Two-dimensional Strain Echocardiography in the Evaluation of Ventricular Function in Patients with Newly Diagnosed Hereditary Hemochromatosis

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ABSTRACT

Background: Hereditary hemochromatosis is a genetic disorder characterized by systemic iron overload which can involve the heart in advanced stages. Early myocardial involvement has not been thoroughly investigated.

Objective: The aim of our study was to evaluate the performance of conventional Doppler-echocardiography and 2D strain echocardiography in a group of patients with newly diagnosed hereditary hemochromatosis vs. a control group.

Methods: Patients with newly diagnosed hereditary hemochromatosis without treatment were included. All the patients underwent conventional Doppler echocardiography and 2D strain echocardiography with evaluation of left ventricular longitudinal, radial and circumferential strain, twist and torsion.

Results: Twenty-three male patients with hereditary hemochromatosis (46±18 years) and 20 male controls (45±15 years) were included. There were no differences in ventricular dimensions and wall thickness. Left ventricular ejection fraction was lower in patients with hereditary hemochromatosis (59±4% vs. 62±4%; p=0.01). There were no differences in MAPSE, TAPSE and left ventricular s’ velocity. There was a significant decrease in global strain in patients with hereditary hemochromatosis, with greater involvement of radial strain (37±12 % vs. 55±17%; p=0.01) and circumferential strain (-19.5±2.8 % vs. -22.5±2.8%; p=0.001), and less involvement of longitudinal strain (-19±1.8 % vs. -21.1±2.5%; p=0.04). Myocardial rotation showed lower twist (17.7±13° vs. 25±7°; p=0.03) and lower torsion (2.3±1.8°/cm vs. 3.3±1.1°/cm; p=0.03). There was no correlation between the different strain parameters and iron metabolism.

Conclusions: Echocardiography, and particularly 2D strain analysis can detect early abnormalities of ventricular mechanics in asymptomatic patients with systemic iron overload due to hereditary hemochromatosis.

Key words: Echocardiography - Hemochromatosis - Heart Diseases - Iron

RESUMEN

Introducción: La hemocromatosis hereditaria es una enfermedad genética que genera una sobrecarga sistémica de hierro, y en etapas avanzadas puede afectar el corazón. El compromiso miocárdico precoz por esta enfermedad no ha sido suficientemente investigado.

Objetivo: Comparar mediante ecocardiografía Doppler convencional y strain 2D un grupo de pacientes con diagnóstico reciente de hemocromatosis hereditaria vs. un grupo control.

Material y métodos: Se estudiaron pacientes con diagnóstico reciente de hemocromatosis hereditaria, no tratados. Se les realizó un ecocardiograma Doppler convencional y strain bidimensional, evaluando la deformación longitudinal, radial, circumferencial, giro y torsión del ventrículo izquierdo.

Resultados: Participaron 23 varones con hemocromatosis hereditaria (46 ± 18 años) y 20 controles (45 ± 15 años). No hubo diferencias en los espesores y tamaños ventriculares. Los pacientes con hemocromatosis hereditaria tuvieron una fracción de eyección del ventrículo izquierdo menor (59 ± 4% vs 62 ± 4%; p=0.01). No hubo diferencias en ESPAM, el TAPSE y onda s´ del ventrículo izquierdo. Se observó una disminución significativa del strain en los pacientes enfermos, con mayor compromiso de la deformación radial (37 ± 12 % vs 55 ± 17%; p=0.01), y circumferencial (-19.5 ± 2.8 % vs -22.5 ± 2.8%; p=0.001), y en menor medida de la longitudinal (-19 ± 1,8 % vs -21,1 ± 2,5 %; p=0.04). También este grupo tuvo menor rotación apical, menor giro (17,7 ±13° vs 25 ±7°; p=0.03) y menor torsión (2,3 ± 1,8°/cm vs 3,3 ± 1,1°/cm; p=0.03). No hubo correlación entre los diferentes tipos de deformación y los parámetros bioquímicos del metabolismo férrico.

Conclusiones: La ecocardiografía y especialmente la evaluación del strain 2D es capaz de detectar de manera temprana ligeras alteraciones de la mecánica ventricular, en pacientes asintomáticos, con sobrecarga sistémica de hierro por hemocromatosis hereditaria.

Palabras clave: Ecocardiografía - Hemocromatosis - Cardiopatías - Hierro
INTRODUCTION
Hereditary hemochromatosis (HH) is a term used to describe a group of genetic disorders characterized by increased iron absorption, in the presence of normal or elevated body iron levels. (1, 2) The accumulation of excess body iron saturates the mechanisms of iron transportation and storage and leads to the formation of reactive oxygen species, the main determinants of cell dysfunction and death, via the Fenton reaction. (3, 4) Epidemiological data show that cardiomyopathy is one of the main causes of morbidity and mortality in patients with HH. (5-7)

In patients with iron overload secondary to β-thalassemia, two-dimensional (2D) strain analysis can detect impairment of contractile function, even in those with preserved left ventricular ejection fraction (LVEF). (8-10) Even though some authors have observed an association between myocardial iron load evaluated by T2* magnetic resonance imaging (MRI) and abnormal strain values, this was not confirmed in other studies. (11, 12)

Patients with β-thalassemia are usually younger and have higher body iron load than those with HH, particularly in the heart; therefore, it is difficult to extrapolate the results obtained from this population to those with HH. Early myocardial involvement in patients with HH has not been thoroughly investigated. The aim of our study was to evaluate the performance of conventional Doppler-echocardiography and 2D strain analysis in a group of untreated patients with recent diagnosis of HH and systemic iron overload versus a control group.

