学 位 論 文 の 要 旨

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学 位 論 文 名	Arterio-Venous Gradient of Active Interleukin-18 Is Associated with Diastolic Dysfunction: A Cross-Sectional Study
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論 文 内 容 の 要 旨

INTRODUCTION

Left ventricular (LV) diastolic dysfunction is a key pathophysiological abnormality underlying heart failure (HF) across the full spectrum of left ventricular ejection fraction (LVEF). It contributes to exercise intolerance, pulmonary congestion, hospitalization, and cardiovascular mortality. With population aging and increasing cardiometabolic disorders such as hypertension, diabetes mellitus, obesity, and chronic kidney disease, the burden of diastolic dysfunction and heart failure with preserved ejection fraction (HFpEF) is steadily rising. Despite its clinical importance, the molecular and inflammatory mechanisms driving diastolic dysfunction and myocardial stiffening remain incompletely understood. Chronic low-grade inflammation is recognized as a critical contributor to myocardial remodeling and ventricular stiffening.

Among inflammatory mediators, interleukin-18 (IL-18) and interleukin-6 (IL-6) have gained attention. IL-18 is synthesized as an inactive precursor and becomes active through inflammasome-dependent cleavage triggered by oxidative stress and mechanical strain. Experimental studies show that IL-18 promotes myocardial fibrosis and impairs diastolic relaxation, whereas IL-18 suppression mitigates remodeling. Clinically, elevated IL-18 levels have been observed in pressure-overload hypertrophy and chronic HF. IL-6 is similarly associated with myocardial fibrosis, renal dysfunction, congestion, and adverse prognosis. However, most clinical studies assess cytokines in peripheral venous blood, reflecting systemic inflammation rather than local cardiopulmonary cytokine activation. Whether IL-18 or IL-6 exhibit measurable arterio-venous (A/V) gradients across the heart and lungs—and whether such gradients relate to LV diastolic dysfunction—remains unclear. Because pulmonary vasculature is subjected to oxidative and mechanical stress, trans-cardiopulmonary cytokine gradients may

offer unique insights into inflammation-driven myocardial remodeling.

Therefore, this study investigated whether the A/V gradient of active IL-18 (aIL-18) and IL-6 is associated with echocardiographic indices of LV diastolic dysfunction in patients undergoing diagnostic cardiac catheterization. To further explore biological plausibility, in vitro experiments were performed to evaluate the direct profibrotic effects of aIL-18 on human cardiac fibroblasts.

MATERIALS AND METHODS

This cross-sectional study included 87 adult patients who underwent diagnostic cardiac catheterization at Shimane University Hospital between August 2021 and January 2023. Patients on maintenance hemodialysis were excluded. The study protocol was approved by the Research Ethics Committee of Shimane University. Clinical data, laboratory findings, and medication use were collected from medical records. Transthoracic echocardiography was performed during the same admission, and diastolic function was assessed using average E/e′ and tricuspid regurgitation pressure gradient (TRPG). HFpEF was defined as LVEF ≥ 50% and an HFA-PEFF score ≥ 5. Arterial blood samples were obtained from the LV or ascending aorta, and venous samples were collected from a peripheral vein. Paired samples were available in 85 patients. Serum concentrations of aIL-18 and IL-6 were measured by ELISA, and A/V ratios were calculated. For in vitro experiments, human cardiac fibroblasts were treated with aIL-18 (1–100 ng/mL). Cell proliferation was assessed by BrdU incorporation, and expression of collagen type I alpha 1 (COL1A1) and α-smooth muscle actin (α-SMA) was evaluated by Western blotting. Statistical analyses included correlation and multivariable regression analyses with adjustment for major clinical covariates. A p-value < 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

