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Effects of Loop Diuretics on Myocardial Fibrosis and Collagen Type I Turnover in Chronic Heart Failure

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OBJECTIVES This individually randomized, open-label, parallel-group pilot study was designed to test the hypothesis that the ability of loop diuretics to interfere with cardiac fibrosis in chronic heart failure (CHF) may be different between compounds.

BACKGROUND The apparent mortality and cardiac benefits seen in studies comparing torasemide with furosemide in CHF suggest that torasemide may have beneficial effects beyond diuresis (e.g., on the process of cardiac fibrosis).

METHODS Patients with New York Heart Association functional class II to IV CHF received diuretic therapy with either 10 to 20 mg/day oral torasemide (n = 19) or 20 to 40 mg/day oral furosemide (n = 17), in addition to their existing standard CHF therapy for eight months. At baseline and after eight months, right septal endomyocardial biopsies were obtained to quantify collagen volume fraction (CVF) with an automated image analysis system. Serum carboxy-terminal peptide of procollagen type I (PIP) and serum carboxy-terminal telopeptide of collagen type I (CITP), indexes of collagen type I synthesis and degradation, respectively, were measured by specific radioimmunoassays.

RESULTS In torasemide-treated patients, CVF decreased from 7.96 ± 0.54% to 4.48 ± 0.26% ($p < 0.01$), and PIP decreased from 143 ± 7 to 111 ± 3 μg/l ($p < 0.01$). Neither CVF nor PIP changed significantly in furosemide-treated patients. In all patients, CVF was directly correlated with PIP ($r = 0.88$, $p < 0.001$) before and after treatment. No changes in CITP were observed with treatment in either group.

CONCLUSIONS These findings suggest that loop diuretics possess different abilities to reverse myocardial fibrosis and reduce collagen type I synthesis in patients with CHF. (J Am Coll Cardiol 2004;43:2028–35) © 2004 by the American College of Cardiology Foundation

Loop diuretics, such as furosemide and torasemide, are currently recommended for the treatment of chronic heart failure (CHF) (1,2). In a recent report of the prospective TORasemide In Chronic heart failure (TORIC) study involving 1,377 CHF patients, the use of torasemide was associated with a lower mortality than furosemide (3). Furthermore, it has been reported recently that torasemide improves left ventricular (LV) diastolic function in CHF patients to a greater extent than furosemide, despite the fact that torasemide induces a more pronounced stimulation of the renin-angiotensin-aldosterone system (4). Because both diuretics exert similar renal effects (5,6), it is likely that torasemide has beneficial effects other than diuresis in patients with CHF.

Numerous findings, as reviewed elsewhere (7), emphasize the role of myocardial accumulation of collagen fibers in the deterioration of LV function in CHF. It has been proposed that myocardial fibrosis is the result of both increased collagen synthesis by fibroblasts and unchanged or decreased extracellular fibrillar collagen degradation (8). It has been proposed that hemodynamic and nonhemodynamic factors may be responsible for such an imbalance (9). For instance, a number of findings suggest that aldosterone may play a role in myocardial fibrosis (10,11). Furthermore, recent clinical studies have shown that the addition of the aldosterone antagonist spironolactone to the regimens of patients with heart failure is associated with changes in serum markers of fibrillar collagen turnover, suggesting a decreased formation of these molecules (12,13). Interestingly, it has been shown that torasemide, but not furosemide, interferes with the secretion and receptor-ligand binding of aldosterone (4,14,15). We have therefore hypothesized that torasemide may interfere with mechanisms involved in alterations of fibrillar collagen turnover and myocardial fibrosis in patients with CHF. To test this hypothesis, the present study was designed to compare changes in the fraction of myocardial volume occupied by collagen, or collagen volume fraction (CVF), and the serum concentrations of the carboxy-terminal peptide of procollagen type I (PIP) and the carboxy-terminal telopeptide of collagen type I (CITP), indexes of collagen type I synthesis and degradation, respectively (16,17), in CHF patients receiving either torasemide or furosemide as diuretic treatment. The primary end point was the change in CVF of

