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Renal endothelin in heart failure and its relation to sodium excretion

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Background Recent studies have shown that endothelin-1 (ET-1) antagonists increase sodium excretion and improve renal blood flow in experimental heart failure (HF). However, despite a number of investigations that have reported a significant increase in ET-1 plasma levels in patients with HF, it is still not known whether increased renal synthesis and urinary excretion of ET-1 occur. Our aim was to investigate renal ET-1 formation and its relation to sodium excretion in patients with HF.

Methods One hundred forty-seven patients with HF, subdivided according to New York Heart Association (NYHA) functional classes, and 28 healthy controls were studied. ET-1 and big ET-1 were measured in plasma and in 24-hour urine by radioimmunoassay. Atrial and brain natriuretic peptide, arginine vasopressin, plasma renin activity, and hemodynamic variables were also investigated.

Results Urinary ET-1 excretion was already increased in NYHA class II patients ($P < .001$ vs controls), whereas plasma ET-1 increased only in NYHA class III and IV patients ($P < .001$). In the 71 subjects who were not receiving diuretic treatment, urinary ET-1 was selected as the strongest predictor of sodium excretion by multivariate stepwise analysis.

Conclusions Urinary ET-1 excretion increases in an earlier phase of HF than plasma ET-1 and appears to be closely correlated with sodium excretion, indicating renal ET-1 is a target for ET-1 antagonists in patients with HF. (*Am Heart J* 2000;140:617-23.)

Endothelin-1 (ET-1), a powerful vasoconstrictor and pressor peptide, and its precursor (big ET-1) have been reported to be increased in the plasma of patients with congestive heart failure (HF).¹ Three lines of evidence indicate the functional significance of the increased plasma ET-1 and big ET-1 levels in HF: (1) the relation to the degree of hemodynamic impairment,² (2) the positive correlation with death,³ and (3) the beneficial effects of long-term treatment with endothelin receptor antagonists on the survival of animals with experimental HF.⁴

Although vascular endothelial cells are the major source of ET-1, the gene that encodes ET-1 is widely expressed in various districts by different cell types.⁵ The kidney is an important site of ET-1 synthesis, and abundant expression of ET-1 peptide and the mRNA of

its precursor, prepro-ET-1 (ppET-1), has been found in the endothelium of the renal vascular bed, including glomerular capillaries, arterioles, and peritubular capillaries, and also in the epithelial cells of the inner medullary collecting ducts.⁶ Renal ET-1 participates in the control of renal function both in normal and pathophysiologic conditions.⁷ The vasoconstrictor and sodium-retentive effects of ET-1 are mediated by ETA receptors,⁸ whereas ETB receptors seem to be involved in water handling, inhibiting vasopressin activity.^{7,8} The renal formation of endothelin may be monitored by measuring urinary excretion of ET-1 and big ET-1,⁹ which are not affected by plasma levels of the same substances.¹⁰ ET-1 renal actions mimic the renal adaptations in HF, and ET-1 inhibition in animals with experimental congestive HF has been shown to improve renal blood flow and sodium excretion.¹¹ More recently, congestive HF in a rat model was found to be associated with enhanced renal expression of the ppET-1 mRNA, particularly in the renal cortex.¹² In human HF, notwithstanding the number of studies investigating the pattern of circulating endothelin,¹⁻³ no information is available on renal ET-1.

We therefore aimed to investigate (1) whether increased renal synthesis and urinary ET-1 excretion occur in HF, (2) the relations between renal ET-1 production and the pro-

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Table I. Demographic, clinical, and hemodynamic characteristics of subjects investigated

