlations were observed between selenoprotein P levels and shear wave elastography of the liver. Kaplan-Meier analysis demonstrated that patients with HF with higher selenoprotein P levels were significantly associated with increased adverse cardiac outcomes including cardiac deaths and worsening HF.

**CONCLUSIONS:** Liver-derived selenoprotein P correlates with hepatic hypoperfusion and may be a novel target involved in cardiohepatic interactions as well as a useful biomarker for predicting prognosis in patients with HF.

**Key Words:** biomarker ■ heart failure ■ hepatokine ■ prognosis ■ selenoprotein P

Cardiac and multiple organ networks are essentially involved in the pathophysiology of heart failure (HF).[1] Noncardiovascular comorbidities accelerate the disease progression and increase the mortality risk.[2] Patients with HF are often comorbid with liver diseases, and 20% to 30% of patients with HF present abnormal liver function tests.[3] HF leads to persistent low perfusion and congestion in the liver accompanied by liver injury and hepatocyte necrosis.[4] Elevated liver enzymes, as well as a higher liver fibrosis score are independent predictors for poor outcomes in patients with HF.[3,5,6] The bidirectional relationships between the heart and the liver play important roles in the onset and progression of HF but their exact

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## CLINICAL PERSPECTIVE

### What Is New?

- This is the first study to demonstrate that up-regulation of the liver-derived hepatokine selenoprotein P is associated with hepatic hypoperfusion rather than hepatic congestion in patients with heart failure.
- Higher selenoprotein P levels are significantly associated with increased adverse cardiac outcomes in patients with heart failure.

### What Are the Clinical Implications?

- Hepatokine selenoprotein P may be a novel target involved in cardiohepatic interactions.
- Selenoprotein P may be a useful biomarker for predicting prognosis in patients with heart failure.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **LRP1** | low-density lipoprotein receptor–related protein 1 |
| **PSV** | peak systolic velocity |

mechanisms in cardiohepatic interactions have not been fully clarified.

Hepatokine, a liver-derived hormone that is synthesized and secreted from hepatocytes, has been shown to have various regulatory functions in metabolic processes.[7] Selenoprotein P, which is originally known as a selenium supply protein,[8] has been recently identified as an important molecule that may contribute to the development of diabetes by inducing insulin resistance and hyperglycemia among the hepatokines.[9] Although hepatokines may be considered as novel molecules that are involved in cardiohepatic interactions, the role and regulation of hepatokines, including selenoprotein P, in the pathogenesis of HF remain to be characterized.

Here, we aimed to clarify the clinical impact of selenoprotein P and its relationship with hepatic hemodynamics, cardiac function, exercise capacity, and prognosis in patients with HF.

## METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Study Subjects

This study enrolled 253 hospitalized patients with symptomatic stage C/D HF who had undergone abdominal ultrasonography at Fukushima Medical University Hospital between May 2018 and February 2020. The diagnosis of HF was made according to the Framingham criteria by independent cardiologists.[10] For the control group, 43 consecutive patients who had never had symptoms of HF or structural cardiac abnormalities on echocardiography and had undergone abdominal ultrasonography during the same period were analyzed. We excluded patients with organic liver diseases such as viral hepatitis, cirrhosis, hepatic tumors, bile duct diseases, and advanced cancer, as well as those undergoing hemodialysis. The study was approved by the Ethics Committee of Fukushima Medical University (approval number, 823) and complied with the Declaration of Helsinki. All patients provided written informed consent for study participation. We followed up all patients with HF by reviewing medical records at the same hospital or referral hospitals for composite cardiac events including cardiac death or unplanned rehospitalization because of worsening HF.

### Measurement of Serum Concentration of Selenoprotein P

The blood samples were collected from patients during hospitalization before hospital discharge. After blood collection from the participants, blood samples were immediately separated by centrifugation at 1670*g* for 15 minutes at room temperature, and then the serum was frozen at −80 °C until assayed. The serum concentration of selenoprotein P was determined by ELISA (CSB-EL021018HU: CUSABIO, Wuhan, China) according to the manufacturer's instruction.[11] The serum samples with a 2000-fold dilution and the serially diluted standards were applied into each well, and then absorbance values were measured at 450 nm with a microplate reader (SpectraMax i3, Molecular Devices, Sunnyvale, CA). The serum selenoprotein P concentrations were calculated on the basis of the standard curve.

### Abdominal Ultrasonography

To assess hepatic hemodynamics, we measured shear wave elastography of the liver and the peak systolic velocity (PSV) of the celiac artery by abdominal ultrasonography, as we previously described.[12] Patients with HF were then categorized into 4 groups according to the presence or absence of liver congestion determined by the median value of shear wave elastography (1.33 m/s) and liver hypoperfusion by PSV (62.4 cm/s).