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
CHF = chronic heart failure
CITP = carboxy-terminal telopeptide of collagen type I
CVF = collagen volume fraction
DT = deceleration time
EF = ejection fraction
K_{LV} = left ventricular chamber stiffness
LVMI = left ventricular mass index
NYHA = New York Heart Association
PIP = carboxy-terminal peptide of procollagen type I

endomyocardial biopsies from baseline to eight months, and the secondary end point was the change in serum concentrations of PIP and CITP.

METHODS

Patients and study protocol. This was an individually randomized, open-label, parallel-group pilot study. All subjects gave written, informed consent before participating in the study. The investigation conformed to the principles outlined in the Helsinki Declaration. All patients were seen at the General Hospital (San Sebastián), and the biopsies were obtained at the Guipuzcoa Polyclinic (San Sebastián). Both centers are integrated in the Donostia University Hospital, and the study protocol was approved by the Institutional Review Committee of the Donostia University Hospital.

The study population consisted of 39 Caucasian patients with different cardiomyopathies. The diagnosis of heart failure syndrome was made on a clinical basis, by the presence of at least one major and two minor criteria of the Framingham Study (1). In addition, the heart failure diagnosis was reinforced by the presence of a depressed ejection fraction (EF) and/or Doppler signs of diastolic dysfunction in all patients. Furthermore, hemodynamic evidence of myocardial failure was obtained in each patient by measuring elevated LV end-diastolic pressure and pulmonary capillary wedge pressure (>12 mm Hg in both cases). After establishing the diagnosis of heart failure, the patient's clinical status was assessed according to his or her extent of disability, according to the New York Heart Association (NYHA) functional classification (18).

All patients initially selected had a previous diagnosis of NYHA functional class II to IV heart failure in accordance with the aforementioned criteria. In addition, they had been receiving standard heart failure treatment (loop diuretic plus an angiotensin-converting enzyme [ACE] inhibitor or angiotensin type I receptor antagonist plus beta blocker) for the previous six months when enrolled. Thus, they were considered as patients having CHF. Patients definitively enrolled were those who did not present with exclusion criteria (previous acute myocardial infarction, significant valvular disease, diabetes mellitus, treatment with spironolactone for at least one year before enrollment, significant electrolyte disturbances, severe ventricular arrhythmia, complete atrioventricular block and dyspnea due to lung disease, and conditions associated with alterations in serum levels of PIP, such as alcoholic liver disease, metabolic bone disease, and hyperthyroidism).

No washout phase was performed to ensure continuous heart failure treatment. Patients were randomly assigned to receive either torasemide or furosemide. After randomization, 20 patients were assigned to 10 to 20 mg/day torasemide (torasemide group) and 19 patients to 20 to 40 mg/day furosemide (furosemide group) for eight months. These doses have been shown to be comparable in terms of diuretic effect (19). Existing salt intake restriction (4 g/day) and concomitant CHF medication were continued during the study, with the exception of aldosterone antagonists, which were not permitted during the study. We chose a treatment period of eight months, just long enough to allow the removal of a significant amount of collagen from the myocardium, in keeping with the half-life of fibrillar collagen (20).

At baseline and after eight months of treatment, a number of procedures were performed to assess different parameters.

Assessment of pressures. Systolic and diastolic blood pressures were monitored in a sitting position at each visit by use of standard cuff equipment. Type I and V phases of the Korotkoff sounds were used; three measurements were obtained in each patient, at 5-min intervals, and averaged.

Left ventricular end-diastolic pressure and pulmonary capillary wedge pressure were measured with a micromanometer catheter system during the angiographic examination, before the biopsy was taken.

