



LEFT ATRIAL FUNCTION AND VOLUME BY MAGNETIC RESONANCE IN PATIENTS WITH HEREDITARY AMYLOIDOSIS

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ABSTRACT

Background: Left atrial (LA) enlargement is a reliable predictor of adverse cardiovascular events, and reduced atrial function is an independent risk factor for mortality in patients with amyloidosis. The objective of this study was to characterize the LA function in Mexican patients with a confirmed diagnosis of hereditary transthyretin amyloidosis (amyloid transthyretin [ATTR]).

Methods: All consecutive patients with diagnosis of hereditary ATTR who underwent a cardiac magnetic resonance study in the period from March 2016 to June 2017 were included in the study; the volumes and function of the left atrium were evaluated. **Results:** Patients were divided into two groups, one with and one without cardiac amyloidosis. Statistically significant differences were observed between both groups in terms of indexed maximal LA volume, 26 mL versus 35.9mL, $p = 0.03$; indexed minimal LA volume, 10.7 mL versus 13.6mL, $p = 0.03$; and indexed LA pre-contraction volume, 17 mL versus 22.4mL, $p = 0.03$. No statistically significant differences were observed between both groups when comparing neither different ejection volumes nor the different ejection fractions. **Conclusions:** Patients with hereditary ATTR with cardiac involvement have remodeling of the left atrium, with increased atrial volumes, without diminishing its function. (REV INVEST CLIN. 2019;71:387-92)

Key words: Left atrial function. Cardiac magnetic resonance. Familial amyloidosis. Amyloid transthyretin. Left atrial volume.

INTRODUCTION

Transthyretin cardiomyopathy is a rare disease characterized by the accumulation of amyloid fibrils of misfolded transthyretin protein in the heart and is an under-recognized cause of heart failure. The disease is

classified by the sequence of the *TTR* gene, either wild-type amyloid transthyretin (ATTR) or hereditary ATTR; the median survival from diagnosis is 3 to 5 years¹⁻³. In the initial phases of amyloidosis cardiomyopathy, the deposits produce a slight diastolic dysfunction, but as it progresses, a thickening of the walls is produced,

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with worsening of the relaxation and distensibility of the ventricle. As the disease progresses, necrosis of the myocytes is produced (in part by the direct toxic effect of the amyloid), with the development of interstitial fibrosis; as a result of all these phenomena, in the advanced phases of the disease, there may be deterioration of systolic function⁴. The increase in pressure generates restrictive physiology in the most advanced phases, with important atrial enlargement⁵.

Left atrial (LA) enlargement is a reliable predictor of adverse cardiovascular events in patients without a history of atrial fibrillation or significant valve disease. The relationship between atrial volume and atrial diameter is non-linear, and it has been confirmed that volume is a superior measurement to diameter to predict cardiovascular events such as atrial fibrillation⁶⁻¹⁰. In the general population, it has also been demonstrated that atrial diameter is an independent predictor of mortality¹¹. Studies have recently been published about LA function determined by magnetic resonance and its prognostic value in patients with amyloidosis. In multivariate analysis, a low atrial ejection fraction was maintained as an independent risk factor for mortality at 2 years^{12,13}.

The characterization and evaluation of LA volume and function in patients with hereditary ATTR with cardiac involvement are important because, through detection of atrial dysfunction, it is possible to establish a prognosis in the presence of potential cardiovascular complications. The majority of studies published to date have been performed in patients with primary amyloidosis or heterogeneous groups with various types of amyloidosis, and there are no studies done in Mexican population.

METHODS

This study was carried out in the period from March 2016 to June 2017, in the Radiology and Image Department of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, a referral academic hospital. We included all consecutive patients who met the following inclusion criterion: confirmed diagnosis of hereditary ATTR (the diagnosis was confirmed in all patients using genetic testing). The exclusion criteria were: patients under 18 years old, chronic kidney disease with creatinine clearance <30

mL/min/1.73m² (calculated using the Modification of Diet in Renal Disease formula), or amyloidosis other than hereditary ATTR.

