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[Review]

Molecular mechanisms and clinical features of heart failure

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Abstract

Heart failure (HF) is a common disease with high prevalence, mortality in hospitalization and after discharge, readmission rates, and burden on healthcare system. Activation of the inflammatory systems is an important role for HF progression, and pentraxin 3 (PTX3) is one of the inflammatory markers. The plasma PTX3 levels increased with advancing the HF severity, and high levels of plasma PTX3 indicated poor prognosis in HF patients. Moreover, we demonstrated that PTX3 had the crucial role for cardiac remodeling under pressure overload using two different genotypes of mice : PTX3 systemic knockout mice and transgenic mice with cardiac-specific overexpression of PTX3.

Diuretics are the essential drug for HF treatment, and we designed multicenter, randomized study for evaluating the efficacy and safety of tolvaptan compared to carperitide. Daily urine volume and serum sodium levels were significantly higher, and cardiovascular events were significantly lower in the tolvaptan group than in the carperitide group. Moreover, we investigated the influence of great earthquake in HF patients, and found out that moving into temporary housing by earthquake might affect the incidence of re-hospitalization due to worsening HF.

In this review article, we would introduce our research on HF which has various aspects as described above.

Key words : heart failure, inflammation, diuretics, earthquake, prognosis

Introduction

Heart failure is a complex syndrome caused by structural and functional defects in the myocardium resulting in impairment of ventricular filling or ejection of blood, and is usually indicated by low cardiac output associated with signs of pulmonary and systemic congestion. Several pathogenic mechanisms that led to heart failure have previously been reported such as increased hemodynamic overload, ischemia-related dysfunction, ventricular remodeling, excessive neuro-humoral stimulation, and inadequate proliferation of the extracellular matrix. In heart failure patients, it is well-known that not only neuro-humoral factors, but also inflammatory cytokines, are activated. In this review article, we summarize our findings for the pathophysiological role of inflammation, the clinical significance of diuretics for decongestion, and the influence of huge earthquake in heart failure patients.

Pentraxin 3 and heart failure

Activation of the inflammatory system plays a pivotal role in the pathogenesis of heart failure. Many studies have demonstrated increases in circulating levels of inflammatory markers and cytokines such as C-reactive protein (CRP), tumor necrosis factor (TNF)- α and interleukin (IL)- 6^{1-4}). CRP is produced in the liver in response to the stimulation of various cytokines, mostly IL- 6^{5} , and is a member of the pentraxin superfamily. Pentraxin 3 (PTX3), which is a long pentraxin, conserves the C-terminal pentraxin domain with the classical short pentraxins

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(e.g. CRP) but differs in the presence of an unrelated long N-terminal domain. A variety of cell types can produce PTX3 upon exposure to primary inflammatory signals, such as IL-1, TNF- α , oxidized low density lipoprotein, and microbial moieties (e.g. lipopolysaccharide, lipoarabinomannans)^{6,7)}.

To examine the clinical significance of PTX3 in heart failure patients, we measured plasma PTX3 levels in 196 heart failure patients (112 men and 84 women, mean age 68.3 ± 13.3 years)⁸⁾. The plasma PTX3 concentration levels were significantly higher in the patients with heart failure than in the control subjects, and increased with advancing New York Heart Association (NYHA) functional class (P <0.0001), especially in severe heart failure patients with NYHA class III and IV (Figure 1). Next, we divided heart failure patients into two groups : normal plasma PTX3 levels (< 4.0 ng/ml, n = 102) and high plasma PTX3 levels (> 4.0 ng/ml, n = 94) based on the plasma PTX3 levels in the control subjects. The cardiac event- (including cardiac death and re-hospitalization due to worsening heart failure) free rate was significantly lower in the high PTX3 group than in the normal PTX3 group (44.7% vs. 89.2%, *P* < 0.0001, Figure 2A). Rates of cardiac death (P < 0.0001) and re-hospitalization due to worsening heart failure (P < 0.0001) were also significantly higher in the patients with high PTX3 than in those with normal PTX3 levels (Figures 2B and 2C). Cox proportional hazard regression analysis showed that plasma PTX3 level was an independent



