

Collagen Synthesis and Heart Failure

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Little is known about collagen metabolism in heart failure, with or without left ventricular systolic dysfunction. We studied serum concentrations of the carboxy-terminal propeptide of procollagen type I (PIP), a marker of collagen type-I synthesis, and of the carboxy-terminal telopeptide of collagen type I (ICTP), a marker of collagen type-I degradation, in 70 patients admitted for heart failure (35 with depressed left ventricular systolic function and 35 with preserved left ventricular systolic function) and in 30 control subjects. Patients with kidney failure, liver disease, metabolic bone disease, rheumatic disease, recent (within 3 months) major trauma or surgery, or serious wounds were excluded. The concentration of the collagen synthesis marker, PIP, was higher in heart failure patients than control subjects, at 140 ± 56.38 mg/L vs 113.66 ± 36.6 µg/L, respectively ($P = .01$). However, there was no difference in the concentration of the collagen degradation marker, ICTP, between heart failure patients and control subjects, at 2.89 ± 2.37 mg/L vs 2.26 ± 1.7 µg/l, respectively. In heart failure patients, left ventricular systolic function had no significant effect on the PIP or ICTP concentration.

Key words: *Fibrosis. Heart failure. Mechanisms. Myocardium. Hypertrophy.*

Síntesis de colágeno e insuficiencia cardíaca

Se desconoce el metabolismo del colágeno en la insuficiencia cardíaca con y sin disfunción sistólica ventricular izquierda. Estudiamos las concentraciones de los marcadores de síntesis de colágeno tipo I (péptido C-terminal del procolágeno tipo I [PIP]) y de degradación (telopéptido del colágeno tipo I [CITP]) en un grupo de 70 pacientes tras un ingreso por insuficiencia cardíaca (35 con función ventricular izquierda deprimida y 35 con función ventricular conservada), así como en 30 individuos sanos. Excluimos a los pacientes con insuficiencia renal, enfermedad hepática, enfermedad autoinmunitaria o del metabolismo óseo, traumatismo mayor y cirugía reciente (< 3 meses) y heridas extensas. Encontramos mayores concentraciones del marcador de síntesis colágena (PIP) en los pacientes con insuficiencia cardíaca respecto al grupo control ($140 \pm 56,38$ frente a $113,66 \pm 36,6$ µg/l; $p = 0,01$), sin que se apreciaran diferencias en el marcador de degradación (CITP) ($2,89 \pm 2,37$ frente a $2,26 \pm 1,7$ µg/l). No observamos diferencias significativas entre los valores medios de PIP y CITP en pacientes con insuficiencia cardíaca con función sistólica conservada frente a deprimida.

Palabras clave: *Fibrosis. Insuficiencia cardíaca. Mecanismos. Miocardio. Hipertrofia.*

INTRODUCTION

Heart failure (HF) is a health problem of growing importance in the Western world due to a high prevalence¹ in association with longer life expectancies, as

well as to high mortality, comparable to that of cancer.² A high percentage of patients hospitalized for HF present normal ventricular function,³ and therefore a better understanding of the mechanisms implicated in the onset and development of HF would allow optimal therapeutic strategies to be developed in order to control this 21st-century "epidemic."¹

Collagen synthesis and degradation in the healthy heart is an ongoing balanced process⁴ that can become altered under certain clinical situations, such as ventricular hypertrophy of hypertensive origin⁵ or after acute myocardial infarction.⁶ A close correlation has been reported between the histological diagnosis of hypertensive myocardial fibrosis in animals⁷ and hy-

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pertensive patients⁶ and noninvasive biochemical markers of myocardial fibrosis,⁴ such as the C-terminal peptide of procollagen type I (PIP) which originates in procollagen type I through a C-terminal endopeptidase during conversion to collagen type I (CITP), or the telopeptide of collagen type I (CITP) which contains the C-terminal end originated by degradation of collagen type I by a collagenase. Although there are several types of collagen, collagen type I is more abundant in myocardial fibrosis than collagen type III.⁸ In addition, collagen type I is the one most closely correlated with histological myocardial fibrosis and which has normalization of its values and histological fibrosis grade after various therapeutic actions.⁹

The purpose of this study was to analyze the relationship between these collagen type I synthesis and degradation markers (PIP and CITP) in a group of patients hospitalized for HF with and without left ventricular systolic dysfunction compared to a control group.