	Controls	NYHA I	NYHA II	NYHA III	NYHA IV
Subjects	28	14	36	63	34
Age (y)	62 ± 17	65 ± 10	65 ± 11	68 ± 10	70 ± 10
Sex (M/F)	20/8	8/6	28/8	47/16	25/9
Height (cm)	165 ± 5	168 ± 4	165 ± 12	162 ± 12	161 ± 14
Weight (kg)	67 ± 6	71 ± 4	75 ± 18	70 ± 13	73 ± 11
Cause					
Ischemic	—	9	27	41	29
Idiopathic	—	5	9	22	5
Treatments					
Digitalis	0	0	24	39	27
Furosemide	0	0	7	63	34
ACE inhibitors	0	0	7	43	26
Heart rate (beats/min)	72 ± 3	73 ± 8	77 ± 5	77 ± 6	75 ± 6
Plasma sodium (mEq/L)	140 ± 3	139 ± 1	140 ± 2	139 ± 3	139 ± 3
Plasma creatinine (mg/dL)	1.1 ± 0.1	1.2 ± 0.1	1.2 ± 0.3	1.3 ± 0.3	1.3 ± 0.4
Diuresis (mL/24 h)	1600 ± 453	1521 ± 570	1215 ± 415	1155 ± 376	1111 ± 323
Urinary Na (mEq/24 h)	110 ± 7	109 ± 11	90 ± 11	83 ± 19	80 ± 19
CVP (mm Hg)	0.8 ± 0.5	0.7 ± 0.6	2.2 ± 2.1*	4.9 ± 4.0†	8.0 ± 5.0†
LVEDD (mm)	50 ± 2	57 ± 2*	61 ± 6†§	66 ± 6†§	73 ± 4†§
LVEF (%)	66 ± 3	53 ± 4*	40 ± 4†§	28 ± 6†§	18 ± 6†§
LVEDVI (mL/m ²)	82 ± 7	85 ± 9	100 ± 19*	129 ± 20†§	178 ± 22†§
CI (L/min/m ²)	3.9 ± 0.4	3.6 ± 0.6	3.0 ± 0.6†§	2.7 ± 0.5†	2.2 ± 0.5††
PVR (dynes · s · cm ⁻⁵)	57 ± 24	67 ± 23	191 ± 83*†	288 ± 90††	403 ± 222††

Values are n or mean ± SD.

CVP, Central venous pressure; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVEDVI, left ventricular end-diastolic volume index; CI, cardiac index; PVR, pulmonary vascular resistance.

*P < .01 vs controls.

†P < .001 vs controls.

‡P < .01 vs previous class.

§P < .001 vs previous class.

gression of the disease, and (3) the relation between renal ET-1 production and sodium excretion.

Methods

Subjects investigated

One hundred forty-seven patients (108 men and 39 women, average age 67 ± 10 years) with HF from idiopathic dilated cardiomyopathy (n = 41) or ischemic dilated cardiomyopathy (n = 106) and 28 healthy controls were investigated. The diagnosis of ischemic or idiopathic dilated cardiomyopathy was based on clinical and echocardiographic examination, cardiac catheterization, and coronary angiography.

HF was diagnosed according to the definition approved by the European Society of Cardiology,¹³ that is, the presence of symptoms of HF either at rest or during exercise and objective evidence of cardiac dysfunction at rest (regional wall motion abnormalities from previous myocardial infarction, left ventricular end-diastolic diameter ≥55 mm, echocardiographic left ventricular ejection fraction ≤50%). HF was classified according to the New York Heart Association (NYHA).¹⁴

Patients with aortic valve disease or congenital heart disease, hypertension, a recent history of effort angina, unstable angina or myocardial infarction (<6 months), renal failure, alteration of urinalysis, abnormal liver function test, diabetes, or malignancy were excluded. All subjects gave their written informed consent to participate in the study.

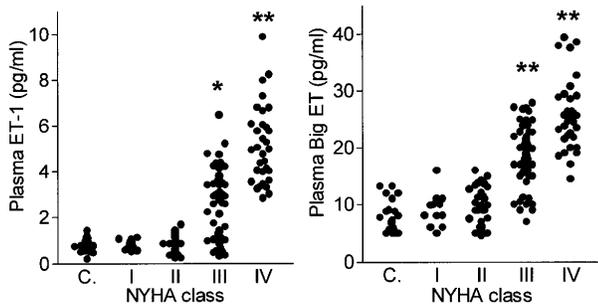
The demographic and clinical characteristics of subjects investigated and drug treatments are reported in Table I.

