Radiología. 2017;59(1):56–63

RADIOLOGÍA

www.elsevier.es/rx

ORIGINAL ARTICLE

Association between ventricular filling patterns and the extent of late enhancement on magnetic resonance imaging in patients with hypertrophic cardiomyopathy☆

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Received 14 January 2016; accepted 8 August 2016

KEYWORDS
Diastole;
Cardiac imaging techniques;
Diastolic heart failure;
Left ventricle

Abstract
Objective: To explore the relationship between ventricular filling curves and the extent of late enhancement on cardiac magnetic resonance imaging (MRI) in patients with hypertrophic cardiomyopathy.
Material and methods: We retrospectively included consecutive patients with suspected and/or confirmed hypertrophic cardiomyopathy and a control group of patients matched for age and sex who underwent cardiac MRI with evaluation of late enhancement. Among other determinations, we evaluated the following parameters on cine sequences: peak filling rate, time to the first peak filling rate, and filling rate normalized to the filling volume.
Results: Late enhancement was observed in 29 (73%) of the 40 patients with hypertrophic cardiomyopathy. The normalized peak filling rate was significantly lower in patients with late enhancement (4.9 ± 1.6 in those with hypertrophic cardiomyopathy positive for late enhancement *vs.* 5.8 ± 2.2 in those with hypertrophic cardiomyopathy negative for late enhancement *vs.* 6.3 ± 1.5 in controls, $p = 0.008$) and the time to peak filling was longer in patients with late enhancement (540.6 ± 89.7 ms *vs.* 505.5 ± 99.3 ms in those with hypertrophic cardiomyopathy negative for late enhancement *vs.* 486.9 ± 86.3 ms in controls, $p = 0.02$). When the population was stratified into three groups in function of the normalized peak filling rate, significant differences were observed among groups for age ($p = 0.002$), mean wall thickness ($p = 0.036$), and myocardial mass ($p = 0.046$) and atrial dimensions, whereas no significant differences with respect to late enhancement were seen.
Conclusions: In patients with hypertrophic cardiomyopathy, we found a significant association between ventricular filling patterns and age, wall thicknesses, and atrial dimensions, but not with the extent of late enhancement.

☆ Please cite this article as: De Zan M, Carrascosa P, Deviggiano A, Capunay C, Rodríguez-Granillo GA. Asociación entre patrones de llenado ventricular y extensión del realce tardío por resonancia magnética en pacientes con miocardiopatía hipertrófica. 2017;59:56–63.

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PALABRAS CLAVE
Diástole;
Técnicas de imagen cardíaca;
Insuficiencia cardíaca diastólica;
Ventrículo izquierdo

Asociación entre patrones de llenado ventricular y extensión del realce tardío por resonancia magnética en pacientes con miocardiopatía hipertrófica

Resumen
Objetivo: Explorar mediante resonancia magnética cardíaca la relación entre las curvas de llenado ventricular y la extensión del realce tardío (RT) en pacientes con miocardiopatía hipertrófica.
Material y métodos: Se incluyeron de forma retrospectiva pacientes consecutivos con sospecha y/o diagnóstico de miocardiopatía hipertrófica, y un grupo control de pacientes pareados según sexo y edad en quienes se realizó una resonancia magnética cardíaca con valoración de RT. Entre otras determinaciones, se evaluaron mediante secuencias cine: tasa de llenado pico, tiempo a la primera tasa de llenado pico y tasa de llenado pico normalizada al volumen de llenado.
Resultados: De los 40 pacientes con miocardiopatía hipertrófica, 29 (73%) presentaron RT. Se evidenciaron diferencias significativas respecto a la tasa de llenado pico normalizada (RT positivo $4{,}9 \pm 1{,}6$, *vs.* RT negativo $5{,}8 \pm 2{,}2$, *vs.* control $6{,}3 \pm 1{,}5$, $p = 0{,}008$) y al tiempo a la tasa de llenado pico ($540{,}6 \pm 89{,}7$ ms, *vs.* $505{,}5 \pm 99{,}3$ ms, *vs.* $486{,}9 \pm 86{,}3$ ms, $p = 0{,}02$). Al estratificar la población en tercios según la tasa de llenado pico normalizada al volumen de llenado se registraron diferencias significativas entre los grupos respecto a la edad ($p = 0{,}002$), espesor parietal medio ($p = 0{,}036$), masa miocárdica ($p = 0{,}046$) y dimensiones auriculares, mientras que no se observaron diferencias significativas respecto al RT.
Conclusiones: En pacientes con miocardiopatía hipertrófica encontramos una asociación significativa entre patrones de llenado ventricular y edad, espesores parietales y dimensiones auriculares, mientras que no se identificó una relación significativa con la extensión del RT.