Assessment of LV mass and function. Two-dimensional echocardiograms, targeted M-mode recordings, and Doppler ultrasound measurements were obtained in each patient. Left ventricular mass was measured, and the left ventricular mass index (LVMI) was calculated, as previously described (21). The following pulsed Doppler measurements were obtained: maximum early transmitral velocity in diastole (V_E); maximum late transmitral velocity in diastole (V_A); the deceleration time of the early mitral filling wave (DT); and isovolumic relaxation time. Left ventricular chamber stiffness (K_{LV}) was calculated according to the following formula (22,23): $K_{LV} = (0.07/DT)^2$, where DT was calculated as the time from the peak of the E wave to the zero-velocity intercept of the regression line of the E-wave velocity deceleration profile (24). Ejection fraction was calculated from the measurements performed in a technetium-99m ventriculography (multigated acquisition scan) (25). Diastolic heart failure was defined as an EF >0.50, as well as alterations in the V_E/V_A ratio, isovolumic relaxation time, and/or DT (26). Systolic heart failure was defined as an EF <0.50.

Biochemical determinations. Serum potassium and serum creatinine were determined by standard laboratory methods. Plasma aldosterone was measured by radioimmunoassay

using a commercial kit. Serum PIP was determined by radioimmunoassay, according to a method previously described (27). The inter- and intra-assay variations for determining PIP were 7% and 3%, respectively. The sensitivity (lower detection limit) was 1.20 μg/l of PIP. Serum CITP was determined by radioimmunoassay, according to a method previously described (28). The inter- and intra-assay variations for determining CITP were both <8%. The sensitivity (lower detection limit) was 0.50 μg/l of CITP.

Histomorphologic study. Transvenous endomyocardial biopsies were taken from the middle area of the interventricular septum with a Cordis 96-cm (7F) bioptome, under fluoroscopic guidance after angiographic examination, as previously reported (21). Up to three biopsies were taken in each intervention. The rationale for the use of this procedure is based on the previous finding that patchy fibrosis present in the septum in postmortem tissue from human hearts is representative of fibrosis existing in the free wall (29). The biopsy procedure was well tolerated in all cases. Histologic evaluation was performed as previously reported (21). Collagen volume fraction was determined by quantitative morphometry with an automated image analysis system (AnalySYS, Soft Imaging System GmbH, Hammer, Germany) in sections stained with collagen-specific picrosirius red (sirius red F3BA in aqueous picric acid). The histomorphologic study was performed by a pathologist blinded to the other characteristics of the patients under study.

Statistical analysis. Differences in parameters at baseline and after treatment between CHF patients treated with either torasemide or furosemide were tested by the Student *t* test for unpaired data once normality was demonstrated (Shapiro-Wilks test); otherwise, a nonparametric test (Mann-Whitney *U* test) was used. Differences in parameters before and after treatment within each group of patients were tested by the Student *t* test for paired data once normality was demonstrated (Shapiro-Wilks test); otherwise, a nonparametric test (Wilcoxon test) was used. Categorical variables were analyzed by the chi-square Fisher exact test when necessary. The correlation between continuously distributed variables was tested by univariate regression analysis. Data are expressed as the mean value ± SEM. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Patient compliance and baseline characteristics. At the end of the treatment period, patients in the torasemide group (n = 19) and the furosemide group (n = 17) received mean daily dosages of 10.6 ± 0.6 mg and 32.2 ± 3.2 mg, respectively. Baseline medications other than loop diuretics were maintained unchanged during the treatment period in the two groups of patients. No adverse effects or complications occurred during the study in either group.

During the treatment period, we observed a small dropout rate of patients at their own request; one patient in the torasemide group and two patients in the furosemide group withdrew consent.

Baseline clinical characteristics were compared for patients who completed the study (Table 1). No significant differences in clinical parameters were observed between the groups in the parameters tested. Although baseline values of CVF, PIP, and CITP were similar in the two groups of patients, they were well above the control values for these parameters reported by our group in healthy subjects (21,27,28,30).

