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Diastolic dysfunction evaluated by cardiac magnetic resonance: the value of the combined assessment of atrial and ventricular function

Giovanni Donato Aquaro[1] · Fausto Pizzino[2] · Anna Terrizzi[3] · Scipione Carerj[3] · Bijoy K. Khandheria[4] · Gianluca Di Bella[3]

Abstract

Objectives We sought to evaluate the role of cardiac magnetic resonance imaging (CMR) in the evaluation of diastolic function by a combined assessment of left ventricular (LV) and left atrial (LA) function in a cohort of subjects with various degrees of diastolic dysfunction (DD) detected by echocardiography.

Methods Forty patients with different stages of DD and 18 healthy controls underwent CMR. Short-axis cine steady-state free precession images covering the entire LA and LV were acquired. Parameters of diastolic function were measured by the analysis of the LV and LA volume/time (V/t) curves and the respective derivative dV/dt curves.

Results At receiver operating characteristic (ROC) curve analysis, the peak of emptying rate A indexed by the LV filling volume with a cut-off of 3.8 was able to detect patients with grade I DD from other groups (area under the curve [AUC] 0.975, 95% confidence interval [CI] 0.86–1). ROC analysis showed that LA ejection fraction with a cut-off of ≤36% was able to distinguish controls and grade I DD patients from those with grade II and grade III DD (AUC 0.996, 95% CI 0.92–1, $p < 0.001$). The isovolumetric pulmonary vein transit ratio with a cut-off of 2.4 allowed class III DD to be distinguished from other groups (AUC 1.0, 95%CI 0.93–1, $p < 0.001$).

Conclusions Analysis of LV and LA V/t curves by CMR may be useful for the evaluation of DD.

Key Points
• *Combined atrial and ventricular volume/time curves allow evaluation of diastolic function.*
• *Atrial emptying fraction allows distinction between impaired relaxation and restrictive/pseudo-normal filling.*
• *Isovolumetric pulmonary vein transit ratio allows distinction between restrictive and pseudo-normal filling.*

Keywords Diastole · Magnetic resonance · Heart failure · Physiology: atrial function · Hypertrophic cardiomyopathy

✉ Giovanni Donato Aquaro
aquaro@ftgm.it

1   Fondazione G. Monasterio CNR-Toscana, Via Giuseppe Moruzzi, 1, 56124 Pisa, Italy

2   Scuola Superiore Sant'Anna di Studi Universitari e di Perfezionamento, Pisa, Italy

3   Dipartimento di Medicina Clinica e Sperimentale, University of Messina, Messina, Italy

4   Aurora Cardiovascular Services, Aurora Sinai/Aurora St. Luke's Medical Centers, University of Wisconsin School of Medicine and Public Health, Milwaukee, WI, USA

Abbreviations

CMR	Cardiac magnetic resonance
DD	Diastolic dysfunction
HF-p-EF	Heart failure with preserved ejection fraction
HF	Heart failure
IPVT	Isovolumetric pulmonary vein transit
IPVTR	Isovolumetric pulmonary vein transit ratio
LA	Left atrial
MACE	Major adverse cardiovascular events
PER-A	Late atrial peak emptying rate
PER-E	Early atrial peak emptying rate
PFR-A	Atrial peak filling rate
PFR-E	Early peak filling rate
ROC	Receiver operator characteristic

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Introduction

Diastolic dysfunction (DD) represents an emerging topic in the clinical and scientific scenario of cardiovascular disease [1–5]. Severe DD can lead to symptoms of heart failure (HF) even in the presence of a normal systolic function; this condition has been defined as HF with preserved ejection fraction (HF-p-EF) and is associated with increased incidence of major adverse cardiovascular events (MACE), mortality, and worsening quality of life [6–10]. Echocardiography represents the best noninvasive instrument in the evaluation of DD [11, 12]. Cardiac magnetic resonance (CMR) is a unique technique providing accurate and reproducible measurements of biventricular volumes and function [13]. Recently, a study by Grassedonio et al [14] on a cohort of patients affected by hypertrophic cardiomyopathy with early DD revealed that the parameters of left atrial (LA) function assessed by CMR were altered before the standard ventricular diastolic indexes as the early peak filling rate and the active peak filling rate. However, LA function parameters able to provide a grading of DD were not investigated.

The aim of our study is to introduce and validate a new method for the evaluation of diastole by CMR based on the simultaneous analysis of atrial and ventricular volume variation across the cardiac cycle.

Methods

Population

We performed CMR on 45 patients with different stages of DD detected during routine echocardiography. Patients with atrial fibrillation and those with systolic dysfunction (LV ejection fraction <55%) were excluded. Twenty age- and sex-matched healthy volunteers also were enrolled as a control group. LA and LV functional CMR parameters were compared with echocardiography evaluation of DD and a diagnostic algorithm was proposed. This diagnostic algorithm was validated in a cohort of 60 non-selected consecutive patients undergoing CMR. Transthoracic echocardiography was repeated on the same day as CMR for the evaluation of diastolic function in all the patients (the echocardiographic protocol is detailed in the supplemental data). The study was approved by the ethical committee our institution and all the patients signed an informed consent to participate in the study.

Cardiac magnetic resonance imaging protocol

CMR was performed using a 1.5-T scanner (Excite HDxt, General Electric Healthcare) with an eight-element (four anterior and posterior) phased-array receiver surface coil. In all subjects, the study of atrial and ventricular function was obtained by acquiring cine steady-state free precession (SSFP),

end-expiratory breath-hold images on short-axis views, perpendicular to the major axis of the left ventricle, from the LV apex to the entire LA. The following parameters were used: 400-mm FOV, 8-mm slice thickness, no gap, 1 NEX, 12 views per segment, TR/TE = 2, flip angle 45°, matrix 224 x 224, 30 cardiac phases.