### Laboratory Data, Echocardiography, Right Heart Catheterization, and Cardiopulmonary Exercise Testing

Clinical information including laboratory data and results of echocardiographic analysis, right heart

catheterization, and cardiopulmonary exercise testing was collected in standard clinical practice.[12–14] In the cardiopulmonary exercise testing, breath-by-breath oxygen consumption and ventilatory response to exercise were determined during incremental symptom-limited exercise testing on an upright cycle ergometer with a ramp protocol. All data were obtained when the patients were in stable condition without changes in medications before hospital discharge.

## Statistical Analysis

Normally distributed data are presented as mean±SD, and nonnormally distributed data are presented as median and interquartile range. The Kolmogorov-Smirnov test was used for testing normality. The statistical significance of differences was analyzed using the unpaired Student *t* test, the Mann-Whitney *U* test, or the Kruskal-Wallis nonparametric ANOVA followed by Dunn's pairwise comparison. Differences in categorical variables were examined by using the chi-square test. Correlations were analyzed by the Spearman correlation test. Event rates were calculated for composites of cardiac death and unplanned rehospitalization because of worsening HF by using Kaplan-Meier analysis with a log-rank test. The univariate Cox proportional hazard model and age- and sex-adjusted multivariate Cox proportional hazard model were applied to assess selenoprotein P levels as a predictor of cardiac events. A $P<0.05$ was considered statistically significant for group pairwise contrasts. As Bonferroni correction can be used for the multiplicity where a large number of independent tests are performed to adjust the probability of statistical type I error (false positive),[15] the Bonferroni-adjusted significance level (0.05 divided by the number of variants) was applied for the correlation analysis with a significance cutoff of $1.9\times10^{-3}$ (0.05/26) and the interaction testing for the subgroup analysis with a significance cutoff of $5.5\times10^{-3}$ (0.05/9). Statistical analyses were performed using Statistical Package for Social Sciences version 24.0 (IBM, Armonk, NY) or Prism version 8.1.2 (GraphPad Software, San Diego, CA).

# RESULTS

The clinical characteristics of all subjects are summarized in Table 1. In patients with HF, the mean age was 68.7±12.9 years, and 56.9% were men. B-type natriuretic peptide was 176.0 (74.5–379.3) pg/mL, and left ventricular ejection fraction (LVEF) was 49.2±17.0%. In abdominal ultrasonography, PSV of the celiac artery was lower and shear wave elastography of the liver was higher in patients with HF than in the control subjects. The levels of serum selenoprotein P in patients with HF were significantly higher than those in the control subjects (Figure 1A). Even when we excluded participants with diabetes in both groups, the levels of serum selenoprotein P in patients with HF (n=164) were significantly higher than those in the control subjects (n=37) (13.1 [8.2–19.1] versus 9.4 [6.0–13.1] mg/L; $P<0.001$).

Next, to assess the regulatory association of circulating selenoprotein P with hepatic hemodynamics, the patients with HF were categorized into 4 groups according to the presence of liver congestion and liver hypoperfusion using abdominal ultrasonography as we previously reported.[12] Of note, selenoprotein P levels were significantly elevated in the patients with liver hypoperfusion compared with those without (Figure 1B). In contrast, selenoprotein P levels were not different between the patients with and without liver congestion. When patients with HF were stratified on the basis of LVEF, selenoprotein P levels were not different among HF with preserved LVEF ≥50% (13.1 [8.2–20.3] mg/dL), HF with mildly reduced LVEF 40% to 50% (15.3 [5.3–18.1] mg/dL), and HF with reduced LVEF <40% (13.0 [8.9–19.5] mg/dL; $P=0.839$). According to the categorization into the etiologies of HF, selenoprotein P levels were not different among patients with HF with valvular heart disease (14.8 [9.7–20.3] mg/dL), cardiomyopathy (13.5 [7.5–18.9] mg/dL), ischemic heart disease (11.9 [6.9–15.9] mg/dL), and others (13.6 [7.1–21.8] mg/dL; $P=0.308$).

Correlation analysis demonstrated that selenoprotein P levels were negatively correlated with PSV of the celiac artery and cardiac output, while there were no correlations between selenoprotein P levels and shear wave elastography of the liver, pulmonary capillary wedge pressure, or right atrial pressure (Table 2). These findings suggest that elevation of selenoprotein P levels is associated with liver tissue hypoperfusion rather than liver congestion in the patients with HF. With regard to the laboratory data, selenoprotein P was positively correlated with B-type natriuretic peptide and troponin I, but negatively correlated with albumin, cholinesterase, insulin, and estimated glomerular filtration rate. There was no association of selenoprotein P with liver enzymes or parameters of glucose metabolism such as fasting glucose and hemoglobin $A_{1c}$. In the cardiopulmonary exercise test, selenoprotein P levels were inversely correlated with peak oxygen consumption, but positively correlated with the minute ventilation/carbon dioxide production slope, indicating that circulating selenoprotein P might have a role in impaired exercise capacity in patients with HF.