Introduction

Most patients with hypertrophic myocardiopathy (HMC) have some degree of diastolic dysfunction.[1,2] Prognosis of patients with con systolic heart failure is similar to that of patients with diastolic dysfunction.[3,4] It can be inferred from this that it is essential to characterize diastolic function in patients with HMC, since it is one of the variables that most influence prognosis.

The role of magnetic resonance (MRI) in the assessment of ventricular systolic function is well-known.[5] However, the diastolic function through MRI is not usually evaluated systematically, despite the fact that many studies have confirmed that there is a correlation with Doppler echocardiogram.[6,7]

Measurement of transmitral flow is one of the most frequently recommended modalities to evaluate diastolic function though it requires acquisition of additional images. On the contrary, the peak ventricular filling rate (PVFR), estimated by ventricular filling curves, is an appealing option, especially due to the fact that it is obtained from usual sequences, that it does not require the injection of contrast and that its value can be normalized as opposed to different parameters and thus become independent from the loading conditions.[8] On the other hand, late enhancement (LE) after the administration of contrast is another tool that has proved to keep a very good correlation with the presence of fibrosis. The association between the presence and spread of LE and the incidence of arrhythmic events and systolic dysfunction is well established in patients with HMC. Nevertheless, its relation with diastolic function parameters is less known.[9–11]

The goal of our study was to analyze through the use of MRIs the relation between atrioventricular filling curves and LE spread in patients with HMC.

Material and methods

Patients

Observational study that included consecutive patients with diagnosis or suspicion of HMC where patients undergo MRI for the evaluation of the morphology, ventricular function and presence of LE. They were selected retrospectively from our database if they had been diagnosed of HMC during the period of time between September 2013 and 2014. The study excluded those patients with cine sequences with movement artifacts that did not allow us to correctly outline the endocardium entirely. The diagnosis of HMC was based on the presence of parietal thickness $\geq$15 mm, for the lack of heart conditions associated with ventricular hypertrophy or serious arterial hypertension.[12]

The control group was made up of non-diabetic individuals who did not have uncontrolled arterial hypertension, with normal MRI, paired in terms of sex and age and studied thorough MRI to rule out myocardiopathy since they showed ventricular arrhythmia, syncope or inconclusive echocardiograms. The MRI was tagged as normal when in presence of cavities with normal size and thickness, normal global and regional systolic function, without pathological signal increase in T1 or T2-weighted sequences, pericardium of normal thickness and signals, large vessels of normal size, absence of valvulopathies, congenital heart disease

and/or masses, and absence of myocardial LE in the early diagnosis.

All proceedings were performed in keeping with the standards of the institutional research ethics committee, and in compliance with the 1964 Helsinki declaration and its subsequent addenda. Written informed consent was obtained from all individuals included in the study.

Acquisition technique of cardiac magnetic resonance images

The images were acquired using a 1.5 T MRI machine (Achieva, Philips Medical Systems, Best, The Netherlands). A five-channel, specific cardiac antenna was used and the images were acquired through cardiac synchronization with vectocardiogram. Cine-MRI turbo gradient echo balanced sequences were obtained in stationary state (TR: 3.5 ms; TE: 1.8 ms and angle: 60°), at the end of expiration, on 2 camera-planes, 4 camera-planes and short axis of the entire left ventricle from the base to the apex for the functional analysis of the ventricle. The LE sequences were obtained through a T1-weighted echo gradient sequence after waiting for 10 min after the IV administration of 0.2 mmol/kg gadolinium contrast.