Postprocessing

Image postprocessing was performed using the previously validated Tracking Tool software [15], which simply allows the user to automatically track the endocardial contours of both the LV and LA cavity in short-axis views. The atrial and ventricular volume/time (V/t) curves were obtained plotting the cavity volumes over time (in msec; Fig. 1, upper left panel). We derived the atrial and ventricular dV/dt curves from the volume curves (Fig. 1, upper right panel). Peaks of the ventricular dV/dt curves were defined as follows: the first positive peak was defined as the early peak filling rate (PFR-E) and the second peak was defined as atrial peak filling rate (PFR-A). PFR-E and PFR-A represent the maximum speed of passive filling and the maximum speed of filling secondary to atrial contraction, respectively. Between the two peaks, a zone of almost zero speed is normally present; this is the phase of diastasis. LV filling volume was defined as the difference between maximal LV volume and minimal LV volume. The evaluation of atrial function by CMR was performed using the same approach adopted for ventricular function. Through an assessment of the atrial V/t curves, we measured atrial emptying volumes as the difference between the maximal and minimal atrial volumes (LAV max and LAV min, respectively); the atrial emptying fraction was measured as the ratio in percentage between atrial emptying volumes and maximal atrial volumes (Fig. 1, lower panels). Other parameters of atrial emptying function were obtained through an analysis of the atrial dV/dt curves, as follows. Briefly, the first negative peak, representing maximal emptying during the conduit phase, was calculated and identified as the early atrial peak emptying rate (PER-E). The second peak, during the booster phase, was identified as the late atrial peak emptying rate (PER-A). In order to obtain more comparable values among the patients, PFR-E and PFR-A as well as PER-E and PER-A also were normalized by the LV filling volume, obtaining, respectively, the PFR-E index, PFR-A index, PER-E index, and PER-A index. The isovolumetric pulmonary vein transit (IPVT) was defined as the amount of LV filling volume flowing directly from the pulmonary veins into the LV cavity without significant change in LA volume. It was measured as: LA emptying volume – LV filling volume. The isovolumetric pulmonary vein transit ratio (IPVTR) was the ratio between IPVT and the atrial emptying volume (Fig. 1). A detailed discussion about atrial function in a healthy condition and in DD is reported in supplemental data.
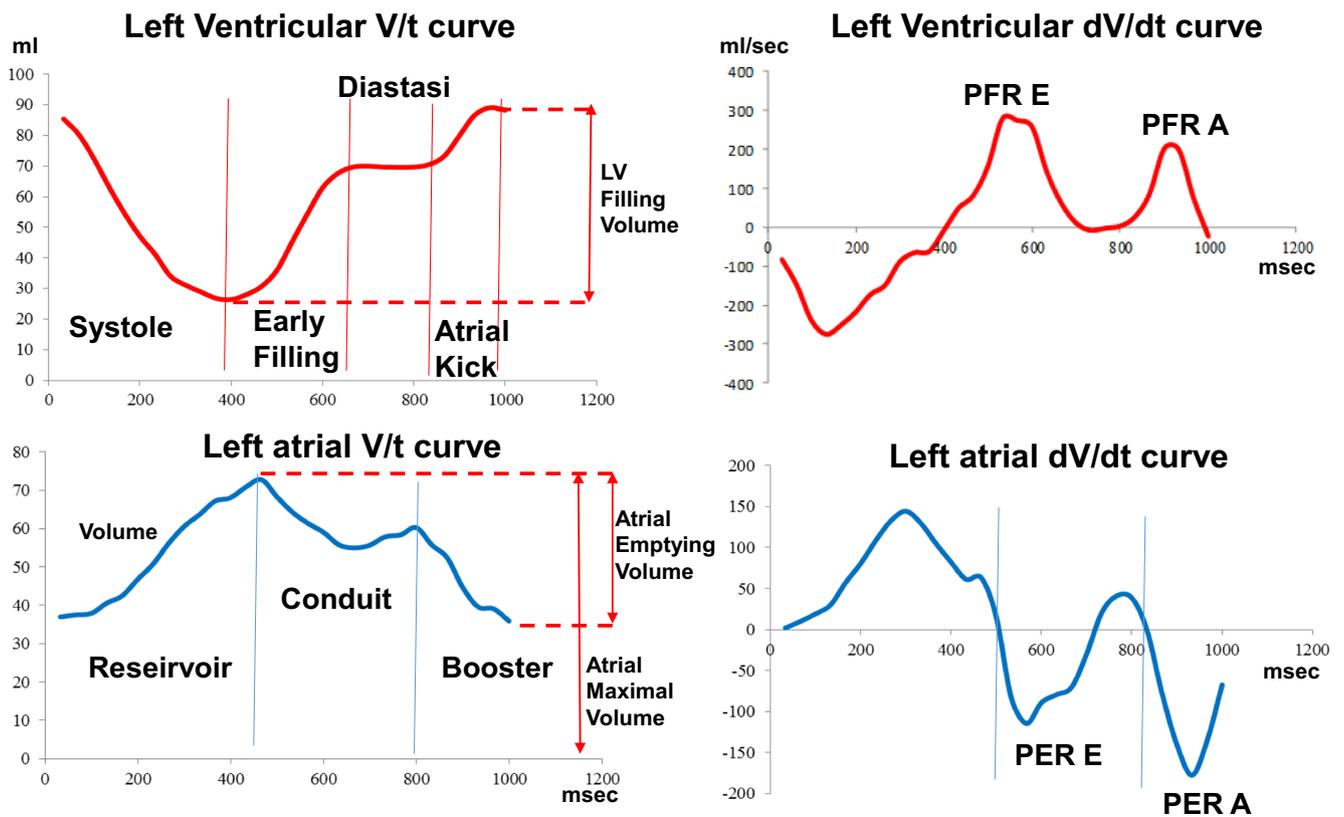
Atrial Emptying Fraction = Atrial Emptying Volume/ Atrial Maximal Volume (%)