To investigate the prognostic impact of selenoprotein P levels in patients with HF, the patients were followed for a median period of 476 days (quartile 1 to quartile 3: 270–707 days), and 37 cardiac events were observed including 9 cardiac deaths and 28 rehospitalizations because of decompensated HF. When the patients were categorized into 2 groups according to the median value

**Table 1. Clinical Characteristics of All Participants, Including Patients With Heart Failure and Control Subjects**

| | Control subjects (n=43) | Patients with heart failure (n=253) | *P* value |
|---|---|---|---|
| Age, y | 63.4±11.2 | 68.7±12.9 | 0.011 |
| Male sex, n (%) | 28 (65.1) | 144 (56.9) | 0.314 |
| Body mass index, kg/m$^2$ | 23.9±3.3 | 23.0±3.9 | 0.121 |
| New York Heart Association, I/II/III/VI, n (%) | N/A | 77 (30.4)/102 (40.3)/63 (24.9)/11 (4.3) | N/A |
| HFpEF/HFmrEF/HFrEF, n (%) | N/A | 156 (61.7)/28 (11.1)/69 (27.2) | N/A |
| Comorbidities | | | |
| Hypertension, n (%) | 25 (58.1) | 164 (64.8) | 0.399 |
| Diabetes, n (%) | 6 (13.9) | 89 (35.1) | 0.006 |
| Dyslipidemia, n (%) | 27 (62.7) | 163 (64.4) | 0.836 |
| Chronic kidney disease, n (%) | 10 (23.3) | 158 (62.4) | <0.001 |
| Atrial fibrillation, n (%) | 14 (32.6) | 94 (37.1) | 0.563 |
| Etiology of heart failure | | | |
| Valvular heart disease, n (%) | N/A | 80 (31.6) | N/A |
| Cardiomyopathy, n (%) | N/A | 72 (28.4) | N/A |
| Ischemic heart disease, n (%) | N/A | 40 (15.8) | N/A |
| Others, n (%) | N/A | 61 (24.1) | N/A |
| Laboratory data | | | |
| B-type natriuretic peptide, pg/mL | 19.0 (10.8–41.9) | 176.0 (74.5–379.3) | <0.001 |
| Troponin I, ng/mL | N/A | 0.021 (0.017–0.079) | N/A |
| Albumin, g/dL | 4.2±0.3 | 3.8±0.5 | <0.001 |
| Aspartate aminotransferase, U/L | 22.0 (19.0–28.0) | 23.0 (18.0–28.0) | 0.996 |
| Alanine transaminase, U/L | 19.0 (14.0–28.0) | 18.0 (13.0–27.0) | 0.500 |
| Cholinesterase, U/L | 320.7±69.6 | 266.9±88.2 | <0.001 |
| Glucose, mg/dL | 102.5±14.5 | 117.8±41.1 | 0.021 |
| Hemoglobin $A_{1c}$, % | 5.7±0.4 | 6.0±0.9 | 0.027 |
| Insulin, μU/mL | 5.9 (3.5–13.5) | 7.6 (4.9–13.9) | 0.230 |
| Creatine, mg/dL | 0.83±0.17 | 1.13±0.70 | <0.001 |
| eGFR, mL/min per 1.73 m$^2$ | 67.9±14.9 | 52.3±17.8 | <0.001 |
| C-reactive protein, mg/dL | 0.090 (0.050–0.200) | 0.160 (0.070–0.482) | 0.013 |
| Echocardiography | | | |
| Left ventricular ejection fraction, % | 64.3±5.3 | 49.2±17.0 | <0.001 |
| Mitral valve E/E′ | 8.8±3.7 | 15.7±8.9 | <0.001 |
| Right ventricular fractional area change, % | 42.7±8.0 | 35.9±11.0 | 0.008 |
| Tricuspid regurgitation pressure gradient, mm Hg | 22.6±10.1 | 27.9±12.4 | 0.017 |
| Abdominal echocardiography | | | |
| PSV of the celiac artery, cm/s | 82.1±18.6 | 64.7±20.2 | <0.001 |
| SWE of the liver, m/s | 1.26±0.22 | 1.42±0.32 | <0.001 |
| Medications | | | |
| Renin-angiotensin system inhibitor, n (%) | 15 (35.7) | 167 (66.0) | <0.001 |
| β-blocker, n (%) | 11 (25.6) | 181 (71.5) | <0.001 |
| Mineralocorticoid receptor antagonist, n (%) | 3 (7.0) | 96 (37.9) | <0.001 |
| Diuretics, n (%) | 4 (9.3) | 166 (65.6) | <0.001 |

Data are presented as mean±SD, median (interquartile range), or number (percentage). eGFR indicates estimated glomerular filtration rate; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; PSV, peak systolic velocity; and SWE, shear wave elastography.