Analysis of cardiac magnetic resonance images

The analysis was performed by an experienced observer (over 10 years of experience in heart imaging), who did not know about the patient's clinical data, at a workstation (View Forum; Philips Medical Systems; Best, The Netherlands) using specific *software*. Analysis of the left atrium: diameter, area and atrial volume at the end of the systole were calculated by outlining the atrial border as well as the anterior–posterior diameter, excluding the ostium of the veins and the left atrial appendage, in 2-, 3- and 4-camera views.

The telediastolic and telesystolic stages were defined in the short-axis cine sequences of the left ventricle and the epicardium and the endocardium were semi-automatically outlined excluding the papillary muscles. This is how the telediastolic volume, the telesystolic volume, the stroke volume and ejection fraction were calculated. The thickness of the myocardium was measured at telediastole in 16 segments (segmentation of the American Heart Association) and the apex was excluded; the average of the 16 segments for each patient was obtained.[13] Quantification of myocardial mass was performed in telediastole.

To characterize the diastolic function the ventricular filling patterns were determined through manual outlining of the endocardial edge by excluding papillary muscles and trabeculae in all stages of the cardiac cycle in all the short-axis cine sequences from base to apex. The following parameters were evaluated: PVFR (ml/s), time to PVFR (tPVFR, ms), PVFR normalized by first filling volume ($nPVFR^{vol}$), PVFR normalized by systolic volume ($PVFR^{sv}$) and second PVFR (ml/s). This is how the ventricular filling curves were obtained (volume in time). The steepest tangent line of the first part of the curve is the first PVFR (Fig. 1), while the tangent line of the second part of the curve is the second PVFR. The software automatically calculates all these parameters.[8]

The presence of LE was defined visually in the post-contrast T1-weighted echo gradient sequences as a significant increase of the signal compared with the remote myocardium; this analysis shows a high correlation with the one obtained using a threshold ≥6 standard deviations than the average intensity of the normal myocardium signal.[14] The total percentage of LE was determined (% LE) in all the short axes, adding the LE areas measured semi-automatically through planimetry in relation with the area of the normal myocardium. The number of segments with LE was also determined.

Statistical analysis

Parametric comparisons were expressed as frequencies and percentages and the continuous variables as mean ± standard deviations in case of normal distribution and as median with interquartile range between groups (age, size of the left atrium, ventricular morphology and function in patients with HMC and the presence and absence of LE *vs*. control group) were performed through ANOVA, and the Fisher test of minimal significant difference for the multiple comparisons (*post hoc*) between the groups. The non-parametric comparisons among the groups (LE according to terciles of $nPVFR^{vol}$) were performed using Kruskal–Wallis and Games–Howell tests. The correlations between the parameters derived from the ventricular filling curves (PVFR/nPVFR) and the demographic morphologic variables (age, atrial sizes, parietal thickness and LE) were performed by obtaining Spearman's correlation coefficients. To evaluate the reproducibility of the filling patterns, the first 25 patients with HMC were reanalyzed by the same observer and the by a second observer (3 years of experience in cardiac images including MRIs). These results (intra and interobserver) were analyzed using intraclass correlation coefficients (two-way random effect models, absolute agreement and average measures) with 95% IC. The level of statistic significance was established at a p value below 0.05. The analyses were conducted using the statistical software SPSS, version 22.0 (Chicago, Illinois, USA).

Results

Out of the 42 patients evaluated with HMC, two were excluded because they showed cine sequences with movement artifacts. Out of the 40 patients with HMC, 29 (73%) showed LE with a HMC-like pattern (group LE+), while in 11 patients (27%) no LE was evident (group LE−). None of the patients of the control group (control group, n = 30) showed LE.

The dimensions of the left atrium were significantly greater in patients with HMC than in the control group, in a consistent manner in all the variables studied. Both in terms of the diameter (LE+ 39.8 ± 9.4 mm *vs*. LE− 39.7 ± 7.1 mm *vs*. control 31.5 ± 6.8 mm, $p < 0.0001$), the area in 2 chambers (LE+ 24.9 ± 9.3 cm^2 *vs*. LE− 25.9 ± 8.0 cm^2 *vs*. control 18.7 ± 5.5 cm^2, $p = 0.004$) the area in 4 chambers (LE+ 26.7 ± 8.4 cm^2 *vs*. LE− 26.9 ± 4.8 cm^2 *vs*. control 20.0 ± 4.0 cm^2, $p < 0.0001$), and volume (LE+ 56.8 ± 26.9 cm^2 *vs*. LE− 56.0 ± 17.1 cm^2 *vs*. control 37.7 ± 10.4 cm^2, $p = 0.001$).