Isovolumetric Pulmonary Vein Transit Volume (IPVT) = LV Filling Volume - Atrial Emptying Volume

Isovolumetric Pulmonary Vein Transit Ratio = IPVT/ Atrial Emptying Volume

Fig. 1 Volume/time (V/t) curves of left ventricle (upper left) and left atrium (lower left) and respective dV/dt curve of left ventricle (upper right) and left atrium (lower right). From the left ventricular V/t curve, the left ventricular filling volume is measured as shown, and from the respective dV/dt curve, parameters of diastolic function as the early peak filling rate and atrial peak filling rate are derived. In the atrial V/t curve, the maximal atrial volume and the atrial emptying volume are measured as shown. The atrial emptying fraction is measured as the ratio between the atrial emptying volume and the maximal atrial volume and is expressed as a percentage. Isovolumetric pulmonary vein transit is measured as the difference between left ventricular filling volume and the atrial emptying volume and represents the flow that transits from the pulmonary veins to the left ventricle with no modification of atrial volumes. The isovolumetric pulmonary transit ratio is obtained as the ratio between isovolumetric pulmonary vein transit and atrial emptying volume. Finally, from the atrial dV/dt curve, the early peak emptying rate, and atrial peak emptying rate are obtained. *LV*, left ventricular; *PER-A*, atrial peak emptying rate; *PER-E*, early peak emptying rate; *PFR-A*, atrial peak filling rate; *PFR-E*, early peak filling rate

Statistical analysis

Parameters were expressed as mean ± SD when normally distributed or as a median (25th–75th percentile) in the presence of non-Gaussian distribution. The Shapiro–Wilk test was used to assess the presence of Gaussian distribution. A *p* value <0.05 was considered statistically significant. The differences between two groups were evaluated with ANOVA test. Bonferroni correction was used for comparison of multiple groups. Receiver operator characteristic (ROC) curves were used to assess the accuracy of diastolic parameters of DD. The sample size of groups of patients with grade I, II, and III DD was calculated using a 'comparison of means' method (type I error of 0.05 and type II error of 0.05, power 0.95) for the main variables of the diastolic function. The inter-rater agreement Kappa (K) value was measured to assess the agreement between echocardiography and CMR for assigning the DD grade for the patients of the validation cohort. The coefficient of variability (calculated as the SD of differences between the two measurements divided by the mean value of the parameter) was used to evaluate the interobserver reproducibility for the measurement of atrial volumes

Results

Two patients were excluded from the final analysis because of the presence of more-than-mild mitral regurgitation, and three

patients were excluded for poor image quality. The final population included 40 patients (22 men, age 54 ±18 years). According to the echocardiography results, 18 patients (45%) showed grade I DD, 12 patients (30%) showed grade II DD, and 10 patients (25%) showed grade III DD. The cause of DD was hypertrophic cardiomyopathy in 17 patients (9 in grade I, 6 in II, 2 in III), cardiac amyloidosis in 11 (6 in grade II, 5 in III), hypertensive cardiomyopathy in 7 (all of them in grade I), and restrictive cardiomyopathy (2 endomyocardial fibrosis and 1 idiopathic restrictive cardiomyopathy, all of them in grade III). Systolic function was normal in all the patients, with an average LV ejection fraction of 59 ±10%. Population characteristics are summarized in Table 1.

Cardiac magnetic resonance imaging

Analysis of ventricular parameters is summarized in Table 2. PFR-E was significantly lower in patients with grade I DD and grade II DD than in controls ($p < 0.0001$); however, no significant difference emerged among grade I, II, and III patients or between grade III and controls. PFR-A was significantly higher in patients with grade I DD than in controls and other grades of DD ($p < 0.001$; Fig. 2). Ventricular PFR-E/PFR-A ratio was significantly lower in patients with grade I DD than in other groups.

Atrial parameters are shown in Table 3. PER-E was significantly lower in patients with grade III DD than in controls (p < 0.05), while PER-A was higher in grade I DD in respect to other groups ($p < 0.001$; Fig. 2). Atrial PER-A ratio showed higher values in controls and grade II DD in comparison with both grade I and grade III DD ($p < 0.001$ and $p < 0.001$, respectively).

We found that patients with grade I DD have significantly higher PER-A index (PER-A normalized by the LV filling volume) values than other groups, and the analysis of the ROC curve revealed that a cut-off of 3.8 was able to differentiate patients with grade I DD from other groups: sensitivity 100% (95% CI 67–100%), specificity 92.6% (95%CI 76–99%), AUC 0.975 (95% CI 0.86–1; Fig. 3, left panel).

Interestingly, the atrial emptying fraction showed a significant decrease proportional to the increase of the grade of DD and was significantly lower in grade II and III than in controls and grade I. At ROC curve analysis, we found that a cut-off of ≤36% can distinguish controls and grade I DD patients from grade II and grade III DD patients with a sensitivity of 100% (95% CI 77–100%), a specificity of 94.6% (95% CI 82–99%), and an AUC of 0.996 (95% CI 0.93–1; Fig. 3, right panel).

Patients with grade III DD had the highest IPVTR values (p < 0.001 vs. other groups); a value of >2.4 was identified by the ROC analysis as an optimal cut-off to identify patients with grade III DD from others (AUC 1.0, 95% CI 0.93–1; Fig. 4).