Fig. 1. Plasma levels of PTX3 in our study population. Control subjects, NYHA functional class I, II, III, and IV. In comparison to age-matched control subjects, there was a progressive increase in plasma PTX3 levels in direct relation to decreasing heart failure functional status. We determined the normal upper limit of plasma PTX3 levels from mean + 2SD value of 60 control subjects (4.0 ng/ml, dash line). *P < 0.01 vs. control, *P < 0.01 vs. NYHA I, *P < 0.01 vs. NYHA I, *P < 0.01 vs. NYHA II



Fig. 2. Kaplan-Meier analysis for all cardiac events (A), cardiac deaths (B), and re-hospitalization (C) between patients with high and normal plasma PTX3 levels.

predictor of cardiac events⁸⁾. These data indicate that plasma PTX3 level is a promising marker that may provide useful prognostic information for clinical outcomes in patients with heart failure.

Next, we examined the molecular biological mechanism of PTX3 on heart failure progression by using two different mice genotypes : PTX3 systemic knockout (PTX3-KO) mice ; and transgenic mice with cardiac-specific overexpression of PTX3 (PTX3-TG). We induced pressure overload in these mice by using the thoracic transverse aortic constriction (TAC) technique, and evaluated cardiac



Fig. 3. Hypertrophic and fibrotic changes after TAC operation. (A) Representative histological micrographs of hematoxylin-eosin-stained and quantitative analysis of the cross-sectional areas of cardiomyocytes. (B) Masson's trichrome-stained sections of the left ventricular myocardium in PTX3-KO mice strain (left) and in PTX3-TG mice strain (right) at 2 weeks after TAC or sham operation. (C) Quantitative analysis of the fibrosis fractions at 2 weeks after TAC or sham operation, respectively (n = 8). *P < 0.01 vs levels in sham-operated mice of the same strain. Results are expressed as mean \pm SD (n = 8).

morphology, cardiac function, and cytokine expression in the mice to examine the role of PTX3 in cardiac remodeling induced by pressure overload⁹. The ratio of heart weight to body weight (HW/BW) was significantly increased after TAC in both the WT and PTX3-KO mice, and was significantly lower in the PTX3-KO mice than in the WT mice at 4 weeks after TAC. On the other hand, the HW/BW ratio was higher in the PTX3-TG mice than in the WT mice at 4 weeks after TAC. Microscopic analysis demonstrated that the cross-sectional areas of cardiomyocytes were increased in both the WT and PTX3-KO mice at 2 weeks after TAC, but this increase was significantly attenuated in the PTX3-KO mice as compared with the WT mice (P < 0.01)(Figure 3A). To confirm the effect of PTX3 on interstitial fibrosis, we performed a quantitative analysis of Masson's trichrome-stained sections (Figure 3B). The degree of myocardial fibrosis after TAC was attenuated in the PTX3-KO mice compared to the WT mice (P < 0.01) (Figure 3C). In the echocardiographic analysis, cardiac remodeling evaluated by enlargement of the left ventricular end-diastolic diameter and lowering of systolic function was suppressed in the PTX3-KO mice but progressed in the PTX3-TG mice compared to the respective WT mice (data not shown). Plasma IL-6 concentrations (Figure 4A) and myocardial IL-6 mRNA expression (Figure 4B) in all TAC-operated mice were significantly higher than those in sham-operated mice, but were lower in the TAC-operated PTX3-KO mice and much higher in the PTX3-TG mice than in the respective WT mice. In this progression of remodeling due to PTX3, phosphorylation of extracellular signal-regulated kinase1/2 (Figure 4C) and NF- κ B p65 activation (Figure 4D) played important roles. From these results, we demonstrated that PTX3 deteriorates left ventricular function and accelerates decompensated diastolic changes through ERK1/2 and NF- κ B activation under pressure overload⁹⁾.