Study protocol

Blood samples for plasma ET-1, big ET-1, plasma renin activity (PRA), arginine vasopressin (AVP), atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) assays, and 24-hour urine collection for the assessment of urinary ET-1 and big ET-1 excretion were taken after 4 days of a diet with normal sodium levels (108 mEq/d) and suppression of diuretics or angiotensin-converting enzyme (ACE) inhibitors. These measurements were taken between the fourth and fifth days after hospital admission. In severely ill patients the blood sampling and urine collection for the assay of endothelin and other neurohumoral variables were postponed until the patient was clinically stable and the temporary suspension of diuretics and ACE inhibitors for at least 3 days was judged to be possible by medical staff.

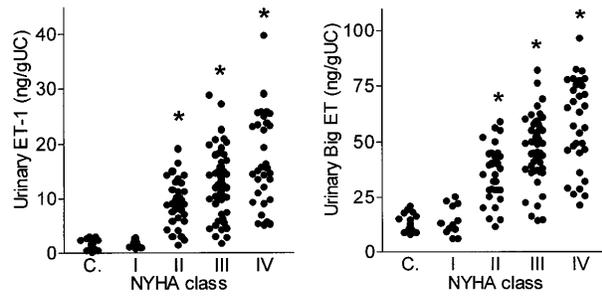
The relation between sodium excretion and both neurohumoral factors and hemodynamic or echocardiographic parameters was investigated in the 71 subjects who were not receiving treatment with diuretics or ACE inhibitors (28 controls, 14 patients in NYHA class I, and 29 in class II). All patients were then monitored for at least 1 year (mean follow-up period of 3.8 years).

Figure 1



Plasma concentration of ET-1 (left) and big ET-1 (right) in controls and patients with HF. **P* < .01 vs controls; ***P* < .001 vs controls.

Figure 2



Urinary excretion of ET-1 (left) and big ET-1 (right) in controls and patients with HF. **P* < .001 vs controls.

Table II. Plasma and urinary levels of neurohumoral variables in controls and patients with HF

	Controls	NYHA I	NYHA II	NYHA III	NYHA IV
Plasma ET-1 (pg/mL)	0.75 ± 0.26	0.81 ± 0.20	0.83 ± 0.35	2.72 ± 1.43*	5.15 ± 1.67†§
Urinary ET-1 (ng/g UC)	1.7 ± 0.8	1.7 ± 0.7	9.2 ± 4.2†§	12.8 ± 5.7†‡	17.0 ± 8.2†§
Plasma big ET-1 (pg/mL)	7.7 ± 2.6	9.1 ± 2.8	9.5 ± 3.5	18.6 ± 5.1†§	25.7 ± 6.2†§
Urinary big ET-1 (ng/g UC)	13 ± 3	14 ± 6	35 ± 12†‡	47 ± 14†	58 ± 20†
ANP (pg/mL)	14 ± 3	21 ± 13	74 ± 29†§	184 ± 50†§	288 ± 60†§
BNP (pg/mL)	25 ± 13	33 ± 16	67 ± 45†§	172 ± 83†§	298 ± 161†§
AVP (pg/mL)	1.1 ± 0.5	1.3 ± 0.6	1.5 ± 1.0	3.9 ± 1.3†§	6.3 ± 1.8†§
PRA (ng/mL/h)	0.7 ± 0.5	1.0 ± 0.5	1.1 ± 1.0	4.1 ± 1.9†§	5.4 ± 2.8†

**P* < .01 vs controls.
†*P* < .001 vs controls.
‡*P* < .01 vs previous class.
§*P* < .001 vs previous class.

Sampling procedures, extraction, and radioimmunoassays

Blood and urine sample collection, extraction, and assay of ET-1 and big ET-1 were performed as previously described.^{10,15} In brief, after extraction with Sep-Pak C₁₈ columns (Waters, Mass), ET-1 and big ET-1 were investigated with specific anti-ET-1 and anti-big ET-1 antibodies (Peninsula Lab Inc). The minimum detectable concentration for both ET-1 and big ET-1 was 0.1 pg/mL. Intraassay and interassay coefficients of variation averaged 2.8% and 9.7% for plasma big ET-1, 4% and 10% for plasma ET-1, 4.4% and 10.2% for urinary big ET-1, and 3% and 12% for urinary ET-1, respectively. The results were expressed as picograms per milliliter for plasma and nanograms per gram of urinary creatinine (UC) for urine.

