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Original Article

Left Ventricular Diastolic Function in CMR Using Transmitral Velocity in Thalassemia Patients: Correlations With Echocardiography

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ABSTRACT

Objectives: We sought to compare diastolic values in cardiac magnetic resonance imaging (CMR) compared with echocardiography in assessing left ventricular diastolic function in patients with thalassemia.

Background: Left ventricular assessment by CMR is mainly limited to the evaluation of the systolic function of the heart and is widely used in clinical practice. On the other hand, the gold standard for diastolic function assessment is echocardiography. The role of CMR in diastolic function assessment is less well-established clinically, despite the importance of the early diagnosis of diastolic dysfunction, which precedes systolic dysfunction.

Methods: Forty-five subjects (mean age =27.8±10.9 y) who underwent CMR and echocardiography on the same day were evaluated. Diastolic function parameters using the technique of the transmitral flow (the E wave, the A wave, the E/A ratio, and the deceleration time) of the left ventricle were evaluated via both CMR and echocardiography.

Results: The E/A ratio of the transmitral flow to assess diastolic parameters in CMR correlated well with echocardiography (r=0.745*, P<0.001), while the E and A values had weak correlations between the 2 modalities (r=0.301, P<0.05 and r=0.343, P<0.05). The measurement of the deceleration time in CMR had no statistically significant correlation with that of echocardiography (r=0.219, P=0.152). A weak correlation existed between the diastolic index measured using the technique of the fractional area change of the left ventricle and the E/A ratio measured in echocardiography (r=0.325, P<0.05).

Conclusions: CMR evaluation of diastolic function using the transmitral flow correlated well with echocardiography. ***(Iranian Heart Journal 2022; 23(4): 20-28)***

KEYWORDS: Cardiac MRI, Thalassemia, Diastolic dysfunction

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Left ventricular (LV) function assessment with cardiac magnetic resonance imaging (CMR)[1] is becoming the gold standard in the evaluation of the systolic function of the heart and is widely used in clinical practice. Nonetheless, it is mainly limited to the evaluation of systolic function, which includes the estimation of the ejection fraction, regional wall motion analysis, and mass and volume measurements.[2] Thus, the role of CMR in the evaluation of diastolic function is less well-established in clinical routine.

LV diastolic function assessment should be included as a part of a routine examination, especially when patients present with dyspnea or heart failure. Approximately half of the patients who are newly diagnosed with heart failure have normal global ejection fractions.[3,4] Hence, these patients are categorized as patients with diastolic heart failure.

Impaired LV diastolic function is often observed at its earliest stage, which usually precedes systolic dysfunction in heart failure. Clinically, there is an increase in end-diastolic pressure, as well as clinical symptoms such as shortness of breath, fatigue, and reduction in exercise tolerance. Currently, echocardiography is the mainstay of noninvasive modality for the evaluation of the diastolic function of the LV.[5]

Diastole is a part of the cardiac cycle and is divided into 4 stages: isovolumetric relaxation, early rapid diastolic filling, diastasis, and late diastolic atrial filling. Diastolic dysfunction refers to the abnormal mechanical diastolic properties of the LV. These diastolic properties comprise the ability of the LV for relaxation, the filling dynamics of the LV, and the distensibility of the LV. In this case, LV ejection fraction could be normal or decreased with the presence or absence of symptoms. When patients are symptomatic, this is termed “diastolic heart failure”.

The parameters for LV diastolic function evaluation in CMR are left atrial (LA) size, transmitral flow and velocity, pulmonary vein flow, LV fractional area change, LV filling curve, myocardial tissue phase contrast, myocardial tagging, magnetic resonance spectroscopy, and resonance elastography. The commonly used parameters for the evaluation of diastolic function in CMR are transmitral velocity and pulmonary venous flow.

In patients with thalassemia, although treatment with regular blood transfusions and iron chelation therapy has proven to improve survival, mortality is still high, with cardiac failure caused by the overload of transfusional iron, accounting for up to 71% of all deaths from cardiac disease. Thus, there is clinical importance to risk-stratify patients that will develop cardiac failure due to iron overload.

