Hormonal and Cardiorenal Responses to Acute Saline Loading in Mild Congestive Heart Failure

— The Effect of Angiotensin Converting Enzyme Inhibition —

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We investigated cardiorenal responses to acute saline loading in patients with mild congestive heart failure (CHF) with and without angiotensin-converting enzyme (ACE) inhibition. Saline loading (infusion of 250 ml of normal saline) was performed on 10 patients with mild CHF and 10 control subjects. Although saline loading reduced plasma renin activity and plasma angiotensin II to a similar extent in both groups, it increased cardiac output, renal blood flow, and the ratio of renal blood flow to cardiac output in the mild CHF group but not in the control group. After saline loading, urinary sodium excretion was higher in the control than in the mild CHF group. In the mild CHF group, saline loading was performed again after an ACE inhibitor (delapril) had been administered for 5 days. Although delapril increased cardiac output and renal blood flow under basal conditions, saline loading did not affect these variables. Delapril improved urinary sodium excretion after saline loading. Thus, the renin-angiotensin-aldosterone axis may contribute to cardiorenal hemodynamics and renal sodium handling in patients with mild CHF. This effect may attenuate the natriuretic response to acute saline loading, and administration of an ACE inhibitor improves this attenuation.

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Key Words: Mild heart failure; Natriuresis; Angiotensin-converting enzyme inhibitor; Renin-angiotensin system; Renal function

It is well known that congestive heart failure (CHF) is characterized by impaired sodium and water handling^{1,2}. Therefore, management of the sodium-water balance is a key element in the treatment of CHF^{1,3,4} and the kidney plays a major role in maintaining this balance. Although the reduction in cardiac output in CHF affects renal function, the activation of several neurohormonal mechanisms also affects renal function and sodium-water balance^{2,4,5}. Some studies have already examined the renal pathophysiology of CHF, and found that the activation of several neurohormonal mechanisms contributes to reduced renal blood flow and glomerular filtration rate and increased filtration fraction in CHF^{3–6}. In particular, the renin-angiotensin system (RAS) is thought to play an important role in the pathophysiology of CHF, including

the regulation of sodium and water balance^{4,6,7}. Angiotensin-converting enzyme (ACE) inhibitors are known to have a favorable effect on mortality in patients with CHF^{8,9} and the AHA/ACC task force recommends the use of ACE inhibitors as the first choice for the management of mild CHF¹⁰. Although experimental studies have demonstrated the beneficial effects of ACE inhibitors on the regulation of sodium-water balance in early heart failure^{11,12}, no conclusion has been reached on whether ACE inhibitors exert beneficial effects on sodium and water handling in patients with mild CHF. The examination of sodium and water handling in patients with CHF has various limitations in a clinical setting. The assessment of natriuretic response to saline infusion, however, is an alternative approach to investigating sodium and water

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handling.^{13,14} Volpe et al¹⁵ reported beneficial effects of ACE inhibitors on cardiovascular hemodynamic and natriuretic responses to saline loading in patients with mild CHF. Whereas glomerular filtration rate, renal blood flow, renal tubular function, and renal perfusion pressure all contribute to natriuresis, the details of the beneficial effects of ACE inhibitors on natriuresis in patients with mild CHF remain obscure. In the management of CHF based on understanding pathophysiological situations, the details of those beneficial effects should be clarified. Some studies^{14,16} have suggested that, in addition to the RAS, atrial natriuretic peptide (ANP) is important in asymptomatic left ventricular dysfunction or mild heart failure, and the relationship between hormonal responses (including the renin-angiotensin-aldosterone axis and ANP) and changes in cardiorenal hemodynamics and renal function in response to saline loading has not been elucidated.

The present study was intended to clarify the importance of the renin-angiotensin-aldosterone axis and the detailed cardiorenal effects of ACE inhibitors in the regulation of sodium and water balance in patients with mild CHF. Examination of sodium and water handling along with changes in cardiorenal hemodynamics, renal function, and hormonal systems in response to saline loading before and after administration of an ACE inhibitor was therefore performed in patients with mild CHF.