Use of tolvaptan in the treatment of acute decompensated heart failure

In many cases of acute decompensated heart failure (ADHF), diuretics are used as the first line for reducing congestion, because patients hospitalized with ADHF almost always have symptoms of congestion¹⁰⁾. Although most ADHF patients receive intravenous loop diuretics during hospitalization¹¹⁾, there are many fatal disadvantages for diuretic therapies including electrolyte abnormalities (e.g. hypokalemia and hyponatremia), worsening of renal function, and poor $prognosis^{12-14}$. On the other hand, intravenous administration of carperitide has been used as an acute phase therapy for ADHF due to natriuretic and vasodilation effects in Japan. Several reports have revealed the efficacy and safety of carperitide in acute phase treatment and improvement of long-term prognosis^{15,16)}. Tolvaptan is a selective vasopressin V₂ receptor antagonist that produces water excretion without changes in renal hemodynamics or sodium and potassium excretion¹⁷⁾. We designed the Acute heart failure Volume



Fig. 4. Cytokine expression and intracellular signaling after TAC operation. (A) Plasma concentrations of IL-6 at 5 days after TAC or sham operation in PTX3-KO mice (left) and PTX3-TG mice (right). (B) IL-6 expression after TAC detected by quantitative PCR in PTX3-KO mice (left) and PTX3-TG mice (right). (C) (D) Increase in phosphorylation of ERK1/2 and NF- κ B after TAC operation in PTX3-KO mice (left) and in PTX3-TG mice (right). **P* < 0.01 vs sham-operated mice of the same strain. Results are expressed as mean ± SD (*n* = 8).

Control Multicenter rAndomized (AVCMA) trial, which was a multicenter, randomized study to determine the efficacy and safety of tolvaptan compared to carperitide in ADHF patients¹⁸⁾. One hundred and nine ADHF patients underwent the standard initial treatment, which included conventional loop diuretic administration, and were randomly assigned into two groups, oral administration of tolvaptan or continuous intravenous infusion of carperitide. There were no significant differences in baseline clinical characteristics between the two groups. The mean administration duration of each drug, the mean length of hospitalization, and concomitant medications were also not significantly different between the two groups (data not shown). As shown in Figure 5, urine volume was significantly higher in the tolvaptan group on Days 2 and 3 (P < 0.01); however, the volume of water intake was also greater in the tolvaptan group than in the carperitide group. The total intake volume including the infusion solution was significantly higher in the tolvaptan group from Days 1 to 4 (P < 0.01). Plasma BNP levels were similarly decreased after treatment in both groups (P < 0.001, Figure 6A). Renal function assessed by estimated glomerular filtration rate



g. 5. Comparisons of trends in urme volume and total volume of water intake (drinking water and infusion solution) between tolvaptan and carperitide groups. *P < 0.01 vs. carperitide group on the same day. T, Tolvaptan group; C, Carperitide group.

(eGFR) was not influenced by either drug (Figure 6B). The serum sodium level was significantly higher in the tolvaptan group than in the carperitide group at Days 2, 3, and 4 after treatment (P < 0.05, respectively), as shown in Figure 6C. The changes in heart rate and blood pressure between baseline and after administration of tolvaptan or carperitide are shown in Figure 7. Although the heart rate was



Fig. 6. Comparisons of trends in plasma B-type natriuretic peptide (BNP) (A), estimated glomerular filtration rate (eGFR) (B), and serum sodium level (C) between tolvaptan and carperitide groups. *P < 0.05 vs. carperitide group at the same day. *P < 0.001 vs. baseline of the same group.



Fig. 7. Comparisons of trends in blood pressure (A) and heart rate (B) during the treatment period between tolvaptan and carperitide groups. *P < 0.05 vs. carperitide group at the same day. *P < 0.05, **P < 0.01 vs. baseline of the same group.

similarly decreased after treatment in both groups (Figure 7A), changes in blood pressure were greater in the carperitide group than in the tolvaptan group (Figure 7B). Systolic and diastolic blood pressures were significantly lower in the carperitide group than in the tolvaptan group at Day 2 (P < 0.05). At Days 3 and 4, the diastolic blood pressure was significantly lower in the carperitide group than in the tolvaptan group (P < 0.05, respectively). In the present study, eight adverse events requiring drug

discontinuation occurred during the study period. In the tolvaptan group, there was only one event of hypernatremia; however, there were seven adverse events in the carperitide group. Although there was no statistically significant difference when considering all adverse events (12.7% vs. 1.9%, P = 0.060), cardiovascular events such as worsening heart failure and hypotension were significantly

higher in the carperitide group than in the tolvaptan group (10.9% vs. 0%, P = 0.027). We demonstrated that the water diuretic, tolvaptan, had a similar effect, yet was safer than the intravenous natriuretic peptide, carperitide, for the treatment of ADHF¹⁸).