Cardiac magnetic resonance (CMR)

CMR was performed with a commercially available 1.5T scanner (Signa, General Electric, Milwaukee, WIS). The studies were conducted following the protocol used by the cardiovascular imaging service: with the patient in supine position and with 8-channel cardiac coil placed on the anterior thorax of the patient; fast imaging employing steady-state acquisition (FIESTA) locator, calibration, and real-time sequences (Fast gradient echo [GRE]-ET) were performed. GRE cinema sequences (FIESTA) in 2, 3, and 4 chamber views and short axis were acquired over periods of apnea with electrocardiographically gating. The mean number of phases was between 25 and 30, which were variable according to the cardiac frequency, to reach a constant time resolution. Furthermore, short T1 inversion recovery (IR) (fast spin echo [FSE]-IR T2) sequences were performed, as well as double IR sequences (FSE-XL T1).

For the evaluation of late gadolinium enhancement (LGE), T1-weighted sequences (Fast GRE IR prepared) were used 10 min after intravenous injection of gadobutrol 0.2 mmol/kg weight (Gadovist 1 mmol/ml, Bayer Schering Pharma, Mexico); the inversion time for a complete myocardial nulling was optimized using a TI scout sequence.

All the CMR images were analyzed using commercially available software GE Report CARD 4.0. To obtain the ejection fraction in the different atrial phases, atrial volumes were calculated in 2 and 4 chamber FIESTA views by the biplane area-length method. For the biplane area-length method, semi-automated segmentation of the LA was performed in the 2- and 4-chamber view; LA volumes were calculated using the following equation: $0.85 \times 4 \text{ chamber area} \times 2 \text{ chamber area/Lmin}$ (shorter long-axis length of the left atrium). The maximal (LAVmax) and minimal (LAVmin) atrial volumes were obtained immediately before mitral opening and at the close of the mitral valve, respectively; pre-atrial contraction (pre-A) volume was obtained before the second diastolic opening of the mitral valves^{12,14-16}.



Pulmonary veins and LA appendage were excluded from the measurements of atrial volume. According to the recommendations in various publications, all volumes were indexed by body surface area obtained by Mosteller formula. Atrial ejection fractions were obtained using the following formulas with indexed volumes¹²:

$$\text{LAEF total} = (\text{LAVmax} - \text{LAVmin}) / \text{LAVmax} * 100$$

$$\text{LAEF passive} = (\text{LAVmax} - \text{LAVpre-A}) / \text{LAVmax} * 100$$

$$\text{LAEF contractile} = (\text{LAVpre-A} - \text{LAVmin}) / \text{LAVpre-A} * 100$$

The patients were divided into two groups according to the results of the CMR: (1) group with cardiac amyloidosis, defined as a CMR with global subendothelial LGE in a non-coronary artery territory distribution, global transmural pattern homogeneous or heterogeneous, patchy focal LGE, suboptimal nulling despite the use of a TI scout; and (2) group without cardiac amyloidosis, defined as a CMR negative for LGE^{3,17,18}.

Statistical analysis

Descriptive statistics were used for baseline characteristics; for quantitative variables with normal distribution, mean and standard deviation were used, and for variables with free distribution, medians with minimum and maximum were used, while percentages were used for qualitative variables. In the comparison of groups, variables with normal distribution used Student's t-test, for variables with non-normal distribution the Mann-Whitney U-test, and for categoric variables, Chi-square squared was used (Pearson or Fisher depending on the expected values). $p < 0.05$ was considered statistically significant. For statistical analysis, the program SPSS Statistics version 22.0 (IBM Corporation) was used.

RESULTS

Study population and baseline characteristics

This study included a total of 30 patients, of whom 16 (53%) showed cardiac involvement. The greater

percentage of patients was female both in the group without amyloidosis and the group with amyloidosis, 57.1% and 75%, respectively, without finding statistical significance between groups. The mean age was similar in both groups, 44 and 45 years, without significant difference ($p = 0.87$). There were also no differences observed between groups regarding body mass index or body surface area, $p = 0.15$ and 0.5, respectively. Comorbidities most frequently found in both groups were dyslipidemia and hypothyroidism, with predominance in the group without amyloidosis, with 2 and 4 cases, respectively; however, no significant differences were observed between groups. Demographic and clinical characteristics are summarized in Table 1.

