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Original Article

A Pathophysiological Role of Plasma Indoxyl Sulfate in Patients with Heart Failure

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SUMMARY

Background: One of uremic toxins, indoxyl sulfate (IS), is associated with cardiovascular events. This study aimed to measure the plasma IS levels in patients with and without chronic heart failure (CHF).
Methods: We measured plasma IS levels in 49 patients with CHF and an estimated glomerular filtration rate (eGFR) of 40–60 ml/min/1.73 m^2 from our institute. These were compared with 31 healthy subjects without CHF (a control), but with comparable eGFR levels, from our resident cohort study. We also test the effect of AST-120 (the oral adsorbent) in 16 CHF patients.
Results: The plasma IS levels in 49 CHF patients increased (1.38 ± 0.84 (SD) vs 0.12 ± 0.07 μg/ml (a control), $p < 0.001$), and fractional shortening (FS) levels were correlated with the plasma IS levels in these subjects. Second, in our database of the hospitalized CHF patients, we retrospectively reviewed the data for eight CHF patients with stage 3–5 chronic kidney disease (CKD) who received treatment with AST-120, before and one year after treatment, and compared these patients with eight sex-matched CHF patients with stage 3–5 CKD without AST-120. AST-120 decreased plasma IS levels and improved cardiac function.
Conclusions: Plasma IS levels increased in patients with CHF along with cardiac systolic dysfunction compared with those in healthy subjects, and AST-120 improved cardiac dysfunction in patients with CHF. Oral adsorbents may represent a novel treatment for CHF.

1. Introduction

In patients with chronic heart failure (CHF), dysfunctions of other organs including kidney, liver and intestine are observed,[1] which may increase uremic toxins. Uremic toxin has a significant role in cardiovascular injury,[2] and indoxyl sulfate (IS) is perhaps the most abundant and potent uremic toxin.[3] As for the production process of IS, tryptophan in food is converted into indole by the tryptophanase enzyme of intestinal bacteria such as *Escherichia coli*. Then, indole is transferred to the liver via the enterohepatic circulation, where the indole is modulated to IS via sulfatase; the resulting IS is excreted via the kidney using organic anion transporters (OATs).[4] Therefore, malfunction at the levels of the intestine, liver, or kidney can each increase the plasma IS levels, suggesting that CHF could have caused their high plasma IS levels via increased production or decreased clearance of IS.

IS increases the expression and activation of ERK, P38MAP kinase, and NFkB, which may affect cardiac remodeling.[5,6] Furthermore, IS activates renin receptors[7] and thereby activates angiotensin receptors.[8] Either of these deleterious actions may affect cardiomyocytes, cardiac fibroblasts, and cardiac endothelial cells[9] and lead to cardiovascular dysfunction. Indeed, in patients with dilated cardiomyopathy (DCM)[10] or who underwent

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percutaneous coronary intervention,[11] plasma IS levels correlated well with the severity of left ventricular (LV) diastolic dysfunction. However, there is no clear consensus of the roles of IS in the pathophysiology of CHF. We, therefore, aimed to measure the plasma IS levels in patients with CHF and healthy controls. We also aimed to assess the CHF-related factors associated with elevated plasma IS levels, and tested whether AST-120, which adsorbs uremic toxins in the gut, could improve the pathophysiology of CHF.

2. Methods

2.1. Protocol 1

2.1.1. The study population

We prospectively included 49 consecutive patients admitted to our department for the treatment of CHF from January to December 2012. Patients were included if they had an estimated glomerular filtration rate (eGFR) of 40–60 ml/min/1.73 m^2; most patients showed a New York Heart Association (NYHA) functional class of II. Diagnosis of CHF was based on the Framingham criteria,[12] and patients were assessed if they had CHF with middle-stage chronic kidney disease (CKD) (Stage 3 CKD).[13] We sampled blood in the stable chronic phase of CHF during hospitalization. We also enrolled 31 subjects without evidence of CHF from the Arita cohort study in Japan (n = 929) as controls; they were also required to have an eGFR of 40–60 ml/min/1.73 m^2.[14,15]

2.1.2. The measurements of biomarkers

Blood was collected in ethylenediaminetetraacetate tubes; the plasma was then separated and frozen in plastic tubes at −80 °C until analysis. We measured IS levels by high-performance liquid chromatography, as previously described.[16] The Japanese-specific eGFR was calculated as [194 × Serum creatinine$^{-1.094}$ × Age$^{-0.287}$ × (0.739 for females)].[17]

2.1.3. Echocardiography

We measured and calculated the LV dimensions, left atrium volume, and LV mass index according to American Society of Echocardiography Guidelines.[18] We calculated the fractional shortening (FS) form the LV dimensions.