ADHF patients are typically divided into two groups, based on the left ventricular systolic function : heart failure with preserved ejection fraction



Daily urine volume

Fig. 8. Comparisons of trends in urine volume between the tolvaptan and carperitide groups with heart failure and preserved ejection fraction (HFpEF) (A), and with heart failure and reduced ejection fraction (HFrEF) patients (B).



Fig. 9. Kaplan-Meier analysis for all events (A), all cardiac events (B), all cause deaths (C), and re-hospitalization (D) between the tolvaptan group and carperitide group.

(HFpEF); and heart failure with reduced ejection fraction (HFrEF). In the sub-analysis of the AVC-MA study, the daily urine volume was not significantly different between the tolvaptan and carperitide groups in HFpEF patients (Figure 8A). However, the daily urine volumes at Days 2, 3, and 4 were all significantly higher in the tolvaptan group than in the carperitide group in HFrEF patients (P< 0.05 for all) as shown in Figure 8B¹⁹.

Moreover, we compared the long-term effects of tolvaptan on cardio-renal function and prognosis with those of carperitide based on the AVCMA study²⁰⁾. All patients were followed-up for almost one year after discharge (mean 296 days, 14-400 days). Cumulative event-free rates from all events (Figure 9A), cardiac events (Figure 9B), all cause deaths (Figure 9C), and re-hospitalizations due to worsening heart failure (Figure 9D) were not significantly different between the tolvaptan and carperitide groups (all events : 72.5% vs. 72.2%, P =0.8647; cardiac events : 74.5% vs. 79.6%, P =0.4561; all cause deaths : 94.1% vs. 87.0%, P =0.3011; re-hospitalization due to worsening heart failure : 78.4% vs. 85.1%, P = 0.3362). These results suggest that tolvaptan had similar effects in terms of prognosis after discharge compared to carperitide²⁰⁾.

Effects of the Great East Japan Earthquake on heart failure in Fukushima

On March 11, 2011, the Great East Japan Earthquake hit the northeast area of Japan and, along with its subsequent tsunami, caused great damage²¹⁾. More than 15,000 lives were lost, and there were approximately 3,000 deaths related to the disaster that occurred after the event. We previously reported an increased incidence of heart failure in the wake of the Great East Japan Earthquake²²⁾. Moreover, it should be noted that the adverse effects of the Great East Japan Earthquake have been prolonged due to the resulting Fukushima Daiichi Nuclear Power Plant accident. Many residents living near the Fukushima Daiichi Nuclear Power Plant were forced to move from their own homes to temporary housing. Therefore, we examined the prognostic influence of moving into temporary housing following the Great East Japan Earthquake in patients with heart failure²³⁾.

We enrolled 743 consecutive heart failure patients who were hospitalized at Fukushima Medical University Hospital between March 11, 2011 and September 30, 2014 (mean age 68.0 years, and 450





Fig. 10. Kaplan-Meier analysis for event rate in all cardiac events (A), cardiac death (B), and re-hospitalization due to worsening heart failure (C), between heart failure patients in temporary housing and those who were not in temporary housing.

men). Among all the patients, 51 (6.9%) had moved into temporary housing. Regarding the baseline clinical characteristics, no significant differences were observed between the patients discharged to temporary housing and those discharged home. During the follow-up period, among the

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subjects who were discharged to their own home, 200 cardiac events occurred (77 cardiac deaths and 123 re-hospitalizations), and in those in temporary housing, there were 24 cardiac events (6 cardiac deaths and 18 re-hospitalizations). The incidence of cardiac events was significantly higher in the patients in temporary housing than in those who were in their own homes (47.0% vs. 28.9%, P = 0.036) as in Figure 10A. Although there was no significant difference regarding the incidence of cardiac death (Figure 10B), the incidence of re-hospitalization with worsening heart failure was significantly higher in the temporary housing group than in the nonevacuation group (35.3% vs. 17.7%, P = 0.007), as shown in Figure 10C. These results suggest that heart failure patients who moved into temporary housing should be treated carefully regarding nutrition and mental health after a large-scale disaster²³.

As mentioned above, heart failure is a complex disease, and research on heart failure has several aspects such as molecular, clinical, and epidemiological approaches. We would like to elucidate the pathological and clinical characteristics of heart failure in order to identify a novel strategy to treat heart failure through basic and clinical examinations.

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