As LV diastolic dysfunction often precedes systolic function and occurs at the early stage of heart failure, LV diastolic function could be a more sensitive marker of the diseases caused by excess myocardial iron loading than systolic function. Diastolic function is routinely assessed by echocardiographic techniques, which are more readily available. Further, diastolic function is deemed the mainstay of diagnosis currently.

In the present study, we aimed to directly compare diastolic function parameters between echocardiography and CMR, focusing especially on the parameters of transmitral velocity and LV fractional area changes in a cohort of patients with transfusion-dependent thalassemia.

METHODS

Study Population

Twenty-nine patients with known thalassemia major or intermedia on regular transfusions were enrolled in this study. Sixteen normal patients with normal hemoglobin levels were also enrolled as the control group.

The exclusion criterion was the presence of underlying congenital cardiac anomalies.

Patients with contraindications to CMR, such as metal implants incompatible with CMR and claustrophobia, were also excluded from the study.

All the patients underwent echocardiography on the same day or within 1 month of CMR. All the echocardiographic examinations were performed by the same appointed sonographer.

Informed consent was obtained from all the participants, and the study protocol was approved by the National Medical Research Register.

CMR Acquisition and Analysis

All the patients were imaged using 1.5 T CMR (Siemens) using 5-channel phased-array cardiac coils. The CMR protocol included the cine imaging of the LV using an electrocardiogram-gated, breath-hold balanced turbo field echo sequence (b-TFE) in the 2-chamber, 4-chamber, and short-axis views with the following parameters: a repetition time (TR)/echo time (TE) of 60.2/1.87, 25 cardiac phases, matrix of 192· 115, a field of view (FOV) of 300, the number of signals averaged (NSA) of 1, a flip angle of 70°, a slice thickness of 8 mm, and a scan time of 7 to 12 seconds.

Transmitral flow was assessed via through-plane phase-contrast images positioned at the tip of the opened mitral valve perpendicular to the LV inflow tract with the following parameters: a repetition time (TR)/echo time (TE) of 47/3.9, matrix of 256 · 192, an FOV of 240, a flip angle of 30°, a slice thickness of 5 mm, and velocity of 150 m/s (Fig. 1).