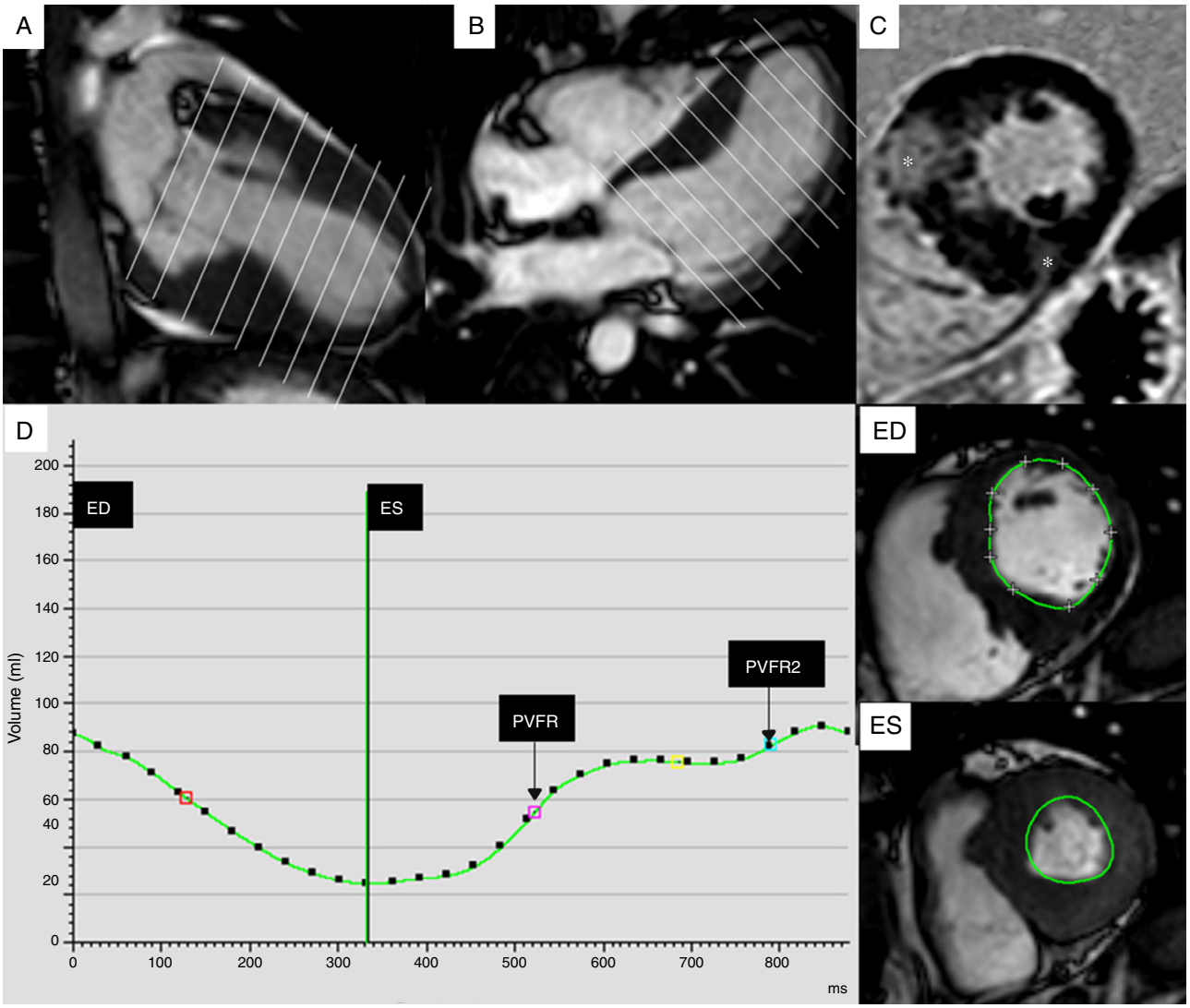

Figure 1 Evaluation of ventricular filling patterns through short-axis cine sequences from base to apex. First, the short axes are obtained from views of 2 and 4 cameras (A and B). Then, the endocardium is outlined manually by excluding the papillary muscles and the trabeculae and the outlines are spread automatically to the entire cardiac cycle, with manual correction (lower right panel). The ventricular filling curves derive from this (D), where after establishing the phases of end-diastole (ED) and end systole (ES) it is possible to identify the peak ventricular filling rate (PVFR) and its corresponding time to the PVFR, and the second PVFR (PVFR 2). In panel (C) we can see the presence of anterior-septal extended late enhancement (*) and to a lesser extent inferior-septal late enhancement in a 53-year-old female patient (450 ml/s PVFR, 8.8 $nTLP^{vol}$).

No significant differences were observed in terms of age (LE+ 50.7 ± 17.8 years *vs.* LE− 51.6 ± 19.1 years *vs.* control 45.1 ± 16.3 years, $p = 0.39$), sex [LE+ 17 (59%) men *vs.* LE− 9 (82%) men *vs.* control 14 (47%) men, $p = 0.13$] or heart rate (LE+ 61.2 ± 8.8 bpm *vs.* RT− 60.9 ± 9.2 bpm *vs.* 64.3 ± 14.8 bpm, $p = 0.54$) between the groups.

Morphology and ventricular function

Both the myocardial mass and the parietal thickness were significantly greater in patients with HMC (Table 1) especially the mean parietal thickness (LE+ 10.1 ± 2.2 mm *vs.* LE− 9.3 ± 1.4 mm *vs.* control 5.7 ± 1.0, $p < 0.0001$).

No significant differences were recorded when it comes to the PVFR among patients with HMC and proof of LE and the control group, while significant differences could be observed between both groups when it comes to the $nPVFR^{sv}$ (LE+ 4.9 ± 1.6 *vs.* LE− 5.8 ± 2.2 *vs.* control 6.3 ± 1.5, $p = 0.008$), the tPVFR (LE+ 540.6 ± 89.7 ms *vs.* RT− 505.5 ± 99.3 ms *vs.* control 486.9 ± 86.3 ms, $p = 0.02$), and the second PVFR (LE+ 331.4 ± 113.7 ml/s RT− 210.9 ± 166.7 ml/s *vs.* control 219.1 ± 90.7 ml/s, $p = 0.001$).