The CVF tended to be higher in patients with diastolic CHF than in patients with systolic CHF in the two groups (furosemide group: 7.76 ± 1.34% vs. 6.97 ± 1.08%; torasemide group: 8.32 ± 0.55% vs. 7.47 ± 1.01%), but the differences did not reach statistical significance.

Effects of treatment. Although CVF decreased in the torasemide group (7.96 ± 0.54% vs. 4.48 ± 0.26%, $p < 0.01$), it remained unchanged in the furosemide group (7.29 ± 0.98% vs. 6.47 ± 0.74%, p = NS) (Fig. 1). In addition, CVF after treatment was lower ($p < 0.005$) in the torasemide group than in the furosemide group. Figure 2 illustrates treatment-induced changes in myocardial fibrosis in one representative patient from each group.

The effect of torasemide on CVF was more intense in patients with diastolic CHF (final value of 4.37 ± 0.21%, $p < 0.001$) than in patients with systolic CHF (final value of 4.81 ± 0.53%, $p < 0.05$). The effects of furosemide on CVF were similar in patients with diastolic CHF (final value of 6.66 ± 1.16%, p = NS) than in patients with systolic CHF (final value of 6.10 ± 0.82%, p = NS).

Administration of torasemide was associated with a reduction in the serum concentration of PIP (143 ± 7 μg/l vs. 111 ± 3 μg/l, $p < 0.01$) (Fig. 3). In contrast, serum PIP did not change after treatment in the furosemide group (133 ± 12 μg/l vs. 133 ± 7 μg/l, p = NS) (Fig. 3). Serum PIP measured after treatment was lower ($p < 0.01$) in the torasemide group than in the furosemide group. A direct correlation was found between serum PIP and CVF ($y = 68.08 + 9.41x$, $r = 0.880$, $p < 0.001$) in all CHF patients before and after treatment (Fig. 4).

As shown in Figure 5, serum CITP remained unchanged after treatment in the torasemide group (5.16 ± 0.84 μg/l vs. 5.14 ± 0.70 μg/l) and the furosemide group (4.89 ± 0.92 μg/l vs. 5.26 ± 0.81 μg/l). No correlation was found between serum CITP and CVF.

As reported in Table 1, the number of patients showing improvement of at least one grade in NYHA functional class was greater ($p < 0.05$) in the torasemide group than in the furosemide group. The K_{LV} values showed a nonsignificant trend toward a decrease in torasemide- but not furosemide-treated patients. The EF values showed a nonsignificant trend toward an increase in torasemide- but not furosemide-treated patients. Plasma levels of aldosterone remained unchanged with treatment in the two groups of CHF patients. Changes induced by treatment in the remaining parameters tested were similar in torasemide- and

Table 1. Effects of Treatment on Parameters Assessed in Chronic Heart Failure Patients Who Finished the Study

Parameter	Furosemide Group		Torasemide Group	
	At Baseline	After Treatment	At Baseline	After Treatment
Age (yrs)	63 ± 3		63 ± 3	
Gender (M/F)	13/4		15/4	
Body weight (kg)	76 ± 3	72 ± 3	84 ± 3	82 ± 3
Causes of CHF				
HHD	10		11	
IHD	4		5	
IDCM	2		1	
Alcoholism	1		2	
Types of CHF				
Diastolic	8		10	
Systolic	9		9	
Medications				
ACEIs or ARAs	17	17	19	19
Beta-blockers	17	17	19	19
Digoxin	5	5	6	6
Diuretics				
Furosemide	10	17	6	0
Torasemide	1	0	6	19
Spironolactone	0	0	0	0
Thiazide + amiloride	4	4	0	0
Blood pressure				
Systolic (mm Hg)	140 ± 4	125 ± 4†	147 ± 3	126 ± 2†
Diastolic (mm Hg)	88 ± 2	76 ± 2†	92 ± 2	74 ± 2†
Hemodynamic parameters				
LVEDP (mm Hg)	19 ± 2		17 ± 1	
PCWP (mm Hg)	16 ± 2		15 ± 1	
Cardiac parameters				
LVMI (g/m^2)	166 ± 20	152 ± 15	148 ± 11	142 ± 11
K_{LV} (mm Hg/ml)	0.14 ± 0.02	0.14 ± 0.02	0.17 ± 0.02	0.14 ± 0.02
EF (%)	38 ± 4	38 ± 4	40 ± 4	44 ± 3
NYHA functional class*				
I	—	0	—	0
II	5	11	8	16
III	11	5	9	3
IV	1	1	2	0
Blood parameters				
Potassium (mmol/l)	4.52 ± 0.10	4.58 ± 0.12	4.66 ± 0.11	4.51 ± 0.13
Creatinine (mg/dl)	1.08 ± 0.05	1.18 ± 0.09	1.11 ± 0.06	1.19 ± 0.05
Aldosteronel (pg/ml)	125 ± 25	100 ± 13	132 ± 30	113 ± 19