The study cohort was elderly, with a mean age of 73.6 years, and 64% were male. Hypertension and diabetes mellitus were present in 86% and 31% of patients, respectively. Most patients exhibited preserved systolic function, with a mean LVEF of 57.4%, while echocardiography demonstrated impaired relaxation and elevated filling pressures, with a mean E/e′ of 13.0. Structural remodeling, including increased LV wall thickness and left atrial enlargement, was also frequently observed, and approximately half of the cohort fulfilled diagnostic criteria for HFpEF based on the HFA-PEFF score. Mean arterial and venous concentrations of aIL-18 were 445.6 and 488.6 pg/mL, respectively. The aIL-18 A/V ratio averaged 1.06, and 54% of patients exhibited ratios greater than 1, indicating higher arterial than venous concentrations and suggesting net cytokine activation or release within the cardiopulmonary circulation in a substantial proportion of patients. IL-6 showed a broader A/V distribution, with a mean ratio of 1.16. Arterial IL-6 correlated positively with arterial aIL-18, whereas venous levels and A/V ratios were not correlated, indicating distinct regulatory mechanisms for systemic versus local cytokine activation.

Absolute arterial or venous aIL-18 concentrations were not significantly associated with echocardiographic indices of diastolic function. In contrast, the aIL-18 A/V ratio showed a

significant positive correlation with both average E/e′ and TRPG, indicating that a higher trans-cardiopulmonary gradient of aIL-18 was associated with elevated LV filling pressure and pulmonary pressure. These associations were particularly strong in patients with aortic stenosis and in those with markedly elevated E/e′, suggesting that mechanical loading and filling pressure may amplify IL-18–related inflammatory signaling. The aIL-18 A/V ratio also correlated with the HFA-PEFF score and was higher in patients meeting diagnostic criteria for HFpEF. In multivariable regression analyses, the aIL-18 A/V ratio remained independently associated with average E/e′ after adjustment for age, sex, body mass index, smoking status, diabetes, hypertension, and renal function, whereas the association with TRPG was attenuated after full adjustment for renal indices. These findings indicate that the trans-cardiopulmonary gradient of IL-18 provides pathophysiological information beyond systemic cytokine concentrations and is closely linked to LV diastolic loading conditions.

In contrast to IL-18, IL-6 concentrations were significantly associated with renal impairment and reduced pulmonary function but showed no significant relationship with E/e′ or TRPG, and the IL-6 A/V ratio was not associated with diastolic indices. These observations suggest that IL-18 and IL-6 reflect distinct organ-specific inflammatory processes in patients with cardiovascular disease.

In vitro experiments demonstrated that aIL-18 significantly enhanced human cardiac fibroblast proliferation and upregulated COL1A1 expression, whereas α-SMA expression remained unchanged. These results indicate that aIL-18 directly stimulates fibroblast proliferation and collagen synthesis, supporting a profibrotic role of IL-18 in myocardial remodeling and ventricular stiffening. From a mechanistic perspective, the pulmonary vasculature represents a plausible site of IL-18 activation, as oxidative stress during oxygenation and mechanical stretch under elevated filling pressures can trigger inflammasome activation in endothelial cells and macrophages. The observed association between the aIL-18 A/V gradient and diastolic dysfunction supports the concept that pulmonary vascular inflammation may contribute to myocardial remodeling via cytokine-mediated signaling within the cardiopulmonary circuit.

This study has several limitations. Because of its cross-sectional design, causal relationships cannot be established. Arterial and venous sampling was not always simultaneous, and echocardiographic indices were used instead of invasive hemodynamics. In addition, this was a single-center study with a heterogeneous population, which may limit generalizability.

CONCLUSION

The arterio-venous gradient of active IL-18 is independently associated with LV diastolic dysfunction, particularly in patients with elevated filling pressures and afterload. These results indicate that local IL-18 activation within the cardiopulmonary circulation reflects inflammatory and fibrotic processes linked to diastolic dysfunction, beyond what is captured by systemic cytokine levels alone. IL-18 may therefore serve not only as a biomarker but also as a potential mechanistic mediator of myocardial remodeling in pressure-stressed heart failure phenotypes.