When staging the population based on $PVFR^{vol}$ terciles, significant differences could be seen between both groups when it comes to age, mean parietal thickness, myocardial mass and atrial dimensions, while no significant differences

Table 1 Differences in the morphological and functional characteristics of patients with hypertrophic myocardiopathy with and without late enhancement and controls.

	HMC with LE (n = 29)	HMC without LE (n = 11)	Control (n = 30)	*p* value
Morphology and systolic function				
Diastolic diameter (mm)	48.1 ± 4.9	50.1 ± 5.5*	48.2 ± 4.1	0.44
Systolic diameter (mm)	30.0 ± 6.0	31.3 ± 6.1	34.1 ± 4.4	0.02
Diastolic volume (ml/m^2)	68.6 ± 11.8	76.6 ± 15.9*	64.2 ± 11.9	0.02
Systolic volume (ml/m^2)	24.7 ± 11.0	27.6 ± 7.7	28.6 ± 8.1	0.28
Ejection fraction (%)	64.9 ± 10.6	64.5 ± 4.6	56.7 ± 5.7	<0.0001
Myocardial mass (g)	157.8 ± 56.0	158.9 ± 48.8	76.7 ± 16.6	<0.0001
Septal thickness (mm)	20.6 ± 4.6	17.8 ± 2.9	8.9 ± 2.0	<0.0001
Lateral wall thickness (mm)	8.3 ± 2.4	9.2 ± 1.7	6.0 ± 1.4	<0.0001
LA area (4-cameras, cm^2)	26.7 ± 8.4	26.9 ± 4.8	20.0 ± 4.0	<0.0001
LA area (2-cameras, cm^2)	24.9 ± 9.3	25.9 ± 8.0	18.7 ± 5.5	0.004
LA diameter (3 cameras, mm)	39.8 ± 9.4	39.7 ± 7.1	31.5 ± 6.8	<0.0001
LA volume (ml/m^2)	56.8 ± 26.9	56.0 ± 17.1	37.7 ± 10.4	0.001
Median parietal thickness (mm)	10.1 ± 2.2	9.3 ± 1.4	5.7 ± 1.0	<0.0001
Late enhancement (n segments)	4.7 ± 2.8	0	0	<0.0001
Late enhancement (%)	7.1 ± 6.9	0	0	<0.0001
LV diastolic function				
First PVFR (ml/s)	346.6 ± 107.4	483.6 ± 153.7	385.7 ± 111.9	0.006
nPVFR^{vol}	6.8 ± 2.4*	7.4 ± 2.7	8.3 ± 2.6	0.10
nPVFR^{vs}	4.9 ± 1.6	5.8 ± 2.2	6.3 ± 1.5	0.008
tPVFR (ms)	540.6 ± 89.7	505.5 ± 99.3	486.9 ± 86.3	0.02
Second PVFR (ml/s)	331.4 ± 113.7	210.9 ± 166.7	219.1 ± 90.7	0.001