Blood samples for ANP and BNP were extracted with Sep-Pak C₁₈ columns and assessed with radioimmunoassays as noted. The intraassay and interassay variations were 3% and 12% for ANP and 4% and 10% for BNP, respectively. PRA measurement was performed with a commercial kit (Sorin Biomedica, Italy) and expressed as nanograms of angiotensin I per 1 mL of plasma per hour of incubation. Blood samples for AVP were extracted and assessed with radioimmunoassay as previously described.¹⁶

Statistical analysis

Data were expressed as mean ± SD. Comparison between multiple groups was performed with 1-way analysis of variance and Student *t* test followed by Tukey multiple-range comparison test, as appropriate.

To discriminate among factors possibly related with ET-1 plasma concentration, ET-1 urinary excretion, and sodium excretion, the following variables were entered in a multiple stepwise regression analysis as independent variables: plasma concentration of ET-1, big ET-1, ANP, BNP, PRA and AVP, urinary excretion of ET-1, big ET-1 and sodium, pulmonary vascular resistance, central venous pressure, left ventricular end-diastolic diameter, left ventricular end-diastolic volume index, left ventricular ejection fraction, and cardiac index. The independent determinant of sodium excretion was only assessed in the 71 subjects who had not been treated with diuretics.

The predictive value of the same neurohumoral variables and hemodynamic parameters on NYHA class worsening was tested by univariate and stepwise multivariate Cox proportional hazards regression analysis in patients in NYHA classes I to III who were rehospitalized. The predictive value of death was assessed with the same method in all patients. Then, quartiles of the variables selected as the strongest pre-

Table III. Correlation between urinary sodium and clinical, hemodynamic, and neurohormonal variables (stepwise regression analysis)

	<i>r</i>	<i>P</i>
Urinary ET-1 (ng/g UC)	-0.80*	<.001
PVR (dynes · s · cm ⁻⁵)	-0.69	<.001
CI (L/min/m ²)	0.61*	<.001
Urinary big ET-1 (ng/g UC)	-0.50	<.001
ANP (pg/mL)	-0.45	<.001
LVEF (%)	0.45	<.001
AVP (pg/mL)	-0.43	<.001
LVEDD (mm)	-0.36	<.01
PRA (ng/mL/h)	-0.32	<.01
CVP (mm Hg)	-0.27	<.05
BNP (pg/mL)	-0.25	<.05
LVEDVI (mL/m ²)	0.21	NS
Plasma big ET-1 (pg/mL)	-0.09	NS
Plasma ET-1 (pg/mL)	-0.01	NS

PVR, Pulmonary vascular resistance; CI, cardiac index; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; CVP, central venous pressure; LVEDVI, left ventricular end-diastolic volume index; NS, not significant.

*Independent variable at stepwise regression analysis.

dictors of NYHA class worsening and death were calculated and Kaplan-Meier curves were plotted.

All calculations were performed with BioMedical Data Processing statistical software.

Results

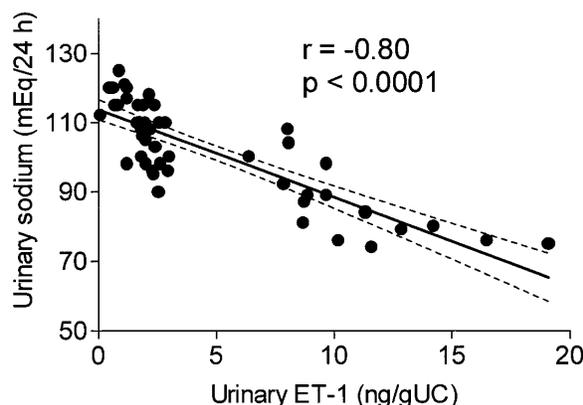
Plasma and urinary endothelins in HF

The individual values of plasma and urinary ET-1 and big ET-1 in the various NYHA classes are shown in Figures 1 and 2.