Due to these results, we propose the diagnostic algorithm shown in Fig. 5 for the evaluation of DD by CMR.

Table 1 Population characteristics

	Class of diastolic dysfunction			
	Healthy controls	I	II	III
n	20	18	12	10
Age, yrs	51 ±16	52 ±10	58 ±18	56 ±13
Male, n (%)	11 (52%)	9 (50%)	8 (67%)	5 (50%)
Weight, kg	77 ±16	79 ±13	80 ±18	77 ±13
Height, cm	173 ±7	171 ±8	168 ±15	172 ±8
SAP, mmHg	120 ±17	128 ±20	124 ±16	115 ±17
DAP, mmHg	74 ±11	84 ±15	78 ±8	770 ±16
Ejection fraction, %	60 ±6	62 ±10	87 ±8	55 ±6
Family history of CAD, n (%)	0	5 (28%)	2 (17%)	1 (10%)
Hypertension, n (%)	0	7 (38%)	4 (33%)	2 (20%)
Diabetes, n (%)	0	3 (17%)	1 (8%)	1 (10%)
Dyslipidemia, n (%)	0	3 (17%)	1 (8%)	1 (10%)
Smoking habit, n (%)	0	4 (22%)	3 (25%)	3 (30%)
HCM, n (%)	0	9 (50%)	6 (50%)	2 (20%)
Hypertensive cardiomyopathy, n (%)	0	7 (38%)	0	0
Cardiac amyloidosis, n (%)	0	0	6 (50%)	5 (50%)
RCM, n (%)	0	0	0	3 (30%)

CAD coronary artery disease, *DAP* diastolic arterial pressure, *HCM* hypertrophic cardiomyopathy, *RCM* restrictive cardiomyopathy, *SAP* systolic arterial pressure

Table 2 Ventricular parameters of diastolic function

	Class of diastolic dysfunction				p value
	HC	I	II	III	
n	25	18	12	10	
Ventricular parameters:					
LV filling volume (mL)	69 ±16	66 ±17	61 ±23	69 ±17	0.72
PFR-E (mL/s)	375 ±63[I,II]	247 ±47[H,II,III]	325 ±47[H,I]	353 ±92[,I]	0.001
PFR-E/LV filling volume (s)	5.4 ±1.3[I]	4 ±0.8[H,III]	4.7 ±2	5.4 ±1.3	0.02
PFR-A (mL/s)	177 ±56[I,III]	238 ±59[H,III]	209 ±83[III]	136 ±37[H,I,II]	0.02
PFR-A/LV filling volume (s)	2.3 ±1.1[I,II]	3.9 ±1.2[H,II,III]	1.5 ±0.8[H,I,III]	2.6 ±1.6[H,I,II]	0.001
PFR-E/PFR-A	2.3 ±1[I]	1.1 ±0.4[H,II,III]	2.1 ±1[I]	2.8 ±1.3[I]	0.001

p values were derived by ANOVA testing with Bonferroni correction for multiple comparisons. The ANOVA test was also used for single comparison between groups: [H] significant difference vs. healthy controls ($p < 0.05$); [I] significant difference vs. grade [I] diastolic dysfunction ($p < 0.05$); [II] significant difference vs. grade [II] ($p < 0.05$); [III] significant difference vs. grade [III] ($p < 0.05$)

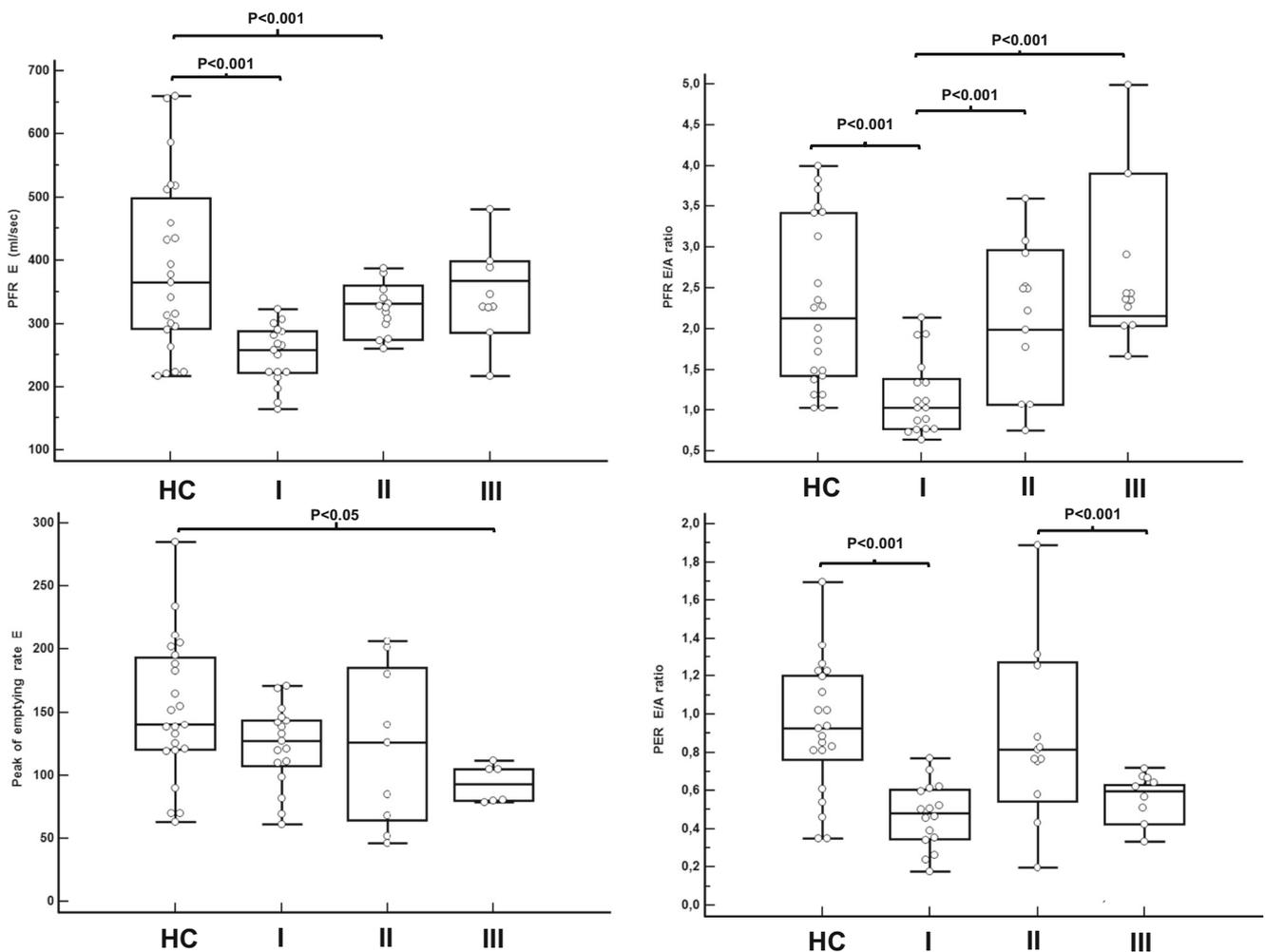*LV* left ventricular, *PFR-A* atrial peak filling rate, *PFR-E* early peak filling rate