METHODS
Population
A prospective, observational and analytical study was performed including patients with recent diagnosis of HH (<3 months). The following criteria were used for diagnosis: serum ferritin >200 ng/ml in women or >300 ng/ml in men or transferrin saturation >45%, without a secondary cause of iron overload and liver biopsy suggestive of HH with absent/mild fibrosis. (2, 3) The patients had not received specific treatment and were recruited between November 2017 and May 2019 in the Hepatology Unit of the Department of Gastroenterology, Hospital de Clínicas “José de San Martín” (Universidad de Buenos Aires, Buenos Aires, Argentina). The following exclusion criteria were considered: NYHA functional class > I, history of any structural heart disease (as coronary artery disease, hypertrophic or idiopathic cardiomyopathy or heart valve disease), history of atrial fibrillation, diabetes, alcoholism, use of cancer treatment drugs, left bundle branch block or suboptimal ultrasonic window. The results were compared with those of a control group from the institutional outpatient Cardiology clinic, considering sex, age and cardiovascular risk factors. These patients had undergone an exercise stress test or stress echocardiography to rule out myocardial ischemia, with normal results.

Echocardiography
The echocardiographic examination was performed at the Echocardiography Laboratory with a Vivid E9 (GE Health-
Genetic testing for HFE mutations reported 1 (4%) C282Y homozygous and 3 (13%) C282Y heterozygous patients, 3 (13%) H63D homozygous and 5 (22%) H63D heterozygous cases, and no mutations in the rest of the cases.

The liver biopsy showed absence of fibrosis in 48% of the patients and mild fibrosis in 52%. In patients with HH, liver iron overload estimated by MRI was moderate in 39.1% of the cases and severe in 60.9%. None of the cases presented iron overload in the heart by T2* MRI (≥20 ms in 100% of cases).

Conventional Doppler echocardiography
Patients with HH had a non-significant trend toward greater left atrial volume (36±10 ml/m2 vs. 32±6 ml/m2; p=0.15) and greater right atrial area (17±3.5 cm2 vs. 15.1±2 cm2; p=0.12). There were no differences in ventricular dimensions and wall thickness. Left ventricular ejection fraction was lower in patients with HH (59±4% vs. 62±4%; p=0.01) but was not <50% in any of the cases. The parameters of longitudinal function (MAPSE, TAPSE and the s’ velocity determined by tissue Doppler imaging) were similar in both groups. In the evaluation of diastolic function, although early diastolic (E) and late (A) wave velocities of both ventricles was similar in both groups, patients with HH showed a tendency toward lower e’ wave velocity determined by tissue Doppler imaging: 0.09±0.02 m/s vs. 0.11±0.03 m/s; p=0.05 in the left ventricle, and 0.13±0.03 m/s vs. 0.15±0.03 m/s; p=0.10 in the right ventricle. Table 2 summarizes the most relevant findings.

2D strain analysis
In the analysis of ventricular mechanics, there was a significant decrease of GLS in patients with HH, with greater involvement of RS (37±12 vs. 55±17%; p=0.01) and CS (-19.5±2.8% vs. -22.5±2.8%; p=0.001), and less involvement of LS (-19±1.8% vs. -21.1±2.5%; p=0.04). The analysis of myocardial rotation showed lower twist (17.7±13° vs. 25±7°; p=0.03) and torsion (2.3±1.8°/cm vs. 3.3±1.1°/cm; p=0.03) in the apical segments (Table 3). There was no correlation between the different types of strain and biochemical parameters of iron metabolism (Table 4).

Intraobserver correlation
The reproducibility of the different deformation indices was tested in 10 randomly selected patients. Intraclass-intraobserver correlation coefficient was 0.98 (95% CI, 0.92-0.99; p <0.0001) for LS, 0.92 (95% CI, 0.85-0.95; p <0.0001) for RS, 0.92 (95% CI, 0.80-0.97; p <0.0001) for CS and 0.95 (95% CI, 0.81-0.98; p <0.0001) for twist.

DISCUSSION
This study analyzed a population with recently diagnosed HH, systemic iron overload documented by laboratory tests, MRI and liver biopsy, and without cardiovascular symptoms. Chamber diameters, wall thickness and LVEF were preserved, which is consistent with the early diagnosis of the disease, as opposed to the typical descriptions of dilated cardiomyopathy and LV dysfunction characteristic of more advanced stages of HH. However, there were differ-
ences between the two groups in LVEF, which were not explained by markers of longitudinal function as MAPSE and Doppler tissue imaging (DTI)–derived mitral annular peak systolic velocity (s').