There were no differences in the mean values of ET-1 and big ET-1 urinary excretion between class I patients and controls (Table II). In class II patients, urinary excretion of both endothelins was significantly increased (9.2 ± 4.2 ng/g UC and 35 ± 12 ng/g UC; $P < .01$ vs both controls and class I for both), whereas ET-1 and big ET-1 plasma concentrations were not (Table II). In patients with severe HF (NYHA classes III and IV), plasma and urinary endothelins were both increased (Table II). No differences between patients with idiopathic or ischemic dilated cardiomyopathy were found in plasma levels or urinary excretion of endothelins.

By stepwise regression analysis, plasma ET-1 concentration was independently related to left ventricular end-diastolic volume index ($F = 188$), pulmonary vascular resistance ($F = 27$), big ET-1 plasma concentration ($F = 16$), and left ventricular end-diastolic diameter ($F = 8$) (multiple $r = 0.94$). Urinary ET-1 was independently related to urinary big ET-1 ($F = 182$) and PRA ($F = 12$) (multiple $r = 0.89$).

In subjects who had not been treated with diuretics, urinary ET-1 ($F = 63$) and cardiac index ($F = 7$) were

Figure 3

Correlation between 24-h sodium and ET-1 urinary excretion in controls and patients with HF who had not been treated with diuretics. Dashed lines represent 95% confidence intervals of regression line.

selected as independent predictors of sodium excretion (multiple $r = 0.83$) (Figure 3, Table III).

Predictors of NYHA class worsening and death

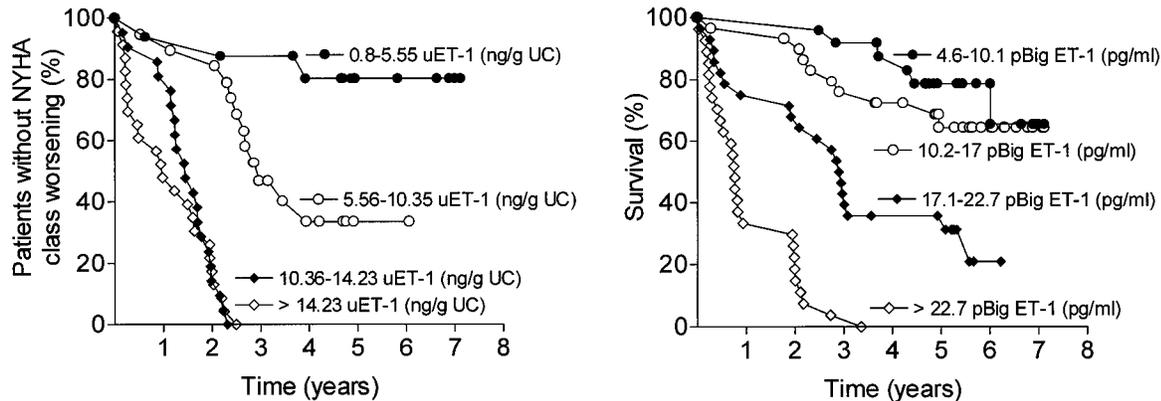
During the study period (mean follow-up of 3.8 years) 81 patients in NYHA class I to III at discharge were rehospitalized after 22 to 2605 days (mean 941 ± 721 days). Twenty-two patients were readmitted without NYHA class worsening, 18 patients previously classified in NYHA class II were rehospitalized in class III, and 41 patients previously classified in class III were rehospitalized in class IV. The significant independent predictors of NYHA class worsening at stepwise multivariate Cox proportional hazards regression analysis were urinary ET-1 excretion ($\chi^2 = 26$, $P < .0001$) and ejection fraction ($\chi^2 = 8$, $P < .005$). Kaplan-Meier curves for quartiles of urinary ET-1 are shown in Figure 4.