Methods

Subjects

Ten patients (8 men and 2 women; mean age 52 ± 11 years) with mild CHF (NYHA class II: dilated cardiomyopathy in 7 patients and ischemic heart disease in 3 patients), and 10 age-matched control subjects (7 men and 3 women; 50 ± 8 years) were admitted to Teikyo University School of Medicine Ichihara Hospital for cardiac catheterization; none of them had significant stenosis of coronary arteries and all had a normal left ventriculogram. All patients with mild CHF had an ejection fraction of $<40\%$ on radionuclide ventriculography. Eight patients were receiving digoxin 0.25 or 0.125 mg/day and 4 were taking furosemide 40 mg/day.

Study Design

After hospitalization, informed consent was obtained from all subjects based on a protocol approved by the Ethics Committee of Teikyo University School of Medicine Ichihara Hospital. During hospitalization, water intake was restricted

to 1000 ml/day, and furosemide was discontinued if it had been prescribed. Subjects were maintained on a daily diet containing 120 mmol/L of sodium and 60 mmol/L of potassium for 3 days. Thereafter, they were switched to a sodium-restricted diet (85 mmol/L of sodium and 60 mmol/L of potassium). Body weight and 24-h urine volume were measured every day and daily 24-h urine samples were analyzed for sodium and potassium excretion for the duration of the sodium-restricted diet.

Saline loading was performed on the 5th day of the sodium-restricted diet. More precisely, at 21.00 h on the 4th day of the sodium-restricted diet, a 5% glucose solution was infused via an intravenous line in the left forearm at a rate of 30 ml/h. At 01.00 h on the 5th day, the solution was changed to a 5% glucose solution containing para-aminohippuric acid (60 mg/ml) and infused at 30 ml/h throughout the experiment. At 06.00 h on the 5th day, subjects were asked to excrete urine completely and then to remain in the supine position. A heparin-lock catheter system was inserted into an antecubital vein in the right forearm. Two hours later (08.00 h), blood samples were taken and baseline urine was obtained for the determination of urine volume and sodium, potassium, creatinine, and para-aminohippuric acid excretions. Thereafter, a 1.0% saline infusion was started at a rate of 220 ml/h for 1 h. Blood and urine samples were collected at 09.00 and 10.00 h. Plasma renin activity, angiotensin II, aldosterone, ANP, vasopressin, norepinephrine, angiotensin-converting enzyme activity, sodium, potassium, creatinine, and para-aminohippuric acid were measured from the blood samples taken at 08.00 and 09.00 h. Only sodium, potassium, creatinine, and para-aminohippuric acid levels were measured from the blood sample taken at 10.00 h. Blood pressure was measured at 20-min intervals using a sphygmomanometer. Cardiac output was determined at 08.00 and 09.00 h by the pulsed-Doppler technique using an echocardiograph equipped with a 2.5-MHz transducer (SSH-140, Toshiba, Tokyo).¹⁷ Heart rate was monitored through an electrocardiographic monitoring system attached to the echocardiographic apparatus. In patients with mild CHF, oral administration of an ACE inhibitor (delapril 7.5 mg twice a day, Takeda, Osaka) was initiated on the 7th day of the sodium-restricted diet, and saline load testing was performed again on the 11th day.

Blood and Urine Sample Analyses

Radioimmunoassay methods were used for measuring plasma renin activity (Gamma-Cortorenin, Travenol, USA), as well as angiotensin II (Angioten-

sin II kit, SRL), aldosterone (Spack-S, Aldosterone-kit, Daiichi-Radioisotope, Japan), ANP (Sionoria-ANP kit, Shionogi, Japan), and vasopressin (AVP-RIA kit, Mitsubishi, Japan). Plasma norepinephrine was determined by high-performance liquid chromatography with electrochemical detection. Plasma angiotensin-converting enzyme activity was determined by photometric methods (ACE-color, Fuji-ebio, Japan). Plasma and urinary para-aminohippuric acid were measured using colorimetric methods. Sodium, potassium, and creatinine were measured by standard laboratory methods using fresh samples of blood and urine. Renal creatinine clearance was used as a measure of glomerular filtration rate, and renal clearance of para-aminohippuric acid was used as a measure of effective renal plasma flow. Renal blood flow was derived as [renal plasma flow/(1-hematocrit)]. The filtration fraction was calculated as the ratio (glomerular filtration rate/renal plasma flow) $\times 100$. Renal to systemic blood flow ratio was obtained as (renal blood flow/cardiac output) $\times 100$.