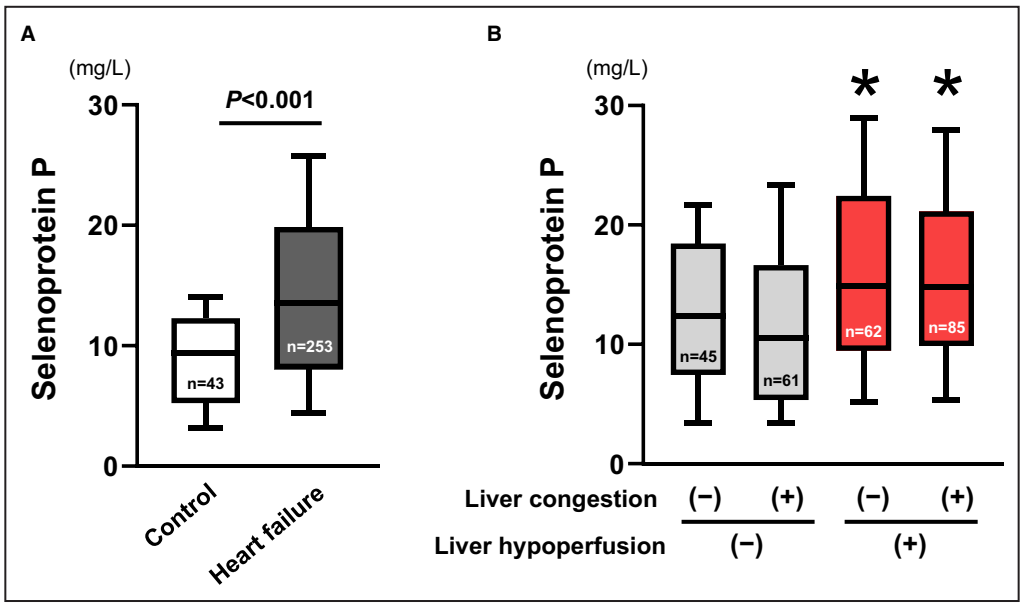


**Figure 1. Serum selenoprotein P levels in patients with heart failure and control subjects.**
**A**, Selenoprotein P levels between control subjects (n=43) and patients with heart failure (n=253). The serum selenoprotein P concentrations were measured by ELISA. Comparisons of values between the 2 groups were performed by the Mann-Whitney *U* test. **B**, Selenoprotein P levels in patients with heart failure based on hepatic hemodynamics assessed by abdominal ultrasonography. The numbers of patients with/without liver congestion and with/without liver hypoperfusion are shown in the graph. Comparisons were performed by the Kruskal-Wallis test followed by Dunn's pairwise comparison. **P*<0.05 vs the corresponding group without liver hypoperfusion. All data are shown as box plots with whiskers; box, interquartile range; line in the box, median values; whiskers, 10th and 90th centiles.

of serum selenoprotein P levels (13.5 mg/mL; Table S1), Kaplan-Meier analysis demonstrated that the patients with higher selenoprotein P levels were significantly associated with increased adverse cardiac outcomes including cardiac deaths and worsening HF (log-rank *P*=0.0125; Figure 2). In addition, univariate Cox proportional hazard analysis showed that patients with HF with higher serum selenoprotein P levels were correlated with increased cardiac event risks compared with those with lower selenoprotein P levels (hazard ratio [HR], 2.388; 95% CI, 1.180–4.835; *P*=0.016). In multivariate Cox proportional hazard analysis adjusted for age and sex, patients with HF with higher serum selenoprotein P levels were associated with higher cardiac events than those with lower selenoprotein P levels (HR, 2.180; 95% CI, 1.036–4.587; *P*=0.040). Furthermore, in the subgroup analysis considering several confounding variables (ie, age, sex, body mass index, New York Heart Association class, and comorbidities), no interactions were found between the prognostic impact of selenoprotein P levels and above confounding variables (Table 3).

## DISCUSSION

To our knowledge, this is the first study to demonstrate that (1) the elevated levels of liver-derived hepatokine selenoprotein P in patients with HF are associated with hepatic hypoperfusion rather than hepatic congestion determined by abdominal ultrasonography and right heart catheterization, (2) selenoprotein P levels are inversely correlated with exercise capacity, and (3) higher levels of selenoprotein P are linked to adverse outcomes in patients with HF.

