Rev Clin Esp. 2016;216(2):55–61

Revista Clínica Española

www.elsevier.es/rce

ORIGINAL ARTICLE

Absence of cystatin C involvement in ventricular remodelling and heart failure☆

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Received 30 August 2015; accepted 1 November 2015
Available online 20 January 2016

KEYWORDS
Cystatin C;
Heart failure;
Ventricular remodeling;
Housekeeping genes;
Cystein proteases

Abstract Cystatin C (CysC) is a protease encoded by housekeeping genes. Although its prognostic value in heart failure (HF) is well known, it is debatable whether this value is due to the greater accuracy of CysC in calculating the glomerular filtration rate or to its involvement in pathological ventricular remodeling. The aim of this study was to determine whether CysC expression changes in the myocardium of fetuses of different ages and in the myocardium of adults with various cardiovascular diseases, as well as to analyze the correlation between its serum concentrations and cardiac structure and morphology in a patient group with HF.
Patients and methods: We analyzed the correlations (Pearson's *r* and Spearman's test) between the serum CysC levels and echocardiographic parameters of 351 patients with HF. We also performed immunohistochemical staining for CysC, metalloproteinase-9 (MMP-9) and desmin in 9 cardiac tissue samples from autopsies of 4 fetuses of different gestational ages and 5 healthy adults or adults with cardiovascular disease.
Results: For the patients with HF, there was no correlation between the CysC concentrations and the cardiac parameters measured by 2D echocardiography. The immunohistochemistry showed a weak background staining for CysC in all samples, regardless of age and the presence or absence of cardiovascular diseases.

☆ Please cite this article as: Pérez-Calvo JI, Castiella Muruzábal T, Búcar Barjud M, Josa Laorden C, Sánchez Marteles M, Lacambra Blasco I, et al. Ausencia de implicación de la cistatina C en el remodelado ventricular y la insuficiencia cardiaca. Rev Clin Esp. 2016;216:55–61.

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Conclusions: Our results suggest that CysC does not have a significant role in the pathological remodeling of the left ventricle in HF.

PALABRAS CLAVE
Cistatina C;
Insuficiencia cardiaca;
Remodelado ventricular;
Genes de mantenimiento;
Cisteín proteasas

Ausencia de implicación de la cistatina C en el remodelado ventricular y la insuficiencia cardiaca

Resumen La cistatina C (CisC) es una proteasa codificada por genes de mantenimiento («*housekeeping genes*»). Aunque su valor pronóstico en la insuficiencia cardiaca (IC) es bien conocido, se debate si es debido a su mayor precisión en la estimación del filtrado glomerular, o a su implicación en el remodelado ventricular patológico. El propósito de este estudio fue comprobar si la expresión de CisC se modificaba en el miocardio de fetos de diferentes edades y en el de adultos con diversas enfermedades cardiovasculares, así como analizar la correlación entre sus concentraciones séricas y la estructura y morfología cardiaca en un grupo de pacientes con IC.
Pacientes y métodos: Se analizaron las correlaciones (test de Pearson y Spearman) entre la CisC sérica y los parámetros ecocardiográficos de 351 pacientes con IC. También se realizó una tinción inmunohistoquímica para CisC, metaloproteinasa 9 (MMP-9) y desmina en 9 muestras de tejido cardiaco procedentes de las autopsias de 4 fetos con diferente edad gestacional y 5 adultos sanos o con enfermedad cardiovascular.
Resultados: En pacientes con IC no se encontró correlación entre las concentraciones de CisC y los parámetros cardiacos medidos por ecocardiografía 2 D. La inmunohistoquímica mostró una débil tinción de fondo para CisC en todas las muestras, independientemente de la edad y la presencia o no de enfermedades cardiovasculares.
Conclusiones: Nuestros resultados sugieren que la CisC no tiene un papel significativo en el remodelado patológico del ventrículo izquierdo en la IC.

Background

Cystatin C (CysC) is a cysteine-rich protease inhibitor protein, which is widely distributed in human biologic fluids.[1] CysC has a low molecular weight and is formed by 120 amino acids in a single chain. It is synthesized as a preprotein and transmits a representative peptide signal of its extracellular function.[2] The gene that encodes CysC is located in chromosome 20[3] and belongs to the genes known as housekeeping genes. There is therefore no specific expression in any tissue, but rather its distribution is ubiquitous (kidneys, liver, pancreas, intestine, stomach, lung, placenta and seminal vesicles).[4] The principal physiological function of CysC is regulating the activity of extracellular cysteine proteases.[5,6] Given its participation in the equilibrium between proteases and antiproteases, it has been suggested that CysC is involved in tissue remodeling,[7] atherosclerosis, aortic aneurysms[8] and left ventricular (LV) hypertrophy[9] and, as a result, in the pathogenesis of heart failure (HF).[10,11]

CysC behaves as a prognostic factor that is inversely related to the quality of aging[12] and directly related, in the general population, with the onset of cardiovascular events[13] and the incidence of HF.[14–16] For individuals who already have HF, CysC is a robust prognostic marker of mortality, both in acute[17–19] and chronic[20] HF, regardless of ejection fraction (EF).[21] It is not known whether the prognostic capacity of CysC is due to its involvement in ventricular remodeling, as suggested by Pate et al.,[10] or to its greater accuracy in calculating the glomerular filtration rate (GFR),[22] whose prognostic capacity in HF is well known.[23]

This study is designed to analyze whether there are changes in CysC expression in the ventricular myocardium that are dependent on age and cardiovascular health. The study also analyzes whether plasma CysC concentrations have any relationship with the structural changes in the heart in already established HF.

Patients and methods

We studied 2 groups of unrelated patients.

Analysis of CysC in myocardial tissue

We selected 9 myocardial tissue samples obtained from clinical autopsies (Table 1), which were subjected to immunohistochemical staining for CysC, matrix metalloproteinase 9 (MMP9) and desmin.