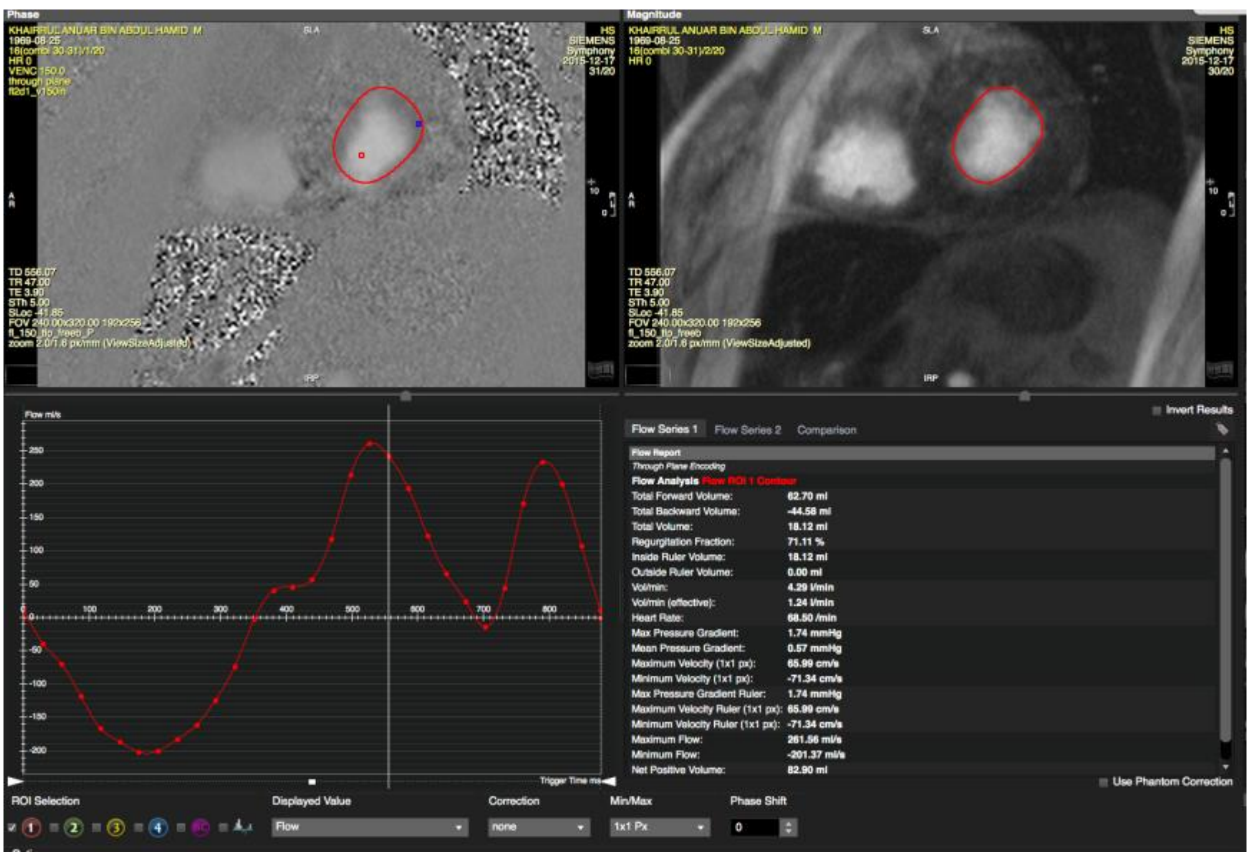

Figure 1: Magnitude and phase-contrast images, as well as the resultant transmitral curve, are presented herein.

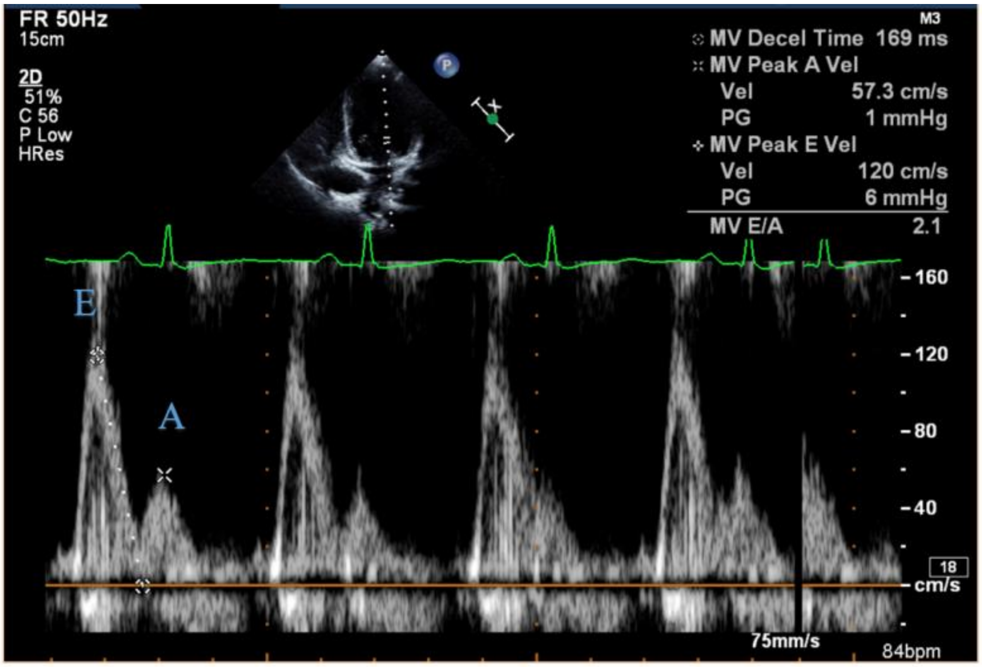

Figure 2: The image shows the transmitral flow curve on Doppler echocardiography.
E peak: Rapid early filling peak; A peak, Late filling peak

Post-processing and measurements were performed by 2 radiologists blinded to the echocardiography results. The radiologists used the cvi42 software, whereby a region of interest (ROI) was placed at the center of the mitral valve orifice in the phase-contrast images and then propagated to the other phases to obtain the transmitral flow curve, the early diastolic peak/late peak velocities ratio (the E/A ratio), and the deceleration time.