Fig. 2 Box and whisker plots evaluating early (PFR-E) and atrial (PFR-A) peak filling rate (left and right upper panels, respectively) and early (PER-E) and atrial (PER-A) peak emptying rate (left and right lower panels, respectively) in healthy controls (HC) and in patients with grade I, II, or III diastolic dysfunction. A great overlap of values is found among the groups. ANOVA testing was used to evaluate difference between groups. HC had significantly higher PFR-E and PER-E than grade I and II. Grade I had a significantly lower PFR E/A ratio than the others. HC had a significantly higher PER-E/PER-A ratio than grade I and III

Table 3 Atrial parameters of diastolic function

	Class of diastolic dysfunction				*p* value
	HC	I	II	III	
n	25	18	12	10	
Atrial parameters:					
Maximal atrial volume (mL)	73 ±24[II,III]	87 ±27[II,III]	127 ±48 [HC,I]	127 ±45 [HC,I]	<0.001
Minimum atrial volume (mL)	35 (27–46) [I]	48 (34–68) [HC]	77 (65–131)	94 (61–165)	<0.001
Atrial emptying volume (mL)	31 ±9 [I,III]	38 ±11 [HC,II,III]	29 ±10 [I,III]	18 ±8 [HC,I,II,III]	<0.001
Atrial emptying fraction (%)	48 ±5 [I,II,III]	44 ±5 [HC,II,II]	25 ±8 [HC,I]	18 ±12 [HC,I]	<0.001
Reservior volume (mL)	29 ±8 [I,III]	37 ±12 [HC,III]	34 ±13 [III]	21 ±12 [HC,I,III]	0.014
Conduit volume (mL)	16 ±6[III]	14 ±6 [III]	14 ±7 [III]	8 ±3 [HC,I,II]	0.023
Booster volume (mL)	17 (12–25) [I]	24 (18–36) [HC,III]	22 (17–27)	15 (7–23)[II]	0.003
IPVT (mL)	36 ±15 [I,III]	25 ±11 [HC,III]	32 ±18[III]	64 ±21 [HC,I,II]	<0.001
PER-E (mL/s)	152 ±55[III]	125 ±32 [III]	123 ±63	94 ±15 [HC,I]	0.047
PER-E/LV filling volume (s)	2.3 ±1 [I,II,III]	1.6 ±0.8 [HC,III]	1.1 ±0.8 [HC]	0.9 ±0.2 [HC,I]	<0.001
PER-A (mL/s)	159 ±47 [I]	263 ±99 [HC,II,III]	165 ±78 [I]	181 ±39 [I]	<0.001
PER-A/LV filling volume (s)	2.4 ±0.8 [I]	4.8 ±0.7 [HC,II,III]	2.5 ±1.1 [I]	2.9 ±1.3 [I]	<0.001
PER-E/PER-A	0.9 ±0.3 [I,III]	0.5 ±0.2 [HC,II]	0.9 ±0.5 [HC,II]	0.5 ±0.1	<0.001
IPVTR	1.2 ±0.6 [I,III]	0.7 ±0.3 [HC,III]	0.9 ±0.5 [III]	4.2 ±1.4 [HC,I,II]	<0.001

IPVT isovolumetric pulmonary vein transit flow, was measured as the difference between the left ventricular filling volume and the atrial emptying volume, *IPVTR* isovolumetric pulmonary vein transit ratio, defined as the ratio between the PRVT and the atrial emptying volume, *LV* left ventricular, *PER-A* peak emptying rate A, *PER-E* peak emptying rate E. Atrial emptying volume is measured as the difference between the maximal and the minimal atrial volume. *p* values were derived by ANOVA testing with Bonferroni correction for multiple comparisons. The ANOVA test was also used for single comparison between groups: [H], significant difference vs. healthy controls ($p < 0.05$); [I] significant difference vs. grade I diastolic dysfunction ($p < 0.05$); [II] significant difference vs. grade [II] ($p < 0.05$); [III] significant difference vs. grade [III] ($p < 0.05$)