LA: left atrium; HMC: hypertrophic myocardiopathy; nPVFR^{vol}: PVFR normalized by the first volume filling; nPVFR^{vs}: PVFR normalized by systolic volume; LE: late enhancement; PVFR: peak ventricular filling rate; tPVFR: time to first PVFR; LV: left ventricle.
* $P < 0.05$ for *post hoc* comparisons (LSD) *vs.* control.

could be observed between the groups when it comes to LE spread (Table 2, Fig. 2).

Correlations

The PVFR was correlated only (and inversely) with age both in patients with HMC [(n = 40); $r = -0.50$, $p = 0.006$] and controls ($r = -0.53$, $p = 0.003$); no significant correlations were identified between the PVFR and parietal thickness, the atrial dimensions or the LE spread. No other significant correlations were observed between ventricular filling parameters and other variables within the control group. When it comes to the normalized PVFR in patients with HMC, significant correlations could be only observed between the nPVFR^{sv} and the mean parietal thickness ($r = -0.43$, $p = 0.02$).

When it comes to the reproducibility of the filling patterns, the intraclass correlation coefficient for PVFR was 0.96 (95% confidence interval [CI] 0.91–0.98), $p < 0.0001$ (intraobserver) and 0.90 (95% CI 0.78–0.96), $p < 0.0001$ (interobserver). For nPVFR^{vol} the intraclass correlation coefficient was 0.84 (95% CI 0.63–0.93), $p < 0.0001$ (intraobserver) and 0.83 (95% CI 0.61–0.92), $p < 0.0001$ (interobserver).

Discussion

The MRI is an excellent modality for the morphological and functional evaluation of patients with HMC, since it allows us to accurately measure myocardial thickness in all the segments.[15] Also the MRI helps us identify the areas of late myocardial enhancement in relation with myocardial fibrosis.[16]

The main findings of this study, though hypothesis-generating due to the limited sample size, could be summarized as follows: 1) we have identified an inverse correlation between age and diastolic function evaluated by conventional cine sequences through cardiac MRI, both in controls and patients with HMC; 2) we have observed a significant correlation between parietal thicknesses and the dimensions of the left atrium and diastolic dysfunction parameters; 3) no significant correlation could be identified between the spread of fibrosis and ventricular filling parameters.

The MRI allows us to evaluate the diastolic function in a reliable, reproducible manner.[8,17–21] Similarly the detriment in prognosis in patients with diastolic dysfunction is confirmed.[3,4] The ventricular filling curves obtained through MRI have been previously validated in several heart conditions.[20,22–24]

Patients with HMC show different compromises of their diastolic function, even though it is still controversial whether this compromise is exclusively due to the presence of fibrosis or not. In our study we observed significant differences between the groups when it comes to ventricular filling patterns.

Highlighting the absence of differences between the groups in terms of age, we found a significant and inverse correlation between age and PVFR, both in the HMC group

Table 2 Age differences and cardiac magnetic resonance parameters based on normalized peak filling rate tertiles to filling volume.