Statistical Analysis

Data are expressed as means $\pm$ SD. Statistical analyses were performed using the SPSS software package (SPSS, Chicago, IL, USA). Differences between 2 groups were evaluated by Wilcoxon's test. Within-group comparisons were performed by Student's *t* test. In the analysis of 24-h urinary sodium excretion, urinary excretion on the 4th day of the sodium-restricted diet was used as a control and values for each day from the 5th to the 11th day were compared with this control value using Student's *t* test adjusted by Bonferroni's method. A level of $p < 0.05$ was accepted as statistically significant.

Results

Table 1 depicts the clinical characteristics of patients with mild CHF and control subjects. Table 2 depicts plasma levels of neurohormonal factors before and after saline loading in control subjects and in patients with mild CHF with and without an ACE inhibitor. Under basal conditions in the saline loading test, only the plasma ANP level was higher in patients with mild CHF than that in control subjects. In control subjects, saline loading increased plasma ANP and significantly decreased plasma renin activity, plasma angiotensin II, and vasopressin levels. In patients with mild CHF, saline loading decreased plasma renin activity, angiotensin II, and vasopressin levels but did not affect plasma ANP. Saline loading did not affect plasma aldosterone or norepinephrine levels in either

Table 1 Characteristics of Patients With Mild CHF and Control Subjects

	CHF patients	Control subjects	<i>p</i> value
Age (years)	52 $\pm$ 11	50 $\pm$ 8	ns
Gender (M/F)	8/2	7/3	ns
Height (cm)	160 $\pm$ 10	158 $\pm$ 8	ns
Weight (kg)	60 $\pm$ 11	57 $\pm$ 10	ns
SBP (mmHg)	119 $\pm$ 14	120 $\pm$ 18	ns
DBP (mmHg)	74 $\pm$ 8	70 $\pm$ 9	ns
HR (beat/min)	72 $\pm$ 10	61 $\pm$ 6	$p < 0.05$
Creatinine (mg/dl)	1.0 $\pm$ 0.1	0.8 $\pm$ 0.1	ns

Abbreviations: CHF, mild congestive heart failure; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

group. The administration of an ACE inhibitor to patients with mild CHF for 5 days significantly reduced plasma ACE activity (from 28 ± 10 to 5 ± 2 IU/ml), plasma angiotensin II, and plasma aldosterone.

Table 3 depicts changes in cardiorenal hemodynamics and renal function as a result of the saline loading in control subjects and in patients with mild CHF with and without an ACE inhibitor.

Under basal conditions in the saline loading test, cardiac output, renal blood flow, glomerular filtration rate, and renal to systemic blood flow ratio were lower and the filtration fraction was higher in patients with mild CHF than in control subjects. Saline loading increased cardiac output, renal blood flow, and renal systemic blood flow ratio only in patients with mild CHF. Saline loading did not affect blood pressure, glomerular filtration rate, or the filtration fraction in either group. Although saline loading increased urinary sodium excretion in both groups, the amounts of urinary sodium excretion during saline loading (08.00–09.00 h) and after saline loading (09.00–10.00 h) were greater in control subjects than in patients with mild CHF.

The administration of an ACE inhibitor decreased blood pressure (from $119 \pm 14/74 \pm 8$ to $110 \pm 12/70 \pm 10$ mmHg, $p < 0.01$) and increased cardiac output and renal blood flow, but did not affect glomerular filtration rate, renal to systemic blood flow ratio, and the filtration fraction. Saline loading did not affect cardiac output or renal blood flow. However, after the administration of an ACE inhibitor, the amounts of urinary sodium excretion during saline loading (08.00–9.00 h) and after saline loading (09.00–10.00 h) were greater than that observed before drug administration.

Fig 1 depicts the changes in daily urinary sodium excretion. Saline loading increased 24-h urinary sodium excretion significantly, but the administration of an ACE inhibitor did not affect this parameter.