Validation study

The diagnostic algorithm of Fig. 5 was tested in 60 consecutive non-selected patients undergoing CMR and compared with echocardiographic grading of DD. Among these patients, 17 patients had LV dysfunction (6 with ischemic heart disease, 11 with dilated cardiomyopathy), 20 had LV hypertrophy (10 with hypertrophic cardiomyopathy, 7 cardiac amyloidosis and 2 with aortic stenosis and 1 with acromegaly), 12 with clinical suspected acute myocarditis, 8 with ventricular arrhythmias (1 patient with aborted cardiac arrest, 3 with runs of non-sustained ventricular tachycardia and 4 with frequent premature ventricular complexes), and 3 with pulmonary hypertension. Image quality was not suitable for adequate post-processing in one patient with frequent premature ventricular complexes. A more-than-mild mitral regurgitation was found in three patients of this cohort. At echocardiography, 18 patients had normal diastolic function, 36 grade I, 2 patients with grade II, and 3 with grade III DD. Using the algorithm of Fig. 5, 17 patients had normal diastolic function, 36 patients had grade I, 2 patients had grade II, and 4 had grade III DD. Mismatch between the two techniques was found in only two patients: in a case with grade II at echocardiography, CMR assigned a grade IV at CMR because of the LA emptying fraction of 35%; the other case was a patient with normal diastolic function at echocardiography and grade I at CMR. A very good agreement between echocardiography and CMR was found (weighted K = 0.92, 95% CI 0.82–1.0).

Inter-observer reproducibility

A very good interobserver reproducibility was demonstrated for the measurement of atrial volumes (coefficient of variability for minimal atrial volume 1.5%, for maximal atrial volume 1.8%). This was expected because semi-automatic software for contours tracing was used and because the investigators made only minimal manual corrections of contours.

Discussion

Results of the current study may be summarized as follows: 1) PER-A index was the best parameter to distinguish grade I DD from healthy controls and other groups (cut-off >3.8); 2) the atrial emptying fraction with a cut-off of <3.6 was able to distinguish grade II–III DD from grade I with 100% specificity and 94.6% sensitivity; 3) the IPVT, representing the blood volume that transits from the pulmonary vein to the LV without modification of LA volume, was significantly greater in the grade III DD group than in other groups; 4) the IPVTR,
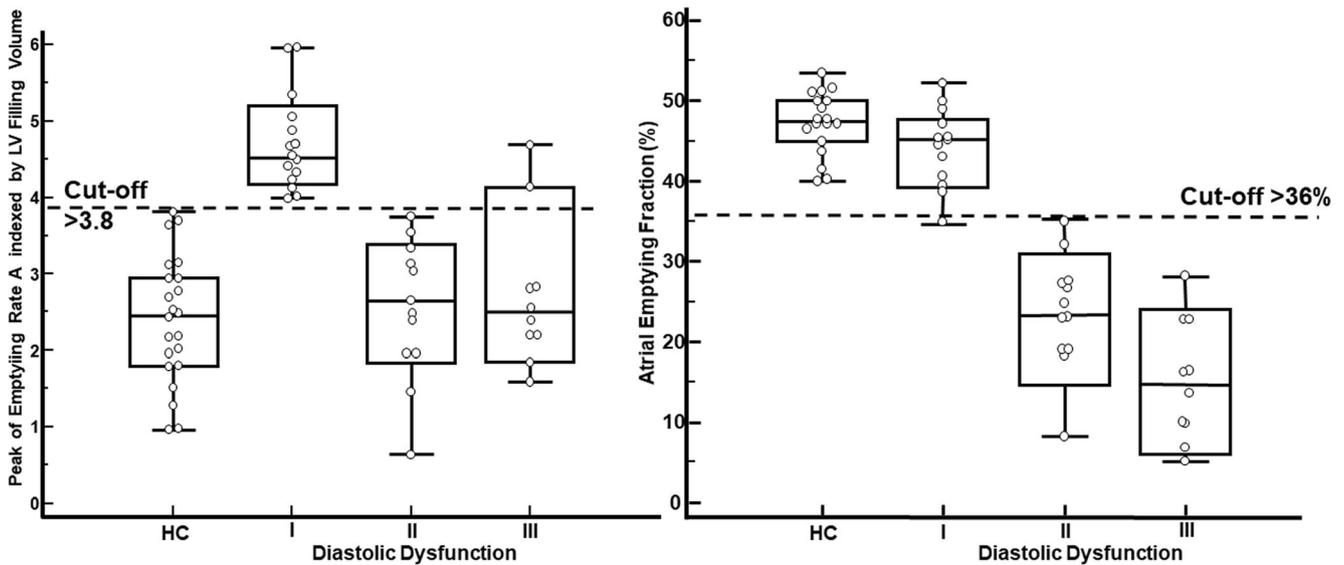
Fig. 3 Box and whisker plots evaluating atrial peak emptying rate index (PER-A index, the ratio between PER-A and left ventricular filling volume) in the left panel, and the atrial emptying fraction in healthy controls (HC) and in patients with grade I, II, or III diastolic dysfunction in the right panel. PER-A index was significantly higher in grade I than in other groups (see Table 2), and with a cut-off of 3.8, it perfectly distinguished between grade I and HC. The atrial emptying fraction was significantly lower in grades II and III than in HC and grade I (see Table 2). In receiver operating characteristic curve analysis, atrial emptying fraction with a cut-off of ≤36% was the best parameter to distinguish grade II and III diastolic dysfunction from HC and grade I

which is the ratio between IPVT and atrial emptying volume, was the best parameter to distinguish grade III DD from other grades of dysfunction and healthy controls (cut-off >2.4).