Although the close relationship between the heart and the kidney in the pathophysiology of HF is known as cardiorenal syndromes,[16–18] the impacts and molecular mechanisms of the link between the heart and the liver have not been fully understood. The liver is a dynamic organ that plays a central role in numerous physiological processes to maintain systemic nutrient homeostasis and also acts as an endocrine organ secreting hepatokines that regulate metabolic pathways in peripheral tissues.[7] The comparisons between the proteins of the liver and those of the corresponding plasma have been illustrated through a quantitative proteomics approach.[19] A number of hepatokines have been identified to be important contributors to metabolic diseases related to nonalcoholic fatty liver disease and insulin resistance.[9,20] In the present study, we examined hepatokine selenoprotein P as one of the hepatokines, as we have thought that selenoprotein P may be the most clinically relevant hepatokine that links to a therapeutic target among the hepatokines.[21] We demonstrated that its circulating levels were upregulated in patients

**Table 2. Correlation Analysis With Serum Selenoprotein P Levels and Other Variables in Patients With Heart Failure (n=253)**

| | Spearman's rho | *P* value |
|---|---|---|
| Age, y | 0.262 | <0.001 |
| Body mass index, kg/m$^2$ | −0.424 | <0.001 |
| Laboratory data | | |
| B-type natriuretic peptide, pg/mL | 0.465 | <0.001 |
| Troponin I, ng/mL | 0.221 | 0.001 |
| Albumin, g/dL | −0.346 | <0.001 |
| Aspartate aminotransferase, U/L | −0.046 | 0.469 |
| Alanine aminotransferase, U/L | −0.213 | 0.154 |
| Cholinesterase, U/L | −0.429 | <0.001 |
| Glucose, mg/dL | −0.054 | 0.420 |
| Hemoglobin $A_{1c}$, % | −0.093 | 0.159 |
| Insulin, μU/mL | −0.330 | <0.001 |
| Creatinine, mg/dL | −0.029 | 0.646 |
| eGFR, mL/min per 1.73 m$^2$ | −0.296 | <0.001 |
| C-reactive protein, mg/dL | 0.176 | 0.007 |
| Echocardiography | | |
| Left ventricular ejection fraction, % | 0.023 | 0.716 |
| Mitral valve E/E′ | 0.138 | 0.331 |
| Right ventricular fractional area change, % | 0.018 | 0.837 |
| Tricuspid regurgitation pressure gradient, mm Hg | 0.104 | 0.127 |
| Abdominal ultrasonography | | |
| PSV of the celiac artery, cm/s | −0.222 | <0.001 |
| SWE of the liver, m/s | −0.008 | 0.894 |
| Right heart catheterization (n=174) | | |
| Cardiac output, L/min | −0.286 | <0.001 |
| Cardiac index, L/min per m$^2$ | −0.089 | 0.253 |
| Pulmonary capillary wedge pressure, mm Hg | −0.008 | 0.918 |
| Right atrial pressure, mm Hg | −0.079 | 0.306 |
| Cardiopulmonary exercise test (n=63) | | |
| Peak oxygen consumption, mL/kg per min | −0.431 | <0.001 |
| VE/$Vco_2$ slope | 0.443 | <0.001 |

eGFR indicates estimated glomerular filtration rate; PSV, peak systolic velocity; SWE, shear wave elastography; and VE/$Vco_2$, minute ventilation/carbon dioxide production.

with HF with hepatic hypoperfusion compared with those with hepatic congestion even though HF patients with hepatic hypoperfusion exhibited some degree of hepatic congestion according to our categorization of HF. Selenoprotein P may be an important molecule linked to the pathogenesis of HF and especially implicated with persistent low perfusion of the liver.

Selenoprotein P is known to function as a protein that transports selenium from the liver to peripheral organs.[22] Recently, it was reported that selenoprotein P serves as a hepatokine that mediates with sedentary lifestyle diseases such as type 2 diabetes and obesity.[9,23] Selenoprotein P causes exercise resistance in the skeletal muscle in a receptor-dependent manner.[23] Although we found a lack of correlation between selenoprotein P levels and plasma glucose or hemoglobin $A_{1c}$ levels in HF patients of the present study, there was a negative correlation of selenoprotein P levels with insulin levels in accordance with the previous report that selenoprotein P impairs insulin secretion in pancreatic β-cells.[21] However, it is suggested that higher values of selenoprotein P in patients with HF were not attributable to the higher percentage of patients with diabetes in the HF group.