Table 2 Plasma Levels of Hormonal Factors Before and After Saline Loading in Control Subjects and in Patients With Mild CHF With and Without an ACE Inhibitor

		CHF	CHF+ACEi	Control subjects
PRA (ng/ml per h)	Pre	3.4±2.8	5.9±3.8 ^{††‡}	1.5±0.9
	Sal	2.8±1.7*	5.0±2.6 ^{††‡}	1.1±0.7*
Ang II (pg/ml)	Pre	26±8	12±4 ^{†‡‡}	20±9
	Sal	20±9*	11±5 ^{†‡‡}	15±5*
Aldo (pg/ml)	Pre	138±74	112±58 [‡]	88±41
	Sal	125±73	101±51 [‡]	77±44
ANP (pg/ml)	Pre	35±17 [†]	33±20 [†]	17±12
	Sal	38±26	35±18	22±13*
ADH (pg/ml)	Pre	1.3±0.3	1.1±0.3	0.9±0.2
	Sal	1.0±0.3*	0.9±0.2*	0.6±0.2*
NEP (pg/ml)	Pre	305±229	278±252	228±148
	Sal	296±198	282±201	210±158

Abbreviations: CHF, patients with mild CHF before ACE inhibitor administration; CHF+ACEi, patients with mild CHF during ACE inhibitor administration; PRA, plasma renin activity; Ang II, plasma angiotensin II level; Aldo, plasma aldosterone level; ANP, plasma ANP level; ADH, plasma vasopressin level; NEP, plasma norepinephrine level; Pre, before saline loading; Sal, after saline loading; **p*<0.05 compared with values before saline loading; [†]*p*<0.05 compared with control value; ^{††}*p*<0.01 compared with control value; [‡]*p*<0.05 compared with CHF value; ^{‡‡}*p*<0.01 compared with CHF value.

Table 3 Changes in Cardiorenal Hemodynamics and Renal Function Before and After Saline Loading in Control Subjects and in Patients With Mild CHF With and Without an ACE Inhibitor

		CHF	CHF+ACEi	Control subjects
CO (L/min)	Pre	2.7±0.3 ^{††}	3.0±0.3 ^{††‡}	4.8±0.5
	Sal 1	2.9±0.3 ^{*††}	3.1±0.3 ^{††}	4.9±0.5
	Sal 2	2.8±0.3 ^{††}	3.0±0.3 ^{††}	4.8±0.5
RBF (ml/min)	Pre	387±141 ^{††}	443±168 ^{††‡}	901±165
	Sal 1	424±135 ^{*††}	463±157 [†]	894±137
	Sal 2	410±151 ^{††}	448±121 ^{††}	887±164
R/C (%)	Pre	13.4±1.8 ^{††}	14.5±1.8 ^{††}	18.2±1.8
	Sal 1	14.9±2.1 ^{*†}	14.4±2.6 [†]	18.9±2.0
	Sal 2	14.6±1.8 ^{††}	14.4±1.9 [†]	18.2±2.1
GFR (ml/min)	Pre	72±32	77±34	101±22
	Sal 1	82±36	79±33	110±36
	Sal 2	79±31	82±37	108±31
FF (%)	Pre	31±10 [†]	29±12 [†]	19±11
	Sal 1	32±11 [†]	29±11 [†]	20±12
	Sal 2	32±11 [†]	30±11 [†]	21±12
UNa (μmol/min)	Pre	27.8±11.8	30.5±11.8	28.5±13.9
	Sal 1	42.3±12.5 ^{*††‡}	65.0±14.0 ^{*††‡}	86.1±14.3 ^{**}
	Sal 2	49.7±12.3 ^{*††}	66.9±10.9 ^{*††}	68.4±14.4 ^{*†}

Abbreviation: CHF, patients with mild CHF before ACE inhibitor administration; CHF+ACEi, patients with mild CHF during ACE inhibitor administration; CO, cardiac output; RBF, renal blood flow; R/C, renal to systemic blood flow ratio; GFR, glomerular filtration rate; FF, the filtration fraction; UNa, urinary sodium excretion rate; Pre, before saline loading; Sal 1, during saline loading (from 08.00 to 09.00 h); Sal 2, after saline loading (from 09.00 to 10.00 h); **p*<0.05 and ***p*<0.01 compared with values baseline conditions in the saline test; [†]*p*<0.05 compared with control value; ^{††}*p*<0.01 compared with control value; [‡]*p*<0.05 compared with CHF value; ^{‡‡}*p*<0.01 compared with CHF value.