PATIENTS AND METHODS

We studied 70 patients admitted to our hospital between September 2000 and April 2001 for HF, 35 with depressed left ventricular systolic function (group A) and 35 with preserved ventricular systolic function (group B). Heart failure was diagnosed according to the European Society of Cardiology criteria and based on the presence of symptoms and signs of HF with objective evidence of some structural or functional anomaly of the heart visualized on echocardiography. We excluded patients with renal insufficiency (plasma creatinine >2 mg/dL), liver, autoimmune, or bone metabolism disease, major trauma or surgery in the recent past (last 3 months), and extensive wounds. Thirty subjects with no heart disease were used as a control group. These subjects were of similar age, with no cardiac history, who had come to our office for an electrocardiogram prior to surgery.

The etiology of HF was considered ischemic if the patient presented coronary stenosis >70% on coronary angiography. Ventricular function was measured as of the fifth month (mean, 165 days) after the last hospitalization due to HF, when blood samples were taken to determine markers of myocardial fibrosis, in order to prevent possible influence by precipitating factors for heart failure and recent changes in therapy. The ejection fraction was calculated quantitatively using the Teicholz or Simpson methods when there were alterations in regional contractility. Ventricular function was considered to be depressed if the ejection fraction was <45%.¹⁰ The PIP and CITP determinations were performed twice using radioimmunoassay (Orion Diagnostica) at the Biochemistry Laboratory of the School of Medicine of Malaga, with the final value

taken as the mean of the 2 determinations. All quantitative data are expressed as the mean \pm standard deviation and qualitative data, as percentages. We performed a univariate analysis of between-group differences using the Student's *t* test for continuous variables and the chi-square or Fisher test for categorical variables. Statistical significance was set at a *P* value of less than .05 and SPSS 8.0 was used for the statistical processing.

RESULTS

The patients with HF in group B were older (mean age, 70.3 vs 63.8 years) and there were more women (68% vs 45%) and more patients with hypertension (91% vs 48%) than in group A (Table). In patients with ventricular dysfunction, the etiology was ischemic in 62% of the patients. The time of evolution prior to HF was similar in both groups (mean, 1.8 years).

Collagen Type I Synthesis and Degradation Markers

The mean PIP values were statistically higher for patients with HF than the control group (140 \pm 56.38 vs 113.66 \pm 36.6 μ g/L; *P*=.01) (Figure). However, the differences between groups A and B or between these groups and the control group were not statistically significant (141.85 \pm 68.8; 138.17 \pm 40.83, and 113.66 \pm 36.66 μ g/L, respectively).

TABLE. Baseline Characteristics of Patients*

	HF \leq 45% (Group A) n=35	HF>45% (Group B) n=35	<i>P</i>
Age, years	63.8 \pm 8.8	70.3 \pm 9.3	.004
Women, %	45.7	68.5	.045
Risk factors			
Hypertension	48.6	91.4	.001
Dyslipidemia	20	22.8	.5
Smoking	40	20	.06
Diabetes mellitus	42.8	48.5	.3
Ischemic heart disease	62.9	14.3	.001
Treatment			
Beta-blockers	42.8	28	.25
Calcium antagonists	12.8	28.2	.10
ACE inhibitors/ARBs	82.8	74.3	.06
Diuretics	68.5	68.5	.5
Digoxin	22.8	28.6	.4
Sinrom	20	22.8	.5
Statins	14.2	17.1	.5
Atrial fibrillation	37.1	45.7	.17
EF, %	33 \pm 11.5	61.9 \pm 7.2	.001

*ACE inhibitors indicates angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; EF, ejection fraction; HF, heart failure. Qualitative variables are expressed in percentages. Quantitative variables are expressed at mean \pm standard deviation.

We found no differences in mean CITP values between HF patients and the control group (2.89 ± 2.37 vs 2.26 ± 1.7 $\mu\text{g/L}$) and there were no differences in CITP values among patients who had HF, with or without ventricular systolic dysfunction.