Intrahepatic hypoperfusion could be evaluated noninvasively by abdominal ultrasonographic imaging.[12] It is likely that circulating selenoprotein P is negatively regulated by hepatic tissue perfusion. Decreased hepatic blood flow induces reduced arterial oxygen delivery, which causes metabolic alteration, intracellular calcium overload, and mitochondrial damage.[1,4] Elevated levels of selenoprotein P may not simply be attributable to hepatocyte cell death, as the level was not correlated with liver enzymes such as aspartate aminotransferase in the present study. An observational study reported that selenoprotein P levels were elevated in cardiogenic shock after acute myocardial infarction and that hemodynamic changes, particularly anti-inflammatory processes resulting from organ hypoperfusion, may contribute to the increased expression of selenoprotein P.[24] Intermittent hypoxia was reported to transcriptionally upregulate selenoprotein P expressions in cultured human hepatocyte cell lines.[25] Decreased resting cardiac output may be predominantly an issue in patients with HF with reduced LVEF, but selenoprotein P levels did not differ among the different HF phenotypes such as stratification by LVEF. Although the precise regulatory mechanisms of synthesis and secretion of selenoprotein P in the liver remain to be elucidated, our data suggest that reduced hepatic perfusion that contributes to hypoxic conditions in the cells may be implicated in the upregulation of selenoprotein P expressions.

It has been reported that a general deficiency of selenoprotein P protected the heart from ischemia/reperfusion injury in mice,[26] but the function of the hepatokine selenoprotein P in the peripheral tissues is considered to be receptor dependent. Low-density lipoprotein receptor–related protein 1 (LRP1) has been reported to be one of the important receptors for selenoprotein P in peripheral tissues such as skeletal

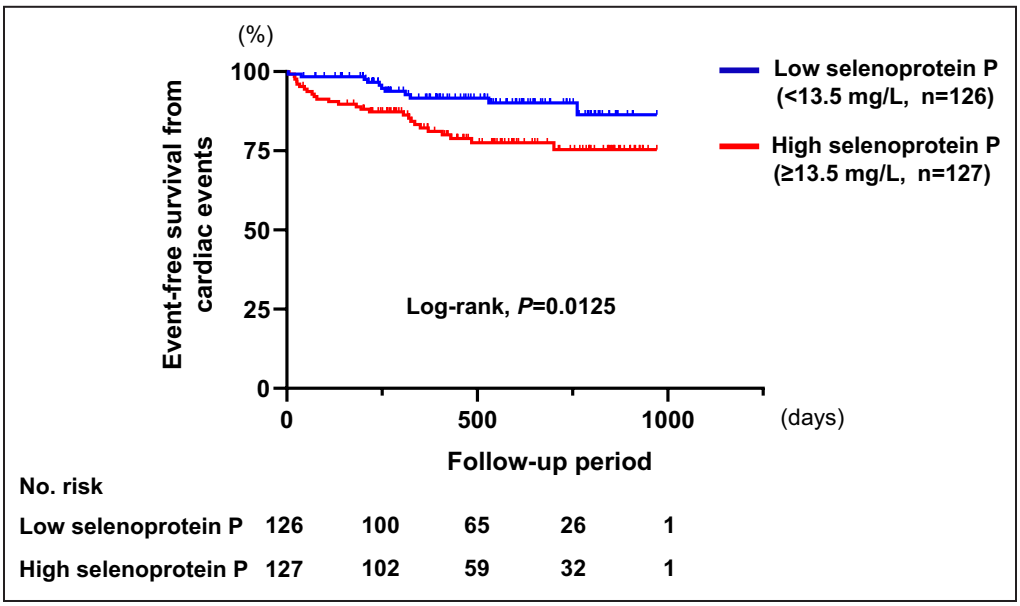


**Figure 2. Kaplan-Meier analysis for cardiac event rates stratified by serum selenoprotein P levels.**
Patients with heart failure were categorized into 2 groups according to the median value of selenoprotein P levels. During a median follow-up period of 476 days (quartile 1 to quartile 3, 270–707 days), 37 cardiac events including 9 cardiac deaths and 28 rehospitalizations because of decompensated heart failure occurred in a total of 253 patients with heart failure. The log-rank test was performed for the statistical comparison.

myocytes.[23] Cardiomyocyte-specific LRP1–deficient mice showed favorable metabolic phenotypes against high-fat diet–induced glucose intolerance and obesity,[27] suggesting that LRP1 has detrimental effects on cardiomyocytes in the metabolic model. The role of cardiac LRP1 needs to be elucidated in animal HF models. In addition, metabolic maladaptation in the skeletal muscle and exercise resistance attributable