Fig 1. Daily changes in 24-h urinary sodium excretion. Open circle, patients with mild CHF prior to ACE inhibitor administration; closed circles, patients with mild CHF during ACE inhibitor administration; open squares, controls; * $p < 0.05$ compared with the 24-h urinary sodium excretion on the 4th day of the sodium-restricted diet; $\uparrow$ indicates the day saline loading test was performed.

Body weight did not change significantly throughout the experiment.

Discussion

Renal Hemodynamics in Patients With Mild CHF

Redistribution of regional blood flow including a reduction in renal blood flow in CHF has been demonstrated⁵⁻⁷ and activation of circulating and tissue hormonal and neurohormonal systems is thought to play a pivotal role in maintaining tissue and organ perfusion^{2,4}. Creager et al¹⁸ suggested that the RAS affects the redistribution of regional blood flow in severe CHF. However, it has not been clear whether the redistribution of regional blood flow is recognized even in patients with mild CHF. The present study demonstrated the redistribution of regional blood flow, the decrease in the renal to systemic blood flow ratio and increase in the filtration fraction in patients with mild CHF.

In normal subjects, saline loading did not affect cardiorenal hemodynamics or the plasma norepinephrine level except by increasing plasma ANP and decreasing plasma renin activity, angiotensin II, and vasopressin levels. These results are compatible with those of previous investigators^{13,14}. In patients with mild CHF, although plasma ANP did not increase, saline loading decreased plasma renin activity, angiotensin II, and vasopressin levels, accompanied by an increase in renal blood flow, cardiac output, and the renal and systemic

blood flow ratio. Thus, acute saline loading promoted different cardiorenal hemodynamic adaptations in normal subjects compared with patients with mild CHF. Although Volpe et al¹⁵ did not evaluate renal hemodynamics, they reported similar hormonal responses, except for the elevation of the plasma norepinephrine level and the impairment of cardiac adaptations to excessive saline and water loading in patients with mild CHF. The differences in sodium-restricted conditions and the amount of saline loading might contribute to the differences in hormonal and hemodynamic responses in both studies. The administration of an ACE inhibitor for 5 days decreased plasma angiotensin II level and increased both cardiac output and renal blood flow under basal conditions and blunted extents of both blood flows during saline loading. The present results suggest that the RAS may play a role in the regulation of cardiorenal hemodynamics, especially renal circulation, in response to acute saline loading in patients with mild CHF.

Although activation of the circulating RAS has been demonstrated in severe CHF, the lack of its activation in early left ventricular dysfunction has already been demonstrated¹⁶. In the present study, although the circulating RAS in mild CHF was not significantly higher than that in normal subjects, acute saline loading affected cardiorenal hemodynamics only in patients with mild CHF. Therefore, we postulate the activation of tissue RAS¹⁹ and/or the acceleration of vascular sensitivity to angiotensin II as in hypertension²⁰ to be

causal for changes of cardiorenal hemodynamics to saline load in patients with mild CHF.