*$p < 0.01$ for changes in NYHA class after treatment †$p < 0.01$ versus values at baseline. Data are expressed as the mean value ± SEM or number of patients.

ACEIs = angiotensin-converting enzyme inhibitors; ARAs = angiotensin receptor antagonists; CHF = chronic heart failure; EF = ejection fraction; HHD = hypertensive heart disease; IDCM = idiopathic dilated cardiomyopathy; IHD = ischemic heart disease; K_{LV} = left ventricular chamber stiffness; LVEDP = left ventricular end-diastolic pressure; LVMI = left ventricular mass index; NYHA = New York Heart Association; PCWP = pulmonary capillary wedge pressure.

furosemide-treated CHF patients. Furthermore, the final values of these parameters were similar in the two groups of patients.

DISCUSSION

Effects on myocardial fibrosis. The main finding of this study is that long-term administration of either torasemide or furosemide is associated with different effects on myocardial fibrosis in CHF patients.

Fibrosis probably plays an important role in diastolic dysfunction and systolic pump function (9), and it is one of the structural substrates for fatal arrhythmogenicity (31), thus playing a major role in the progression of heart failure and sudden death. We (30,32) and others (33,34) have shown that a reduction of myocardial fibrosis is associated with improvement of LV function parameters in hypertensive patients receiving long-term treatment with different antihypertensive agents. Our findings that torasemide exerts an antifibrotic effect in CHF patients, whereas furosemide does not, may be related to the greater improvement of NYHA functional class observed in torasemide-treated CHF patients than in those treated with furosemide. This is supported by changes in parameters assessing cardiac function (e.g., K_{LV} and EF). Although these were not statistically significant, overall changes are consistent with the conclusion that torasemide, but not furosemide, exerts

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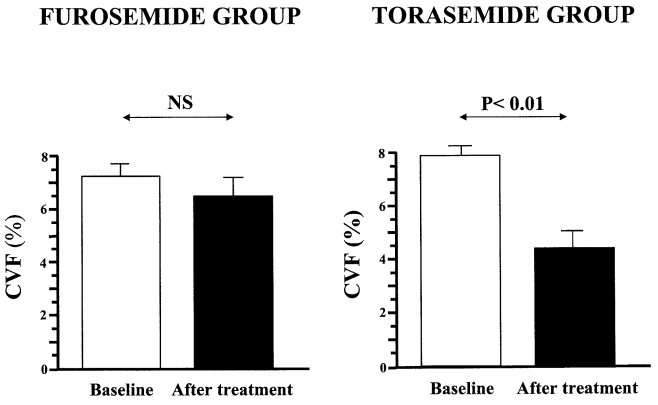

Figure 1. Effects of furosemide (n = 17) and torasemide (n = 19) on collagen volume fraction (CVF) in patients with chronic heart failure. NS = nonsignificant.