**Table 3. Subgroup Analysis for Cardiac Events Including Cardiac Death and Worsening Heart Failure (37 Events in 253 Patients With Heart Failure)**

| Factor | Subgroup | No. | Hazard ratio (95% CI) | *P* value | Interaction *P* value |
|---|---|---|---|---|---|
| Total | … | | 2.388 (1.180–4.835) | 0.016 | … |
| Age, y | ≥71.0 | 127 | 1.532 (0.594–3.952) | 0.378 | 0.265 |
| | <71.0 | 126 | 3.414 (1.185–9.834) | 0.023 | |
| Sex | Male | 144 | 3.393 (1.369–8.409) | 0.008 | 0.234 |
| | Female | 109 | 1.406 (0.452–4.369) | 0.556 | |
| Body mass index, kg/m$^2$ | ≥22.8 | 127 | 3.493 (1.142–10.680) | 0.492 | 0.333 |
| | <22.8 | 126 | 1.393 (0.549–3.484) | 0.028 | |
| New York Heart Association | I/II | 177 | 1.881 (0.769–4.605) | 0.166 | 0.315 |
| | III/VI | 74 | 2.601 (0.747–9.056) | 0.133 | |
| Hypertension | 1 | 164 | 2.476 (0.745–8.229) | 0.139 | 0.754 |
| | 0 | 89 | 2.340 (0.977–5.603) | 0.112 | |
| Diabetes | 1 | 89 | 1.645 (0.655–4.136) | 0.290 | 0.025 |
| | 0 | 164 | 3.513 (1.145–10.776) | 0.028 | |
| Dyslipidemia | 1 | 163 | 3.008 (1.247–7.255) | 0.014 | 0.195 |
| | 0 | 90 | 1.491 (0.458–4.584) | 0.507 | |
| Chronic kidney disease | 1 | 158 | 1.915 (0.843–4.349) | 0.120 | 0.014 |
| | 0 | 95 | 3.230 (0.808–12.916) | 0.097 | |
| Atrial fibrillation | 1 | 94 | 3.224 (0.887–11.715) | 0.075 | 0.214 |
| | 0 | 159 | 2.063 (0.882–4.821) | 0.095 | |

to selenoprotein P–induced suppression of AMP-activated protein kinase phosphorylation through the LRP1 receptor[23] may in part contribute to the pathogenesis of HF.[28] Our data from cardiopulmonary exercise testing suggest that selenoprotein P is also associated with reduced exercise capacity in patients with HF. Exercise intolerance limits activities in patients with HF, which links with all-cause mortality.[29] Taken together, the vicious cycle of liver hypoperfusion and elevated levels of selenoprotein P may be causally related to the development of HF. Selenoprotein P seems to be the only hepatokine that is related to the exercise tolerance among the hepatokines, and therefore targeting selenoprotein P is potential for HF treatment to modify exercise tolerance. In addition, as it has been reported that inhibition of selenoprotein P by neutralizing antibodies improved glucose intolerance and insulin secretion,[21] the blockade of selenoprotein P is a potential therapeutic intervention for patients with HF in addition to diabetes.

Low selenium concentrations are associated with an increased risk of coronary heart diseases, but the effect of selenium supplementation on the risk is still controversial.[30] Selenoprotein P may not function solely as a selenium transporter into the cells.[9] In the general population, low concentrations of plasma selenoprotein P are related to increased cardiovascular morbidity and mortality.[31] Recently, low levels of selenoprotein P in patients with acute HF have been reported to be associated with a risk of 30-day hospitalization,[32] while high serum levels of selenoprotein P were associated with increased risks of all-cause death and lung transplantation in patients with pulmonary arterial hypertension.[33] Our data revealed that higher levels of serum selenoprotein P were associated not only with adverse cardiac outcomes but also with impaired exercise capacity, and selenoprotein P has detrimental effects in patients with HF. Although we need to clarify the causal relationship of elevated selenoprotein P levels with outcomes in patients with HF, the implementation of selenoprotein P measurement may be a notable step forward to predict the adverse outcomes in such patients with HF.

## Study Limitations

First, this was a prospective cohort study conducted at a single institution with a short follow-up period and a relatively small number of patients, which limits study power. Second, the patients were at relatively low risk of HF, and low rates of adverse events during the follow-up period were observed, so the present results might not be the representative of the general HF population. Third, although patients with organic liver diseases were excluded, we could not completely exclude the presence of liver disease. Fourth, we determined the hepatic hypoperfusion as less than the median value of 62.4 cm/s of PSV of the celiac artery according to our previous study[12] because of lack of established definition of hepatic hypoperfusion; therefore, we could not define the predictive accuracy for PSV of the celiac artery for hepatic hypoperfusion. Fifth, since right heart catheterization and cardiopulmonary exercise testing were not performed in the whole study population at the discretion of the attending physicians, there might be a potential selection bias: therefore, this study cannot exclude the risk of confounding and bias. Because the causal relationship could not be fully demonstrated because of the nature of the observational study, further studies are needed to clarify the causal relationship between elevated selenoprotein P and HF pathogenesis.

# CONCLUSIONS

Our findings demonstrate that upregulation of liver-derived selenoprotein P is associated with hepatic hypoperfusion and impaired exercise capacity and predicts adverse cardiac events in patients with HF. Selenoprotein P may be a novel target involved in cardiohepatic interactions, as well as a useful biomarker for predicting prognosis in patients with HF.