This observation justifies a more profound analysis of the pathophysiology of myocardial involvement due to hereditary iron overload.

Iron accumulation in the subepicardial layers of both ventricles has been described in pathology reports. (15, 16) This preferential involvement of the more external myocardial fibers motivates our interest in the study of ventricular mechanics in these patients. Given the normal double helical arrangement of the myocardial fibers with opposite orientation, the involvement of the outermost fibers would justify CS impairment and ventricular torsion in early stages of the disease, even when the subendocardial fibers, which contribute to LS, may be less affected or even preserved. (17-21) Therefore, a selective analysis of the different types of strain that contribute to the complex ventricular mechanics demonstrates a predominant involvement of CS, RS, twist and torsion, even below reference values in some patients, and with significant differences compared to the control group.
This could explain the difference found in LVEF between both groups and a mild but also significant involvement of LS. It is worth mentioning that similar findings have been reported in studies that also evaluated ventricular mechanics in β-thalassemia, another disease associated with myocardial iron overload. In a study comparing 27 patients with β-thalassemia and very high serum ferritin with 27 controls, Monte et al. observed a significant reduction in rotation, twist and torsion with no differences in LS. (11) Recently, Rozwadowska et al. reported a significant reduction in rotation, twist and torsion in 24 patients with HH, with LS reduction as in our study and no differences in LVEF. (22) Byrne et al. evaluated 25 cases with HH and reported a decrease in RS similar to our results, with significantly improvement following a 1-year course of venesection. (23)

Looking at myocardial strain analysis from a pathophysiological point of view, we would like to emphasize that there are not many conditions generating a predominant involvement of the subepicardial layers, as hypertension, coronary artery disease and amyloidosis, to mention a few examples, cause more involvement of subendocardial fibers and LS. (19, 24, 25) Iron overload and pericardial diseases are two of the few entities with subepicardial involvement, resulting in CS impairment, making them an interesting object of study.

Another interesting fact is that in our population with HH, T2* showed absence of myocardial iron deposition. This observation is opposed to the echocardiographic findings suggesting early LV function impairment. Two explanations could justify these findings. Firstly, iron deposition is not the only determining factor in the pathophysiology of the disease, and a possible abnormality of systemic redox status, together with inflammatory, immunological, genetic and environmental factors could directly participate or favor certain susceptibility to cardiac injury caused by iron. (4, 26-28). In fact, in an unpublished investigation, members of this working group together with researchers from the School of Pharmacy and Biochemistry of the University of Buenos Aires found decreased serum levels of coenzyme Q10 (a potent endogenous antioxidant) in patients with HH. Furthermore, this hypothesis could be supported by the lack of correlation observed between echocardiographic parameters and biochemical markers of iron overload, which has also been reported in other studies. (12) Another explanation could be that the normal value of cardiac T2* would be around 40 ms, but that a cutoff point of 20 ms has been accepted to avoid false positive results. (29, 30) In addition, we should add the findings of a recent study of cardiac MRI with T1 mapping technique, which showed that up to two-thirds of patients with systemic iron overload and T2* >20 ms
may have myocardial iron deposition; therefore, some investigators have already proposed T1 mapping as a complement to T2* in the evaluation of these patients. (31, 32)

Beyond these hypotheses, we know that MRI has an undeniable value in the early stages of myocardial iron overload diagnosis; yet, we should bear in mind that Doppler echocardiography is a much more accessible method and that the evaluation of ventricular mechanics by speckle tracking echocardiography provides a more accurate functional evaluation, even in the early stages of the disease, and a more complete understanding of the pathophysiology of myocardial involvement by iron overload.

We consider that this research contributes to the understanding of myocardial functional involvement due to iron overload especially in patients with HH, since most of the current evidence comes from studies in patients with β-thalassemia. In addition, we think that the study of these diseases broadens the field of investigation of ventricular mechanics, focusing on LV rotational dynamics and CS.

The impact of the early diagnosis of myocardial functional involvement in patients with HH remains unknown as well as whether these findings can be translated into a specific treatment with clinical benefit, as has already been proposed for patients with β-thalassemia. (33)

Study limitations
Although the number of patients is significant considering the rarity of the disease, it is a limiting factor for statistical purposes.

CONCLUSION
Patients with recent diagnosis of HH had lower radial strain and circumferential strain, and a minor reduction of longitudinal strain. Rotation, twist and torsion were also lower than in subjects without HH with similar age, sex and cardiovascular risk factors. Echocardiography, and particularly 2D strain echocardiography could be useful to detect early ventricular mechanical abnormalities in asymptomatic patients with systemic iron overload due to HH.

Conflicts of interests
None declared.

(See authors’ conflicts of interest forms on the website/Supplementary material).

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