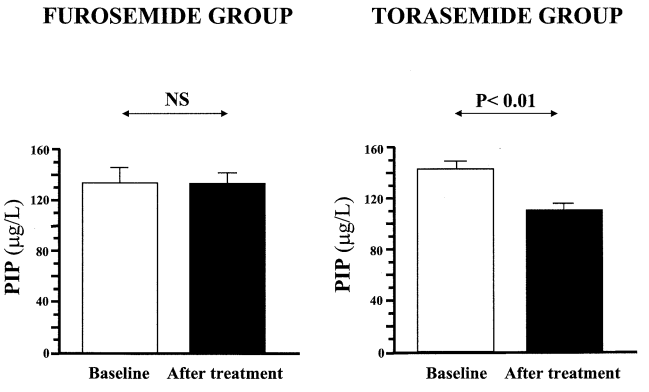

Figure 3. Effects of furosemide (n = 17) and torasemide (n=19) on serum carboxy-terminal peptide of procollagen type I (PIP) in patients with chronic heart failure. NS = nonsignificant.

beneficial effects on myocardial function in the hearts of CHF patients. This can be of particular interest in diastolic CHF, as suggested by our observation that the ability of torasemide to reduce myocardial fibrosis tended to be higher in patients with diastolic CHF than in those with systolic CHF. It is clear that further studies enrolling larger samples of patients are required to test this possibility.

Although a similar reduction in blood pressure was attained in the two groups of CHF patients after treatment, only torasemide-treated patients exhibited a significant reduction in myocardial fibrosis. Therefore, the possibility exists that the ability of torasemide to decrease myocardial fibrosis in CHF patients is not only linked to diminished mechanical overload but may also be related to interference