## ARTICLE INFORMATION

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### Disclosures

None.

### Supplemental Material

Table S1

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# SUPPLEMENTAL MATERIAL

**Table S1. Characteristics of patients with heart failure according to selenoprotein P levels.**

| | High selenoprotein P (≥ 13.5 mg/L, n = 127) | Low selenoprotein P (< 13.5 mg/L, n = 126) | P value |
|---|---|---|---|
| Age, years | 71.7 ± 12.1 | 65.7 ± 12.9 | < 0.001 |
| Male, n (%) | 54 (42.5) | 90 (71.4) | < 0.001 |
| Body mass index, kg/m$^2$ | 21.4 ± 3.6 | 24.5 ± 3.5 | < 0.001 |
| New York Heart Association, III/VI, n (%) | 47 (37.0) | 27 (21.4) | 0.006 |
| Etiology of heart failure | | | 0.369 |
| Valvular heart disease, n (%) | 43 (33.8) | 37 (29.3) | |
| Cardiomyopathy, n (%) | 37 (29.1) | 35 (28.3) | |
| Ischemic heart disease, n (%) | 15 (11.8) | 25 (19.8) | |
| Others, n (%) | 32 (25.1) | 29 (23.0) | |
| Laboratory data | | | |
| B-type natriuretic peptide, pg/mL | 263.1 (119.4–482.1) | 94.8 (37.7–205.9) | < 0.001 |
| Troponin I, ng/mL | 0.029 (0.017–0.088) | 0.017 (0.017–0.059) | 0.002 |
| Albumin, g/dL | 3.70 ± 0.56 | 4.01 ± 0.56 | < 0.001 |
| Aspartate aminotransferase, U/L | 23.0 (18.0–29.0) | 22.0 (18.0–27.0) | 0.438 |
| Alanine transaminase, U/L | 17.0 (12.0–27.0) | 19.0 (14.7–26.2) | 0.043 |
| Cholinesterase, U/L | 238.0 ± 77.0 | 295.5 ± 89.5 | < 0.001 |
| Glucose, mg/dL | 118.4 ± 46.3 | 117.2 ± 35.1 | 0.829 |
| Hemoglobin A1c, % | 6.0 ± 0.8 | 6.1 ± 0.9 | 0.603 |
| Insulin, μU/mL | 6.1 (3.6–9.5) | 10.3 (6.2–17.2) | < 0.001 |
| Creatine, mg/dL | 1.24 ± 0.93 | 1.02 ± 0.31 | 0.016 |
| eGFR, mL/min/1.73 m$^2$ | 48.0 ± 18.8 | 56.7 ± 15.6 | < 0.001 |
| C-reactive protein, mg/dL | 0.225 (0.090–0.582) | 0.110 (0.060–0.395) | 0.599 |
| Echocardiography | | | |
| Left ventricular ejection fraction, % | 46.3 ± 17.2 | 52.1 ± 16.4 | 0.007 |
| Mitral valve E/E' | 17.3 ± 9.6 | 14.2 ± 7.8 | 0.006 |
| Right ventricular fractional area change, % | 36.4 ± 12.4 | 35.3 ±9.3 | 0.575 |
| Tricuspid regurgitation pressure gradient, mmHg | 28.0 ± 10.9 | 27.8 ± 13.9 | 0.891 |
| Abdominal ultrasonography | | | |
| PSV of the celiac artery, cm/s | 62.5 ± 22.2 | 66.9 ± 17.7 | 0.081 |
| SWE of the liver, m/s | 1.43 ± 0.37 | 1.41 ± 0.26 | 0.619 |
| Right heart catheterization (n = 174) | | | |
| Cardiac output, L/min | 3.68 ± 0.89 | 4.27 ± 1.04 | < 0.001 |
| Cardiac index, L/min/m$^2$ | 2.45 ± 0.54 | 2.55 ± 0.55 | 0.224 |
| Pulmonary capillary wedge pressure, mmHg | 14.4 ± 7.4 | 14.6 ± 6.9 | 0.856 |
| Right atrial pressure, mmHg | 7.0 ± 4.3 | 7.2 ± 3.2 | 0.672 |
| Cardiopulmonary exercise test (n = 63) | | | |
| Peak $VO_2$ (mL/kg/min) | 13.9 ± 5.0 | 16.1 ± 4.0 | 0.055 |
| $VE/VCO_2$ slope | 37.1 ± 8.2 | 32.1 ± 5.3 | 0.002 |

Data are presented as mean ± SD, median (interquartile range), or number (percentage). eGFR, estimated glomerular filtration rate; PSV, peak systolic velocity; SWE, shear wave elastography; $VO_2$, oxygen consumption; $VE/VCO_2$, minute ventilation/carbon dioxide production.