Cardiac hypertrophy is suppressed by reducing uremic toxins at the early stage of chronic kidney disease.

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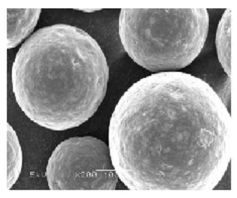
Introduction

- Patients with chronic kidney disease (CKD) generally have higher risk of complications including cardiovascular disease than the general population.

  Left ventricular hypertrophy is a well-known feature of renal disease, but this mechanism remains unsolved.

➢ Recently, AST-120, which is used for the treatment of CKD, has been reported to prevent the progression of cardiac damage in CKD model rats[*1] and patients[*2, 3].

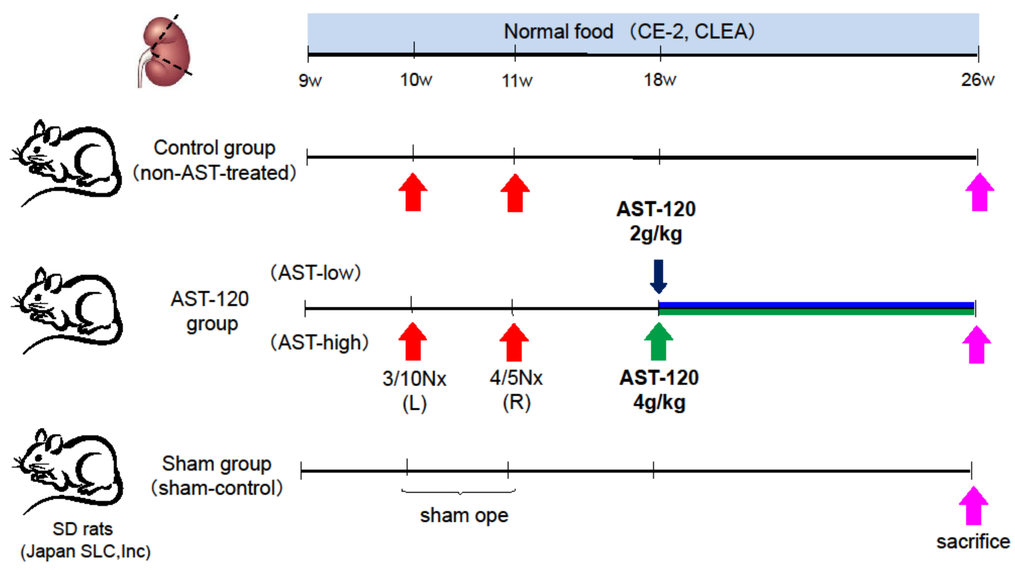


AST-120

Objectives

We confirmed the correlation between cardiac hypertrophy and serum levels of uremic toxins that are the target of AST-120 action.