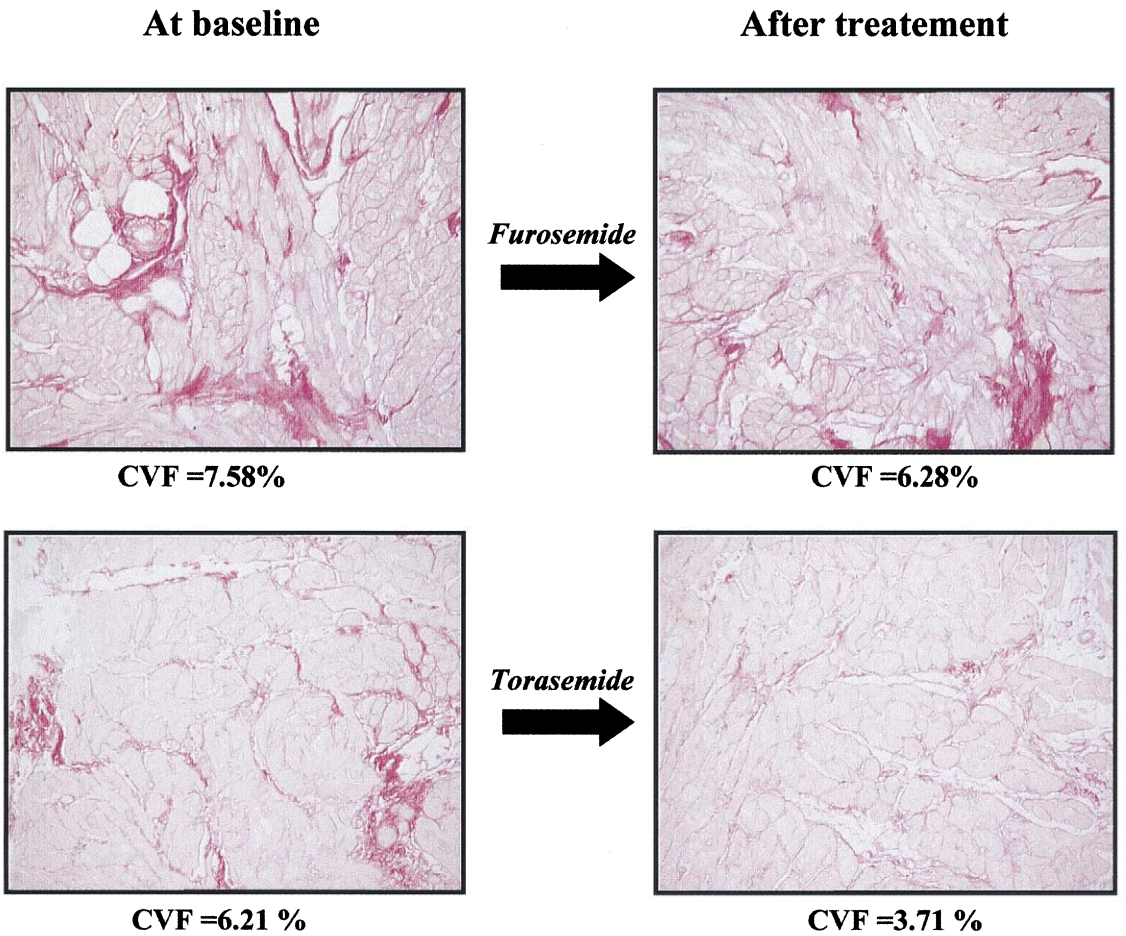

Figure 2. Histologic sections of a myocardial biopsy specimen from a patient with chronic heart failure before **(upper left panel)** and after **(upper right panel)** treatment with furosemide. Histologic sections of a myocardial biopsy specimen from a patient before **(lower left panel)** and after **(lower right panel)** treatment with torasemide. (Picrosirius red stain; magnification ×20.) CVF = collagen volume fraction.

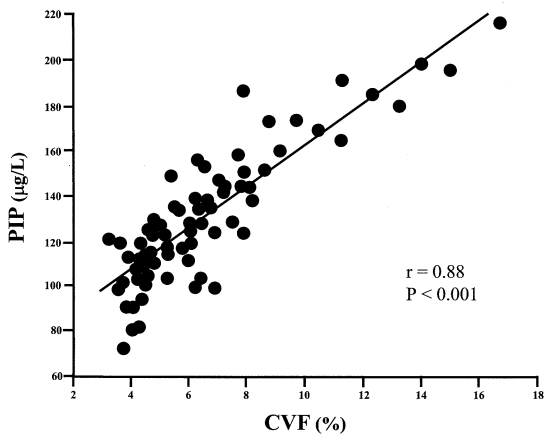

Figure 4. Direct correlation (y = 68.08 + 9.41x) between collagen volume fraction (CVF) and serum carboxy-terminal peptide of procollagen type I (PIP) in patients with chronic heart failure before and after treatment.

with humoral profibrotic factors such as aldosterone (10,11) and angiotensin II (35). Although recent experimental (14) and clinical (4) findings show that torasemide, but not furosemide, inhibits the secretion of aldosterone, data herein reported do not support the ability of torasemide to diminish plasma levels of this hormone. Nevertheless, the possibility remains that, as shown in in vitro studies, torasemide blocks the binding of the hormone to its mineralocorticoid receptor (15). On the other hand, it has been reported that, in vitro, torasemide, but not furosemide, inhibits angiotensin II-stimulated signaling pathways in vascular cells, whereas furosemide does not (36,37). Alternatively, torasemide may stimulate antifibrotic humoral factors such as prostacyclin (38,39). In fact, it has been reported that in patients with CHF, torasemide stimulates the release of prostacyclin to a greater extent than does furosemide (40). Clearly, further studies are required to investigate the precise mechanism(s) of the antifibrotic effect of torasemide in CHF patients.

Effects on collagen type I turnover. A second finding of this study is that the synthesis of collagen type I molecules, as assessed by the serum level of PIP, is reduced after treatment in torasemide-treated CHF patients, but not in furosemide-treated CHF patients.