DISCUSSION

Numerous observations indicate that the transition from compensating hypertrophy to HF is related to various cellular and tissue changes: loss of the number of cardiomyocytes due to both apoptosis and necrosis, changes in the motor unit and cytoskeleton of the cardiomyocytes and alterations in the extracellular matrix metabolism that leads to fibrosis of the myocardium.¹¹ Under biomechanical stress conditions secondary to pressure overload or ischemia, cardiac fibroblasts are stimulated and increase the synthesis of collagen type I and III molecule precursors, resulting in the collagen fiber build-up that characterizes fibrosis, an effect further enhanced due to reduced collagen degradation caused by inhibition of myocardial collagenase due to hypertension or ischemia. In biopsies of patients with dilated cardiomyopathy, greater synthesis of collagen type I has been reported in patients with ventricular dysfunction versus those without, as well as a higher percentage of collagen type I than collagen type III, which shows greater rigidity.¹² In hypertrophic cardiomyopathy, a predominance of synthesis on collagen type I degradation is also observed.¹³

As far as we are aware, this study is the first to analyze the relationship between the biochemical synthesis and degradation markers of collagen type I (PIP and CITP) in patients with HF. The results of our study appear to indicate differences in the collagen type I synthesis marker among the entire group of patients with HF compared to the control group, without differences in the collagen type I degradation marker. This suggests increased myocardial fibrosis in both types of HF with increased synthesis, without variations in collagen type I degradation.

It is well established that myocardial fibrosis in patients with hypertension is due to an increase in PIP values with normal concentrations of CITP, which favors myocardial fibrosis.¹⁴ Several therapeutic approaches based on drugs that control the major physiological stimuli on myocardial fibrosis—angiotensin II and aldosterone—(e.g., angiotensin receptor antagonists,¹⁴ angiotensin receptor antagonists¹⁵ or spironolactone¹⁶) are able to reduce the levels of collagen synthesis markers.

In HF, the situation appears to be similar to that described in patients with hypertension. Elevated concentrations of collagen synthesis markers (PIP) and normal values of degradation markers (CITP) are

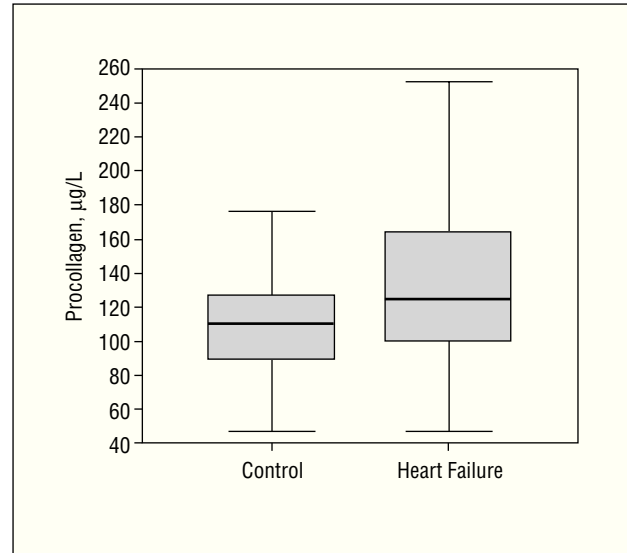


Figure. C-terminal peptide of procollagen type I (PIP) in patients with HF and in control group.

observed, favoring myocardium collagen deposits and myocardial fibrosis.

LIMITATIONS

The small number of patients in our study could have limited the statistical power for finding differences between the groups. We do not know if the time point at which myocardial fibrosis markers are determined after hospitalization for HF has any influence or if there is any temporal relationship with the start of the process, although no differences were found between the groups of patients with HF. Many of the patients had been previously treated with drugs that can alter the fibrosis process, another potential limitation of this study. Apart from ejection fraction, the groups with and without systolic dysfunction differ in other variables, such as age, percentage of ischemic etiology, and hypertension, which could also have affected the results (including fibrosis markers) in some way.

CONCLUSIONS

Higher concentrations of collagen type I synthesis and degradation markers were observed in patients diagnosed with HF than a control group of healthy volunteers.

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