	Lower tertile ($nPVFR^{vol}$ < 6.4)	Middle tertile ($nPVFR^{vol}$ 6.4–8.3)	Upper tertile ($nPVFR^{vol}$ > 8.3)	*p* value	*p* value T1 *vs.* T3*
Age (years)	55.4 ± 15.8	50.5 ± 16.0	37.7 ± 16.3	0.002	0.001
Parietal thickness (mm)	9.0 ± 2.4	8.1 ± 2.8	7.0 ± 2.3	0.036	0.01
Myocardial mass (g)	139.6 ± 49.7	130.1 ± 71.1	97.8 ± 41.3	0.046	0.02
LE (%)	2.0 (0.0; 7.0)	0.0 (0.0; 1.5)	0.0 (0.0; 2.0)	0.17	0.98
LE (n segments)	3.0 (0.0; 4.0)	0.0 (0.0; 3.0)	0.0 (0.0; 2.0)	0.21	0.56
LA area (4 cameras, cm^2)	27.3 ± 6.7	23.1 ± 8.0	21, 0 ± 4.9	0.01	0.003
LA area (2 cameras, cm^2)	26.0 ± 7.6	21.0 ± 9.0	19.9 ± 6.7	0.026	0.01
LA volume (ml/m^2)	56.8 ± 18.4	46.3 ± 28.3	42.0 ± 12.5	0.065	0.03
LA diameter (3 cameras, mm)	40.9 ± 8.6	34.5 ± 8.3	32.6 ± 7.8	0.003	0.001

LA: left atrium; $nPVFR^{vol}$: normalized peak ventricular filling rate to filling volume; LE: late enhancement.
* Using Fisher and Games–Howell's Least Significant Difference Test. Non-parametric comparisons were performed using Kruskal–Wallis test.