Sixty-seven patients died from a cardiac cause after 10 to 2193 days (mean 734 ± 561 days). Plasma level of big ET-1 ($\chi^2 = 28$, $P < .0001$) was the strongest predictor of death, with a minor contribution of BNP ($\chi^2 = 4$, $P < .05$). Kaplan-Meier survival curves for quartiles of plasma big ET-1 in NYHA class I to IV patients are shown in Figure 4.

Discussion

These results indicate that in HF the renal formation of ET-1, as evaluated by its urinary excretion, precedes the rise in plasma ET-1, increases with the progression of the disease, and appears to be an independent predictor of urinary sodium excretion.

Figure 4



Kaplan Meier curves of NYHA class worsening for quartiles of urinary ET-1 excretion in NYHA class I to III patients (left). B, Kaplan-Meier curves of survival for quartiles of plasma big ET-1 in NYHA class I to IV patients (right).

Factors possibly responsible for increased renal ET-1 production

There is evidence that urinary endothelin excretion reflects renal synthesis and is not influenced by circulating ET-1.^{9,10,16} In this study the enhanced urinary ET-1 excretion was independently correlated with excretion of its precursor big ET-1 but not with plasma ET-1 and big ET-1 concentrations, thus suggesting that it in fact reflects renal ET-1 formation in HF patients also. In healthy subjects, venous distension and increased venous pressure after volume expansion cause a marked decrease in urinary ET-1 excretion.¹⁰ In contrast, in HF patients the increased central venous pressure was associated with a progressive increase in ET-1 excretion, thus indicating the occurrence of a dysregulation of renal ET-1 formation.

ANP infusion has been reported to increase urinary ET-1 excretion in human beings,¹⁷ but a number of studies have shown that ANP inhibits basal and stimulated ET-1 formation in cultured human and porcine endothelial and mesangial cells.¹⁸ In vitro studies have shown that AVP stimulates ppET-1 mRNA expression,¹⁹ and a close correlation has also been reported between AVP plasma levels and urinary ET-1 excretion in volume-depleted exercising healthy subjects.¹⁶ However, stepwise regression analysis revealed that in patients with HF, ANP, BNP, or AVP plasma concentrations were not independently related with urinary ET-1 excretion. Thus it seems unlikely that the increased renal ET-1 production might be caused by an increase in plasma ANP, BNP, or AVP concentrations.

The relations between the renin angiotensin system (RAS) and renal ET-1 synthesis appear more complex and intriguing. Angiotensin II has been found to induce ppET-1 mRNA expression and the secretion of mature

ET-1 in a dose-dependent manner in cultured bovine, rat, and human endothelial cells.¹⁹ However, although the increased urinary ET-1 excretion observed in normal subjects on a low sodium diet paralleled PRA, ACE inhibition reduced ET-1 excretion by only 20%,⁹ thus indicating that in this physiologic setting renal ET-1 formation is largely independent of the RAS. In NYHA class II patients urinary ET-1 excretion was increased despite the absence of PRA increase (Table II). This finding does not rule out the possibility that in the early phase of HF a locally (intrarenal) activated RAS may contribute to the enhanced renal ET-1 formation. An impaired renal vasodilatory response to amino acid infusion, restored by ACE inhibitor or angiotensin AT-1 receptor antagonist administration, has been reported in NYHA class I patients with normal PRA,²⁰ suggesting that angiotensin II may play a major role in the development of early renal abnormalities in HF, even in the absence of systemic RAS activation. The positive independent contribution of circulating PRA to urinary ET-1 excretion observed in this study at stepwise regression analysis could be attributed to the inclusion of patients in more advanced stages of the disease.