Method – animal study



Results

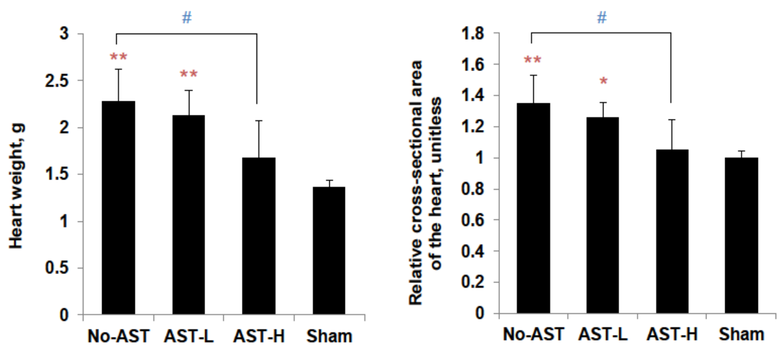


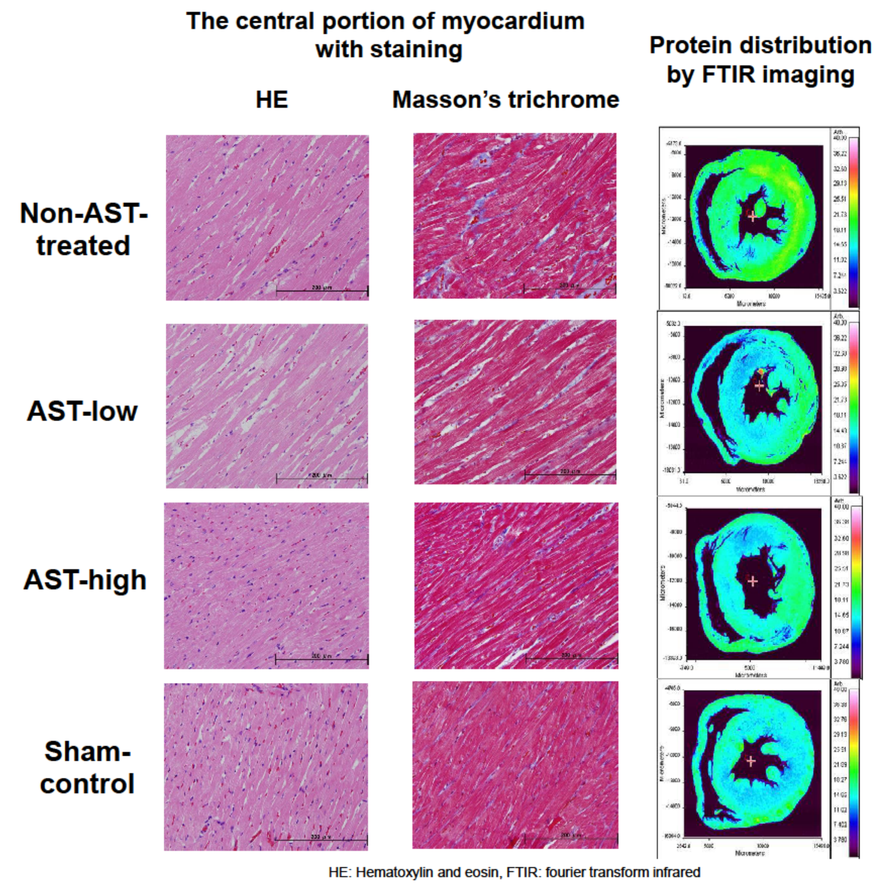
Fig.1 Heart weight and cross sectional area of the heart in CKD and sham rats

The cross sectional area is the part where the largest cut surface is provided under the right atrium.

No-AST: non-AST-treated group
AST-L: AST-low group
AST-H: AST-high group
Sham: sham-control group

vs Sham group ; ** :p<0.01, * :p<0.05,
vs No-AST group ; # :p<0.05,
by Dunnett's test

- Heart weight and the cross sectional area of the heart in non-AST-treated group were significantly greater than in sham-control group, and these were reduced in AST-high group. (Fig.1)
- The width of myocardium fiber was increased in non-AST-treated and AST-low rats compared to sham-control rats. (HE staining of the central portion of myocardium)
- The amount of protein was increased in non-AST-treated group in comparison with AST-low, AST-high and sham-control groups (protein distribution by FTIR imaging), but myocardial fibrosis was not obviously detected in all rats. (Masson's trichrome staining of the central portion of myocardium)
- The difference was observed between non-AST-treated group and sham-control group in several biochemical parameters, but no significant differences except serum uremic toxin levels among non-AST-treated, AST-low and AST-high groups.(Table.1 and 2)



HE: Hematoxylin and eosin, FTIR: fourier transform infrared

Table.1 Animal characteristics, 26w

	Non-AST-treated (n=5)	AST-low (n=6)	AST-high (n=4)	Sham-control (n=6)
Body weight, g	540.4±22.9	528.7±56.1	521.7±39.4	538.9±30.6
SBP, mmHg *4	**163.0±26.5** **	**149.2±20.7** *	**146.4±17.6**	**115.5±7.9**
CCr, mL/min	1.58±0.15 **	1.44±0.54 **	1.79±0.92 **	4.48±0.42
Serum Cr, mg/dl	0.96±0.11 **	1.08±0.30 **	0.96±0.54 **	0.29±0.03
BUN, mg/dl	62.8±5.9 **	67.8±12.6 **	64.7±24.2 **	20.9±0.6
Serum P, mg/dl *5	**6.0±0.6**	**6.4±0.5**	**6.4±0.7**	**5.9±0.3**
Serum Ca, mg/dl	9.8±0.1	9.9±0.1	9.9±0.2	9.8±0.2
PTH, pg/ml *6	**1040.5±360.5**	**1578.1±996.0**	**1689.2±1908.3**	**292.7±109.3**
FGF23, μg/ml *7	**674.1±114.9**	**1035.5±656.4**	**1458.5±1185.2** *	**292.7±109.3**
Hb, g/dl *8	**13.8±0.6** **	**13.2±0.6** **	**13.3±1.0** **	**16.1±0.3**
Urinary protein, mg/dl	168.3±55.6 *	215.7±106.0 **	159.1±141.9 *	12.4±3.8

SBP: systolic blood pressure, CCr: creatinine clearance, Cr: creatinine, BUN: blood urea nitrogen, P: inorganic phosphorus, Ca: calcium, PTH: parathyroid hormone, FGF23: fibroblast growth factor 23, Hb: hemoglobin.