2.2. Protocol 2

We retrospectively investigated the effects of removing plasma IS on the severity of CHF. Of the patients with CHF with such renal dysfunction in our database of CHF patients, eight patients were found to have been treated with AST-120 for 1 year (With AST-120 group). We then tried to enroll age- and sex-matched patients, but we could not identify an appropriate set of patients. Since we could find eight sex-matched patients without AST-120 treatment, the control group consisted of the data of these eight patients (Without AST-120 group).

2.2.1. Ethics

In Protocol 1, written informed consent was obtained from all participants. This study was approved by the Institutional Ethics Committee of the National Cerebral and Cardiovascular Center and was conducted in accordance with the Declaration of Helsinki. In Protocol 2, the Committee decided that the informed consent of the 16 subjects was not required according to Japanese Clinical Research Guidelines because this was a retrospective observational study. Instead, we made a public announcement in accordance with the request of the Ethics Committee and the Guideline.

2.2.2. Statistical analysis

All data are expressed as the mean ± standard deviation. Statistical significance between two groups was evaluated by either the Student's *t*-test or Wilcoxon's rank sum test for continuous variables and by the chi-square test for categorical variables. Pearson's correlation coefficient analysis and univariate linear regression analysis were used to assess the relationships between IS levels and the other variables. All tests were 2-tailed, and $P < 0.05$ was considered significant. Analyses were performed with JMP software for Windows (version 8.0.2, SAS Inc., NC, USA).

3. Results

3.1. Protocol 1

The characteristics of the 49 included patients with CHF and the control subjects from our Arita cohort study are shown in Table 1. Plasma IS levels in patients with CHF increased compared with in patients without CHF, however there were no differences between eGFR levels of these patients. Table 2 characterizes the echocardiographic data of CHF patients and Fig. 1 shows that the plasma IS levels correlated with the FS in the CHF and control groups, but not with the ratio of mitral peak velocity of early filling to early diastolic mitral annular velocity, the ratio of the early to late ventricular filling velocities (i.e., the E/A ratio; Log E/A: r = 0.37, p = 0.093), or the deceleration time (DcT; Log DcT: r = −0.08, p = 0.609) in these subjects.

3.2. Protocol 2

Tables 3 and 4 show the patients' characteristics for the groups that received and did not receive AST-120. In contrast to the patients' characteristics of Protocol 1, they were suffered from severe renal and cardiac dysfunction as are revealed by eGFR and plasma BNP levels. Tables 3 and 4, and Fig. 2 show that AST-120 improved

Table 1
Characteristics of Control group and CHF group.

	Control group	CHF group	P value
	n = 31	n = 49	
Demographic data			
Age, yr	66 ± 8	67 ± 11	0.406
Female, n (%)	13 (42)	26 (53)	0.332
Systolic BP, mmHg	135 ± 17	109 ± 16	<0.001
Diastolic BP, mmHg	81 ± 9	64 ± 13	<0.001
HR, bpm	61 ± 8	69 ± 11	0.005
BMI, kg/m^2	23 ± 3	23 ± 4	0.917
NYHA class I, n (%)	–	6 (12)	–
NYHA class II, n (%)	–	39 (80)	–
NYHA class III, n (%)	–	4 (8)	–
Etiology			
Cardiomyopathy, n (%)	–	19 (39)	–
Valvular disease, n (%)	–	22 (45)	–
Ischemic heart disease, n (%)	–	3 (6)	–
Hypertensive heart disease, n (%)	–	4 (8)	–
Others, n (%)	–	1 (2)	–
Laboratory data			
IS, μg/ml	0.12 ± 0.07	1.38 ± 0.84	<0.001
Albumin, g/dl	4.5 ± 0.3	4.2 ± 0.4	<0.001
Hemoglobin, g/dl	13.7 ± 1.3	13.3 ± 2.0	0.423
Creatinine, mg/dl	0.98 ± 0.14	0.95 ± 0.17	0.392
eGFR, mL/min/1.73m^2	54 ± 4	53 ± 5	0.969
Uric acid, mg/dl	5.8 ± 1.2	6.9 ± 2.0	0.009
BNP, pg/ml	57 ± 193	236 ± 282	<0.001

Data are expressed as percentages, mean ± SD.
BNP = brain natriuretic peptide. BMI = body mass index. BP = blood pressure. eGFR = estimated glomerular filtration rate. IS = indoxyl sulfate. Others = corrected transposition of the great arteries.