Effects of an ACE Inhibitor on Sodium Balance

The acute saline loading, which reduced plasma renin activity, increased the renal and systemic blood flow ratio. The administration of an ACE inhibitor for 5 days reduced plasma angiotensin II level more potently than acute saline loading. Apart from that, administration of an ACE inhibitor for 5 days in our clinical setting did not affect the renal and systemic blood flow ratio. Some compensating mechanisms may affect the ACE inhibitor-induced redistribution of regional blood flow. The administration of an ACE inhibitor did not alter glomerular filtration rate or the filtration fraction, but it increased renal blood flow under basal conditions. ACE inhibitors have the effect of not only reducing the generation of angiotensin II, but also increasing kinins.²¹ These effects might increase both afferent and efferent arteriolar blood flows to a similar extent, and increase renal blood flow without changing glomerular filtration rate and the filtration fraction. Although the increase in renal blood flow can improve sodium retention, administration of ACE inhibitors did not affect sodium balance and body weight under sodium-restricted conditions. However, administration of ACE inhibitors improved natriuretic response to saline loading without changing glomerular filtration rate, renal blood flow, or the filtration fraction. These results suggest that an ACE inhibitor prevents excessive sodium retention through the potent inhibition of RAS, and a change in renal tubular function and/or intrarenal hemodynamics contributes to the beneficial effect of an ACE inhibitor on sodium handling.

Besides the RAS, aldosterone, catecholamines, vasopressin, and ANP also affect sodium handling. In patients with mild CHF, saline loading reduced the plasma vasopressin level to a similar extent before rather than after the administration of an ACE inhibitor, whereas this drug did not reduce the plasma vasopressin level under basal conditions. Although delayed reduction of plasma vasopressin by an ACE inhibitor has been reported,²² the present results suggested that vasopressin does not significantly contribute to the ACE inhibitor-induced improvement in the natriuretic response. The elevation of plasma ANP with saline loading was blunted in patients with CHF. Volpe et al¹⁴ observed a similar result and concluded that the lack of elevation of the plasma ANP level upon saline loading may contribute to the attenuated natriuretic response to saline loading in mild CHF. However, the present study demonstrated that im-

provement in the natriuretic response with an ACE inhibitor was accompanied by suppression of the plasma aldosterone level even though plasma ANP levels remained unchanged. Thus, the changes in the renin-angiotensin-aldosterone axis caused by the administration of an ACE inhibitor may mainly contribute to the improvement of the natriuretic response to saline loading in patients with mild CHF.

Clinical Implications and Limitations of this Study

The present study demonstrated that ACE inhibitors have beneficial effects on sodium and water handling in patients with mild CHF. The use of diuretics to improve sodium retention induces aggravation of the neurohormonal system.³ Although it has not been concluded that this aggravation leads to an adverse outcome regarding mortality,^{1,3} the AHA/ACC task force recommends the cautious use of diuretics.¹⁰ The present results suggest that ACE inhibitors alleviate the situation, indicating the use of diuretics in patients with mild CHF.

In this protocol, delapril was started at 7.5 mg twice a day to prevent hypotension, and this regimen reduced the generation of angiotensin II and inhibited ACE activity significantly. Recently, however, favorable outcomes have been reported in patients with CHF who received higher doses of ACE inhibitors, as low doses did not inhibit ACE activity sufficiently in the long term.²³ Neurohormonal compensation for the inhibition of ACE activity may occur during long-term administration of ACE inhibitors. The natriuretic effects during long-term administration of ACE inhibitors should be investigated in patients with mild CHF. In addition, the effects of ACE inhibitors on chronic saline load also remain to be examined.

ACE also degrades kinins such as kininase II.²¹ Administration of an ACE inhibitor not only reduces the generation of angiotensin II, but also increases kinins.²¹ These substances induce both natriuresis and vasodilation.²¹ However, the present study did not examine the role of kinins in ACE inhibitor-induced hemodynamic and natriuretic effects. Recently, non-peptide angiotensin II antagonists have become available²⁴ and may be useful as pharmacological probes to clarify the influence of kinins on the natriuretic effects induced by ACE inhibition.

The present study demonstrated the predominant significance of the renin-angiotensin-aldosterone axis in sodium and water handling in mild CHF. However, the number of subjects in this study was small and this study did not exclude the contribution of other neurohormonal systems, other than RAS, to sodium and water handling. Further studies are proposed to evalu-

ate the values of those other neurohormonal systems.

Conclusion

In patients with mild CHF, the renin-angiotensin-aldosterone axis may predominantly contribute to the regulation of renal blood flow and sodium-water balance. This effect may attenuate the natriuretic response to acute saline loading, and administration of an ACE inhibitor improves this attenuated response. In addition to increased renal blood flow, the change in renal tubular function and/or the change in intrarenal hemodynamics may contribute to this improvement.

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