* :parameters written in bold letters were reported to be associated with cardiac hypertrophy

Table.2 Animal characteristics (serum uremic toxins, 26w)

	Non-AST-treated (n=5)	AST-low (n=6)	AST-high (n=4)	Sham-control (n=6)
Creatinine (Cr), mg/dl	0.96±0.11 **	1.08±0.30 **	0.96±0.54 **	0.29±0.03
Indoxyl sulfate (IS), mg/dl	0.46±0.04 **	0.28±0.11 **##	0.12±0.05 ##$$	0.10±0.03
p-Cresyl sulfate (PCS), μg/dl	4.60±1.67 **	3.00±1.10	0.75±0.96 ##$	1.33±0.47
p-Cresyl glucuronide (PCG), μg/dl	11.60±7.64 **	6.33±3.56	1.75±0.96 $$	1.33±0.52
Hippuric acid (HA), mg/dl	0.60±0.13 **	0.49±0.23 *	0.22±0.15 ##$	0.17±0.06

- Strong positive correlations were observed between cross sectional area of hearts and serum levels of uremic toxins. (Fig.2)
- From the degree of cardiac hypertrophy in AST-low group (Fig.1), it could be thought that the values of serum PCS and HA levels relate to the degree of hypertrophied heart. (Fig.2 and 3)

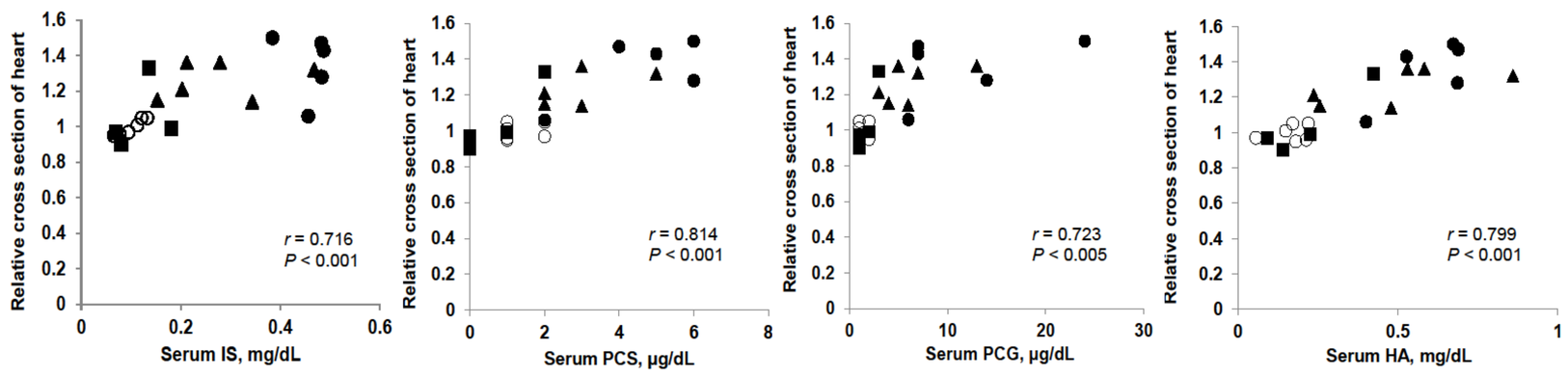


Fig.2 Correlation between cardiac hypertrophy and uremic toxins

●:non-AST-treated, ▲:AST-low, ■:AST-high, ○:sham-control

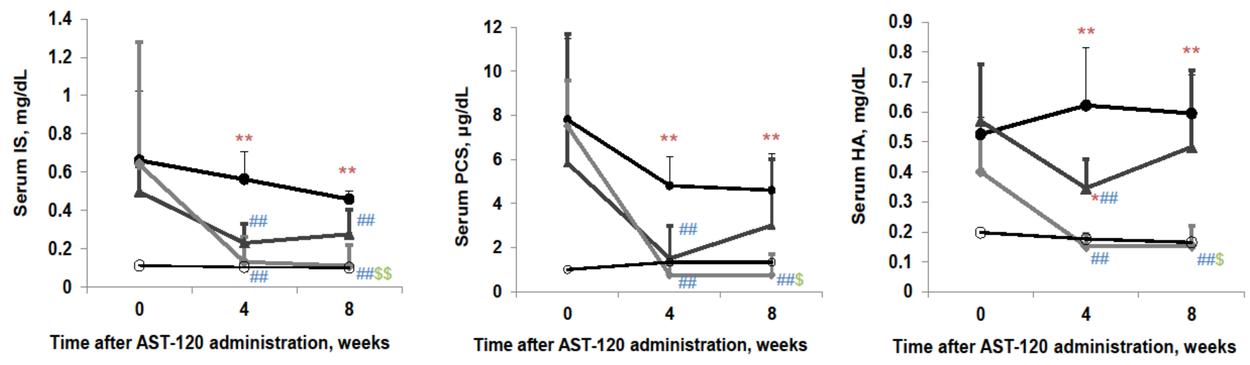


Fig.3 Changes of serum uremic toxin levels during experimental period

●:non-AST-treated, ▲:AST-low, ■:AST-high, ○:sham-control

vs sham-control group ; ** :p<0.01, * :p<0.05, vs non-AST-treated group ; ## :p<0.01,
vs AST-low group ; $$:p<0.01, $:p<0.05 by Dunnett's test

Conclusions

There is a possibility that some serum uremic toxins (PCS, HA) may be involved in cardiac hypertrophy at the stage of moderate renal function impairment.

It is necessary to continue maintaining the amount of these uremic toxins at the same level of normal condition for the suppression of cardiac hypertrophy in CKD.

References

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