HF-p-EF represents the clinical manifestation of DD. It is characterized by increased LV filling pressures that lead to increased upstream pressures, capillary hypertension, interstitial edema, and decreased efficiency of the alveolar gas exchange. Usually, the *primum movens* of DD is thought of as

increased LV stiffness, which makes the LV unable to properly relax, thus leading to decreased suction during the conduit phase that is compensated by a more efficient LA contraction. This condition represents grade I DD. In our study, patients with grade I DD showed a greater atrial contribution to LV filling, reflected by a higher PER-A index than in normal controls and other groups. PER-A index represents the proportion of the LV filling volume determined by the atrial

Fig. 4 Box and whisker plots evaluating the isovolumetric pulmonary vein transit ratio (IPVTR, the ratio between the isovolumetric pulmonary vein transit and the atrial emptying volume) in healthy controls (HC) and people with grade I, II, or III diastolic dysfunction. IPVTR was significantly higher in grade III than in the other groups (see Table 2), and with a cut-off of 2.4, it perfectly distinguished between grade III and grade II. ANOVA test was used for comparison among two groups
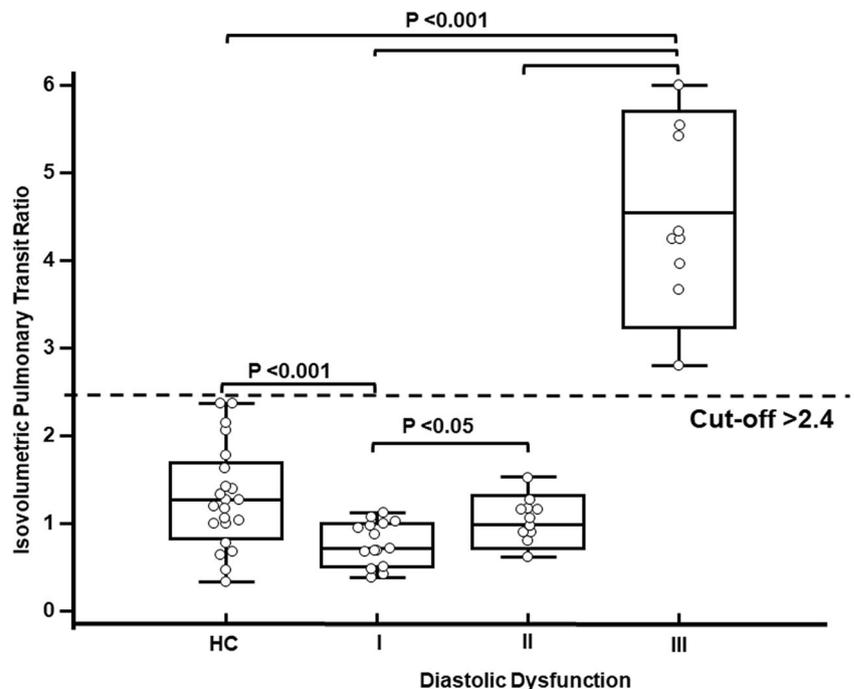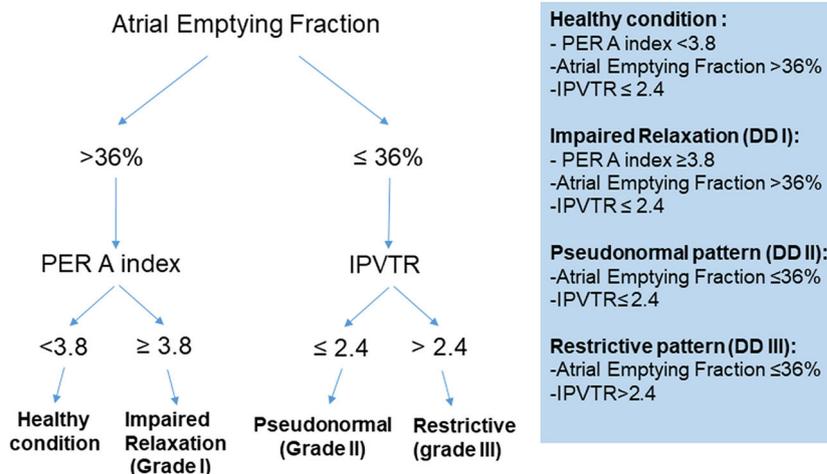
Fig. 5 Based on the results of this study, a diagnostic algorithm to identify and classify diastolic dysfunction is proposed. *DD* diastolic dysfunction; *IPVTR* isovolumetric pulmonary vein transit ratio; *PER-A* atrial peak emptying rate

Diagnostic algorithm for diastolic dysfunction

Atrial Emptying Fraction

>36%   ≤ 36%

PER A index   **IPVTR**

<3.8   ≥ 3.8   ≤ 2.4   > 2.4

Healthy condition   **Impaired Relaxation (Grade I)**   **Pseudonormal (Grade II)**   **Restrictive (grade III)**

Healthy condition :
- PER A index <3.8
-Atrial Emptying Fraction >36%
-IPVTR ≤ 2.4

Impaired Relaxation (DD I):
- PER A index ≥3.8
-Atrial Emptying Fraction >36%
-IPVTR ≤ 2.4

Pseudonormal pattern (DD II):
-Atrial Emptying Fraction ≤36%
-IPVTR≤ 2.4

Restrictive pattern (DD III):
-Atrial Emptying Fraction ≤36%
-IPVTR>2.4

booster function. The cut-off of >3.8 for PER-A index to identify grade I DD from other groups means that the contribution of booster function in LV filling is fourfold greater than that of passive filling. In grade I DD, atrial emptying fraction is similar to that in controls and the contribution of the IPVT is low because of the low contribution of the blood flowing from pulmonary drainage in comparison with the amount of flow provided by the atrial contraction.