Another possible stimulus of ET-1 synthesis not specifically investigated in our study could also be sympathetic activation, which was reported to have already occurred in NYHA class I to II patients.²¹ In vitro studies have shown that epinephrine and the α -adrenergic receptor agonist phenylephrine increase ppET-1 mRNA expression by cultured rat and human endothelial cells.⁵ In healthy human beings, increased sympathetic activity induced by mental stress was reported to be associated with reduced renal flow and increased urinary ET-1

excretion.²² Sympathetic activity might also indirectly activate ET-1 synthesis by a renal flow reduction, which has also been reported to cause increased renal ET-1 excretion.²³

Functional activity of renal ET-1

Experimental evidence indicates that ET-1 causes sodium retention by stimulation of the renal ETA receptor.⁸ The sodium retentive activity of circulating ET-1 in human beings was demonstrated by low-dose infusion of exogenous ET-1 (1 ng/kg per minute), which caused sodium retention without any changes in renal plasma flow.²⁴ ET-1 locally produced in the kidney also seems to participate in sodium and water handling, favoring sodium retention and increasing free water clearance.⁹ In experimental severe HF, the administration of ETA antagonists reduced sodium retention, whereas ETB antagonists had no effect.¹¹ This observation raises an important question for drug treatment but does not allow discrimination between the relative contributions of the two systems in HF. According to our findings, NYHA functional class II was characterized by enhanced renal ET-1 formation with normal ET-1 in plasma, and in this early phase renal ET-1 was the strongest independent predictor of sodium excretion. Furthermore, follow-up analysis showed that urinary ET-1 is a significant independent predictor of NYHA class worsening in patients with HF if used with hemodynamic parameters such as left ventricular ejection fraction, left ventricular end-diastolic volume index, and cardiac index. Thus, although both plasma and renal ET-1 formation might contribute to sodium retention in severe HF, in the early phase the enhanced renal formation might constitute an important factor in the development of symptomatic HF and a target for the clinical use of ET-1 antagonists.

The independent predictive value of plasma big ET-1 on mortality rate confirms previous observations.³ The potential pathophysiologic significance of increased plasma ET-1 levels might be related either to the increase in peripheral vascular resistance, which further impairs cardiac function, or to a direct cardiac effect. Indeed, although ET-1 has a potent *in vivo* and *in vitro* positive inotropic effect on the normal myocardium of several species, including human beings,⁵ ET-1 causes negative inotropic effects in failing hearts.²⁵

In conclusion, during the clinical course of HF an early increase in urinary endothelin excretion occurs in close relation with sodium retention and onset or worsening of clinical symptoms, whereas increased plasma endothelin concentration is found at a more advanced stage of the disease and is closely related with reduced survival.

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Efficacy, safety, and effects on quality of life of bisoprolol/hydrochlorothiazide versus amlodipine in elderly patients with systolic hypertension

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Background Several studies have shown the benefits of antihypertensive treatment in elderly patients in terms of cardiovascular morbidity and mortality rate reduction. Low-dose drug combinations may be of interest in treating older subjects. A randomized, multicenter, double-blind, parallel group study was conducted to compare the efficacy and safety of bisoprolol 2.5 mg/hydrochlorothiazide 6.25 mg (n = 84) to amlodipine 5 mg (n = 80) in isolated systolic hypertension in patients older than 60 years.

Methods After a 2- to 4-week placebo washout period, both drugs were administered once daily and taken for 12 weeks. Blood pressure was measured 24 hours after treatment administration.

Results Systolic and diastolic blood pressure changes from base-

line to week 12 were similar for both the bisoprolol and amlodipine groups (-20.0/-4.5 mm Hg and -19.6/-2.4 mm Hg, respectively). Overall adverse events for bisoprolol and amlodipine were 39% and 40%, respectively. Changes in quality of life scores were +2.5 for bisoprolol and +3.2 for amlodipine, with a positive change indicating improvement.

Conclusions This study demonstrates comparable efficacy and tolerability of bisoprolol 2.5 mg/hydrochlorothiazide 6.25 mg and amlodipine 5 mg. The low-dose combination of bisoprolol and hydrochlorothiazide may be an appropriate alternative for elderly patients with systolic hypertension. (*Am Heart J* 2000;140:e11.)
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