CMR left ventricle volumes and function

Left ventricle volumes and ejection fraction were within the normal range when indexed for body surface area, both in the group with and in the group without cardiac amyloidosis^{19,20}. There were no statistically significant differences between the two groups (Table 1).

CMR LA volumes and function

LA volumes (indexed for body surface area) and phasic (reservoir, conduit, and pump) functions also were within the normal range in both groups. There were statistically significant differences between the two groups with regard to maximum, minimum, and pre-atrial contraction LA volumes, with higher volumes in the cardiac amyloidosis group (maximum indexed LA volume, 26 mL vs. 35.9 mL, $p = 0.03$; minimum indexed LA volume, 10.7 mL vs. 13.6 mL, $p = 0.03$; and indexed pre-atrial contraction volume, 17 mL vs. 22.4 mL, $p = 0.03$). There were no statistically significant differences in LA phasic (reservoir, conduit, and pump) function between the two groups (Table 2).

DISCUSSION

The objective of this study was to characterize LA volumes, as well as LA function, in patients with hereditary ATTR. It has been demonstrated in previous



Table 1. Demographic, clinical, and CMR characteristics of patients with hereditary transthyretin amyloidosis (ATTR)

Clinical data	Without cardiac hereditary ATTR (n = 14)	With cardiac hereditary ATTR (n = 16)	p (Student's t-test)
Age (years)	44 (± 19)*	45 (± 11)*	0.87
Female sex	8 (57.1)	12 (75)	0.44**
BMI (kg/m ²)	26 (± 4.7)*	24 (± 3.9)*	0.15
BSA (Mosteller)	1.81 (± 0.25)*	1.65 (± 0.19)*	0.05
Comorbidities			
DM type 2	1 (7.1)	0 (0)	0.46**
CKD	1 (7.1)	0 (0)	0.46**
Arterial hypertension	1 (7.1)	1 (6.3)	1.0**
Hypothyroidism	2 (14.3)	1 (6.3)	0.58**
Dyslipidemia	4 (28.6)	1 (6.3)	0.15**
CMR			
LV EDV (mL)	100.8 (± 30)*	102.8 (± 17.9)*	0.82
LV EDV index (mL/m ²)	55.4 (± 15)*	63.2 (± 14.7)*	0.16
LV ESV (mL)	36 (± 13)*	38.3 (± 12.7)*	0.63
LV ESV index (mL/m ²)	19.9 (± 7)*	23.6 (± 8.8)*	0.22
LVEF (%)	64 (± 5)*	63 (± 8)*	0.67

*Mean (\pm Standard deviation). **Fisher's exact test. BMI: body mass index; BSA: body surface area; CMR: cardiac magnetic resonance; DM: diabetes mellitus; CKD: chronic kidney disease; LV EDV: left ventricular end-diastolic volume; LV ESV: left ventricular end-systolic volume; LVEF: left ventricular ejection fraction; ATTR: amyloid transthyretin.

studies that a reduction in LA function in patients with amyloidosis is an independent risk factor for mortality at 2 years, and to date, the reports on atrial function determined by CMR in patients with amyloidosis have been performed in primary amyloidosis (amyloid light [AL]), but none have been performed specifically in patients with hereditary ATTR^{12,13}.

In this study, statistically significant differences were found between both groups in regard to maximum, minimum, and pre-atrial contraction volume, with $p = 0.03$, 0.03 , and 0.03 , respectively, finding greater indexed LA volumes in the group with cardiac amyloidosis, which agrees with the findings of Mohty et al., who documented greater indexed atrial volumes in patients with AL compared with patients without cardiac amyloidosis ($p < 0.0001$)¹³.