In subjects with grade II DD, the LA starts to enlarge and its function progressively decreases because of wall fibrosis and continuous stretching stress. As a result, our group of patients with grade II DD showed a significantly lower atrial emptying fraction than the control and grade I DD groups, but atrial emptying volume and IPVT remained higher than in the grade III DD group. In grade III DD, the LV is characterized by severely increased wall stiffness and by severely impaired atrial function. Consequently, the atrial emptying fraction is significantly lower than in grades I and II DD; moreover, a distinctive feature of grade III DD is the relatively low contribution of the LA contraction to LV filling in absolute and relative terms. This was revealed by the fact that the majority of the total LV filling volume derived from blood that flowed directly from the pulmonary veins to the LV (IPVT). Also, in grade III DD, the IPVTR, which is the ratio between IPVT and atrial filling volume, is higher than in the other groups; the cut-off of >2.4 perfectly distinguished grade II from grade III DD.

Using these three parameters together (atrial emptying fraction, PER-A index, and IPVTR) with the thresholds found at ROC curve analysis, it is possible to generate the diagnostic algorithm shown in Fig. 5.

Most of the previous studies regarding the evaluation of diastolic function by CMR used phase contrast (PC) sequences to measure transmitral flow. Ashrafpoor et al [16] demonstrated an association of E' and transmitral flow parameters obtained by PC imaging with age and a relationship between LV

relaxation parameters (E', DT, and isovolumetric relaxation time) with LV mass/end-diastolic volume and myocardial wall thickness. Buss et al [16] showed a strong correlation between echocardiography-derived parameters (E, A, and E/E') and the same parameters measured by CMR, with 95% of patients correctly categorized. Wu et al [17] found a good correlation between tissue Doppler parameters and values obtained using a three-dimensional volume tracking technique with a sweep volume measured at the atrioventricular junction following the movement of the mitral annulus. Future studies are necessary to compare our novel technique for evaluation of diastolic function and these PC-based methods. Analysis of LV V/t filling curves to evaluate diastolic function is a validated method; the most commonly used parameters are PFR and time to peak filling rate [18]. Rodriguez-Granillo et al [19] used parameters derived from LV V/t curves to demonstrate that absolute and normalized peak filling rates were significantly lower in patients with prior myocardial infarction than in controls and that patients with lower peak filling rates showed greater infarct size. However, evaluation of the LA gained a central role in the study of DD and of HF-p-EF [20, 21]. New echocardiography methods, particularly speckle-tracking imaging, demonstrated high accuracy in the evaluation of LA function, demonstrating that LA impairment is an early marker of high risk of atrial fibrillation onset [22], mortality [23], and hospitalization [24]. Recently, Santos et al [25] evaluated LA volumes and function with echocardiography and speckle-tracking analysis in a cohort of patients with HF-p-EF enrolled in the PARAMOUNT trial. The authors revealed that lower systolic strain was associated with higher prevalence of prior HF hospitalization and a history of atrial fibrillation, as well as worse LV systolic function, and greater LV mass and LA volume; moreover, compared with controls, HF-p-EF patients had worse LA reservoir, conduit, and pump function. These results are in line with the research of Freed et al [24] who showed that

in a group of 308 patients with HF-p-EF, LA reservoir strain was the strongest correlate of adverse events and was strongly associated with increased pulmonary resistance ($p < 0.0001$) and decreased peak oxygen consumption ($p = 0.0001$). Echocardiography remains the first-line investigation for DD because of its availability and because it is cheaper, faster, and easier than CMR. However, echocardiography suffers from limitations related to acoustic window (particularly affecting speckle-tracking imaging) and to angle dependence of Doppler measurements. Furthermore, echocardiographic evaluation of E/E' may be difficult in patients with severe mitral regurgitation and mitral stenosis due to an inaccurate evaluation of transmitral flow, as in patients with valvular prosthesis because of the impairment of the longitudinal strain. Then, in selected patients, CMR may be a valid alternative to the echocardiography for the evaluation of diastolic function. CMR represents the best technique for the noninvasive measurement of intracardiac volumes with elevated accuracy and reproducibility. In our study, we confirmed the importance of the LA in the physiopathology of DD and demonstrated that CMR can perform a reliable grading of DD when compared with echocardiography.

Some limitations of the current study have to be mentioned. First, the size of the enrolled population was small. However, the sample size analysis confirmed that our population was sufficient to evaluate combined LV and LA function in patients with varying degrees of DD. Future studies are needed to evaluate this approach in a clinical setting. Second, we excluded patients with systolic dysfunction and those with atrial fibrillation. Different results could have been found evaluating these two populations. Third, we classified the grade of DD using echocardiography and evaluated CMR findings with this classification. Maybe a direct comparison with LV and LA catheterism could provide additional information about the effectiveness of CMR in the evaluation of DD. Finally, we excluded three patients from image analysis because of sub-optimal image quality. This may appear as a limitation of this novel method for evaluation of diastolic function. However, the exclusion of patients with sub-optimal images was made 'a priori' because this was a methodological study and we preferred to remove any potential confounding factors, including images of low quality. Future clinical studies are needed to assess the effectiveness and feasibility of this novel CMR technique for the evaluation of diastolic function.

Conclusions

The combined evaluation of LA and LV V/t curves by CMR may allow evaluation of DD with results similar to those achieved by echocardiography. Future studies are needed to evaluate the role of CMR in the clinical setting.

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