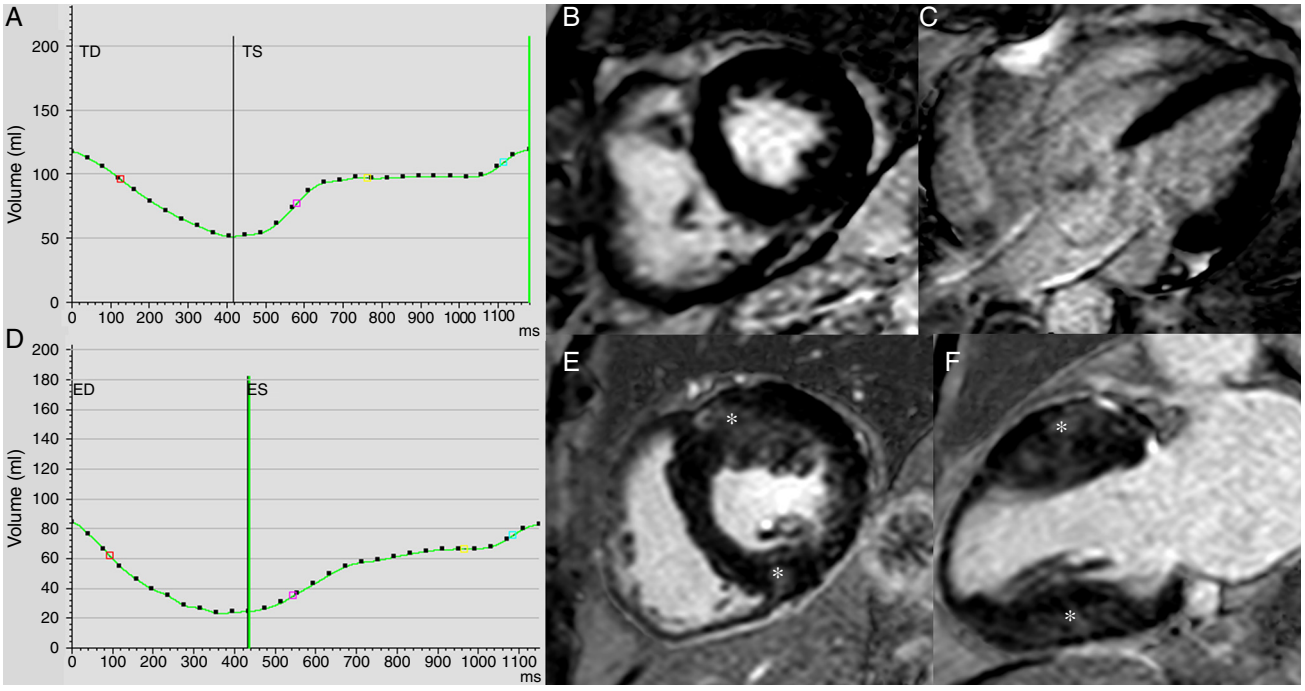

Figure 2 Filling curves of a 68-year-old woman without evidence of structural heart condition (A–C), with mean parietal thickness of 5.6 mm (10.3-maximum thickness), 340 ml/s PVFR, 5.1 $nPVFR^{sv}$, 7.4 $nPVFR^{vol}$ and absence of late enhancement. In the lower panel (D–F) we can see the filling curves of a 62-year-old woman with hypertrophic myocardiopathy, with mean parietal thickness of 12.4 mm (22.5 mm-maximum thickness), 170 ml/s PVFR, 3.4 $nPVFR^{sv}$, 4.2 $nPVFR^{vol}$, characteristic of late enhancement of hypertrophic myocardiopathy (8% of myocardial mass).

and in the control group. It is important to underscore that of all the variables studied, age was the only one that correlated significantly with PVFR, which is possibly associated with an increase in the collagen deposits observed with age.[25] When staging the population by $nPVFR^{vol}$ terciles we observed significant differences between the different groups in terms of mean parietal thickness, and to a lesser extent, in terms of myocardial mass.

Regarding the presence of late enhancement, the prognostic implications of the spread of the segments with late enhancement have already been documented, even though there are opposing opinions on the association between late enhancement and the presence of diastolic dysfunction in patients with HMC.[16,22,26–28] It has been postulated that diastolic dysfunction could be due to the abnormal dissociation of actin and myosin filaments during the active phase of relaxation, while the late phase (passive) would be affected by an increase of interstitial fibrosis.[29] Following this same line, the expansion and disorganization of the collagen matrix have been indicated as the possible cause for diastolic dysfunction. That is how Noureldin et al. explain that the abnormalities found in the diastole would be early, direct manifestations of sarcomere mutation, rather than a representation of ventricular hypertrophy, fibrosis and myofibrillar disorder.[26] Consistent with these findings, we did not find any significant correlation between the spread of fibrosis, confirmed by the presence of LE and abnormalities of diastolic function in our study.

Lastly, when staging the population by terciles of diastolic disorder evidenced by filling patterns, we recorded significant differences between the groups in terms of atrial dimensions.

One of the main and outstanding points made by our work is the fact that data was obtained from conventional sequences, without the need to extend the study by adding additional sequences.

Our results could eventually suggest the use of ventricular filling patterns, obtained routinely within the conventional assessment of patients with HMC through MRIs. However, the prognostic value of our findings should be explored in larger longitudinal studies.

Our study includes a relatively small sample of patients, with a potential selection bias. The number of patients with HMC without evidence of late enhancement is small. In addition, though the control group was made up of non-diabetic patients with normal MRI, we cannot conclusively rule out that such patients could show some degree of underlying diffuse fibrosis perhaps detectable through T1-weighted mapping techniques, which in turn were not evaluated in this study. Therefore, along with their observational nature our findings should be regarded as hypothesis-generating findings.

In sum in this study we were able to identify that in patients with HMC there is a significant association between ventricular filling patterns and age, parietal thickness, myocardial mass and atrial dimensions, while no significant correlation could be identified with late enhancement spread.

Ethical responsibilities

Protection of people and animals. The authors declare that the proceedings followed abide by the ethical regulations established by the World Health Organization Committee on Human Experiment s and the Helsinki Declaration.

Data confidentiality. The authors confirm that they have followed their centers protocols on the disclosure of patient personal information.

Right to privacy and informed consent. The authors confirm that they have obtained the prior written informed consent from the patients. This document belongs to the corresponding author.

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2. Study idea: GRG.
3. Study design: GRG.
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9. Critical review of the manuscript with intellectually relevant remarks: MDZ, PC, AD, CC and GRG.
10. Approval of final version: MDZ, AD, CC, GRG and PC.

Conflict of interest

We hereby declare that Dr. Patricia Carrascosa, MD is a consultant at Ge. There is no conflict of interest whatsoever associated with any of the other authors.

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