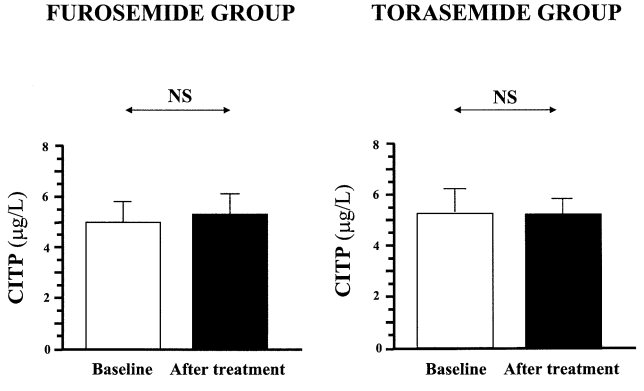

Figure 5. Effects of furosemide (n = 17) and torasemide (n = 19) on serum carboxy-terminal telopeptide of collage type I (CITP) in patients with chronic heart failure. NS = nonsignificant.

The 100-kd C-peptide PIP is freed during the extracellular processing of procollagen type I into the fibril-forming collagen type I molecules (41). The released peptide is found in an immunochemically intact form in blood. A certain amount of clinical and experimental evidence supports the notion that the serum concentration of PIP reflects the rate of extracellular synthesis of collagen type I (9,42). Due to its pharmacologic properties (5,43), torasemide does not seem to be able to interfere with the hepatobiliary elimination of PIP. Thus, our finding that serum PIP diminishes in torasemide-treated CHF patients suggests that this agent inhibits the extracellular synthesis of collagen type I molecules.

A number of observations have led to the proposal that the increased production of PIP is associated with exaggerated myocardial deposition of collagen type I fibers in cardiac diseases (44–46). This is further reinforced by the correlation found here between CVF and PIP in all CHF patients before and after treatment. It is thus tempting to speculate that the ability of torasemide to inhibit the cardiac synthesis of collagen type I might be involved in its capacity to reduce myocardial fibrosis in CHF patients.

The 12-kd, cross-linked C-terminal telopeptide CITP, which results from the cleavage of collagen type I by collagenase, is found in an immunochemically intact form in blood (47). On the basis of a number of clinical and experimental observations, it has been suggested that the serum concentration of CITP reflects the rate of extracellular degradation of collagen type I (17,42). Because circulating CITP is excreted by glomerular filtration, it is unlikely that torasemide modifies the serum concentration of this peptide through changes in its rate of renal clearance. Thus, the tendency toward increased CITP, despite the decrease in PIP, observed in torasemide-treated CHF patients suggests that this compound stimulates the degradation of collagen type I fibers and tends to restore the equilibrium between collagen type I synthesis and degradation in CHF patients.

Study limitations. This was an individually randomized, open-label, parallel-group pilot study involving a relatively small number of patients. However, because of the nature of the hypothesis under investigation, this design is appropriate. While appreciating that therapy with ACE inhibitors or angiotensin receptor antagonists and beta-blockers may have influenced the main parameters tested, one must consider that, as standard therapies for CHF, it would be unreasonable to withdraw any of them for the purposes of this investigation, and in this study, the groups were balanced for these therapies at baseline.

As picrosirius red binds to collagen molecules other than type I, such as type III, and an excess of collagen type III deposition occurs in the myocardium of patients with CHF (8), we cannot exclude the possibility that the changes in myocardial fibrosis found in our patients are also caused by

changes in the deposition of fibril-forming collagen type III molecules.

Conclusions. We have shown, for the first time, that long-term treatment with different loop diuretics may have a variable impact on myocardial fibrosis in CHF patients. In fact, although torasemide-treated patients exhibited a reduction of myocardial collagen accumulation and a diminution of collagen type I synthesis, furosemide-treated patients did not. Further studies are required to definitively prove that torasemide possesses cardioreparative properties that, in turn, may provide an additional benefit, on top of ACE inhibitors or angiotensin receptor antagonists and beta-blockers, in CHF patients receiving this agent.

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