Regarding LA ejection fraction, both total and reserve, passive or conduct, as well as active or pump, no statistically significant differences were noted, with $p = 0.25$, 0.95 , and 0.14 , respectively. In both

groups, the mean ejection volumes found were within the reference limits published^{20,21}.

Finally, no statistically significant differences were found in the various ejection fractions between groups, with $p = 0.55$, 0.39 , and 0.97 for total ejection fraction (reserve), passive (conduct), and active (pump), respectively. As in the case of ejection fractions, the mean of the various ejection fractions was also found within the reference limits. This finding is different from that reported by Kwong et al. and by Mohty et al., who observed lower total ejection fractions in patients with AL with cardiac involvement, with $p = 0.0006$ in the study by Kwong et al., and $p < 0.0001$ in the study by Mohty et al.; however, it should be noted that in both studies, the majority or all patients were diagnosed with AL and only one patient with hereditary ATTR was included in the study by Kwong et al. In addition, in those studies, the proportion of atrial enhancement in patients with cardiac amyloidosis was greater than in the control groups, and the infiltration of the atrial



Table 2. Phasic left atrial volume and ejection fraction in patients with hereditary ATTR

CMR measurements	Without cardiac hereditary ATTR (n = 14) Median (Min-Max)	With cardiac hereditary ATTR (n = 14) Median (Min-Max)	p (Mann-Whitney U-test)
LAV max (mL)	46.8 (34.7-98.1)	56.9 (33.6-99.6)	0.14
LAV max index (mL/m ²)	26 (18.8-50.8)	35.9 (18.1-66.4)	0.03
LAV min (mL)	20.8 (13.1-44.7)	23.6 (6.8-57.3)	0.22
LAV min index (mL/m ²)	10.7 (7.8-24.3)	13.6 (3.7-38.2)	0.03
LAV pre-A (mL)	31 (18.2-59)	38.8 (21.1-77.8)	0.16
LAV pre-A index (mL/m ²)	17 (10.7-32)	22.4 (12.4-43.3)	0.03
LAEV total [Reservoir] (mL)	16.8 (±7.4)*	19.7 (±6.3)*	0.25**
LAEF total AI [Reservoir] (%)	57 (±11)*	54 (±13)*	0.55**
LAEV passive [Conduit] (mL)	9.4 (2.2-26.7)	9.5 (5.6-25.1)	0.95
LAEF passive [Conduit] (%)	35 (±13)*	31 (±11)*	0.39**
LAEV active [Pump] (mL)	6.9 (2.1-9.6)	8.1 (2.7-18.7)	0.14
LAEF Active [Pump] (%)	33 (±9)*	34 (±16)*	0.97**

*Mean (± Standard deviation).

**Student's t-test.

LAV: left atrial volume; max: maximal; min: minimal; pre-A: pre-atrial contraction;

LAEV: left atrial ejection volume; LAEF: left atrial ejection fraction; ATTR: amyloid transthyretin.

myocardium may have contributed to a decrease in LA function, which has been shown to be an independent predictor of outcome in the AL population^{12,13,21}.

Our study suggests that patients with hereditary ATTR with cardiac involvement show LA remodeling, with increased atrial volume in its various phases. However, no alteration was shown in ejection volumes and fractions, which may have implications in the better prognosis of these patients compared with AL cardiac involvement, with a median survival from diagnosis of 3 to 5 years versus <12 months, respectively³.

Within the limitations of this study are the fact that it is a secondary analysis of a cohort of patients with hereditary ATTR, so it was not specifically designed considering the object of the study, and the LA measurements were made using the biplane area-length method which underestimates atrial volumes compared with the short-axis method^{14,15}. Another limitation is that the control group consisted of patients with hereditary ATTR, but without data of myocardial involvement determined by CMR, and is not a control group of healthy individuals. However, we decided to perform this study

since to date; nothing has been published on patients exclusively with hereditary ATTR evaluated by CMR.

Studies are required that are specifically designed to establish the clinical and prognostic potential of measuring LA volumes and function in various phases using the short-axis method in patients with hereditary ATTR.

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