LV Diastolic Dysfunction Analysis

Diastolic function was considered normal if the E/A was 1 to 2 and the deceleration time exceeded 200 milliseconds; Grade I if the E/A fell below 1; Grade II if the E/A was 1 to 2 with the deceleration time of 160 to 200 milliseconds; and Grade III if the E/A was above 2 and the deceleration time was less than 160 milliseconds.[6]

Echocardiography Acquisition and Analysis

The echocardiographic and Doppler readings were performed by an appointed experienced sonographer. Echocardiography was done using a Philips machine. The apical 4-chamber view was used to record the Doppler wave of the mitral inflow. The sample volume was placed at the tip of the mitral leaflet. The E wave, the A wave, the E/A ratio, and the deceleration time of the transmitral inflow were measured (Fig. 2). Manual tracing of the end-diastolic and end-systolic endocardial borders was done in the apical 4-chamber view to determine LV end-diastolic volume, LV end-systolic volume, and LV ejection fraction via the modified Simpson method.

Statistical Analysis

Commercially available software IBM SPSS Statistics v25 (IBM, USA) was used for the statistical analyses. Baseline descriptive data, continuous variables, and differences in various parameters were expressed as the mean ± the standard deviation. Categorical variables were expressed as numbers and percentages.

The paired sample *t* test and the ANOVA test were conducted to compare the mean values of diastolic functional variables between normal patients and patients with thalassemia, as well as between CMR and echocardiography.

The correlation tests measured the strength of the linear association and direction of the correlation between 2 numerical variables. Normally distributed data sets were subjected to the Pearson correlation test. The correlations between the E wave, the A wave, the E/A ratio, and the deceleration time measurements by phase-contrast CMR and Doppler echocardiography were determined using the Pearson correlation coefficient.

The correlations between the diastolic index in the cine images of CMR and the diastolic parameters in Doppler echocardiography were also determined using the Pearson correlation coefficient. A confidence interval of 95% and a *P* value of less than 0.05 were deemed statistically significant. This statistical significance was used to test the null hypothesis that there was a correlation in LV diastolic function values between these 2 modalities. The strength of the correlation was categorized based on the *r* value (the Pearson correlation, *r*=0.00–0.19 "very weak", *r*=0.20–0.39 "weak", *r*=0.40–0.59 "moderate", *r*=0.60–0.79 "strong", and *r*=0.80–1.0 "very strong"). The Bland–Altman analysis was used to determine the agreement between the modalities further by calculating the bias (mean difference) and the 95% limits of agreement.

RESULTS

All the imaging examinations were performed successfully in all the patients, without any major complications. Good-quality images of each imaging modality were obtained for functional analysis.

Demographic Data

Over a period of 18 months, 45 subjects, consisting of 26 males and 19 females, were recruited for the study and included in the final analysis and post-processing. The study population consisted of 29 subjects with a known history of thalassemia, either major or intermedia, and 16 normal controls. The participants' age ranged from 13 to 58 years. The mean age was 27.7±11.9 years in the thalassemia group and 28.3±9.3 years in the control group, with an overall mean age of 27.8±10.9 years. The basic characteristics of the enrolled patients are summarized in Table 1.

Table 1: Demographic data of the enrolled patients

Age (y)	*27.87 ± 10.9
- Normal	*27.7 ± 11.9
- Thalassemia	*28.3 ± 9.3
Age by Group (%)	
- 10-19	11 (24.4%)
- 20-29	17 (37.8%)
- 30-39	9 (20%)
- > 40	8 (17.8)
Sex n (%)	
- male	26 (57.8%)
- female	19 (42.2%)
Type of Thalassemia (%)	
- major	17 (58.6%)
- intermedia	12 (41.3%)
Frequency of Chelation	
- Twice weekly	3 (10.3%)
- Monthly	2 (6.9%)
- Twice monthly	12 (41.4%)
- Three times monthly	12 (41.4%)
Liver Iron Load (%)	
- No iron load	42 (93.3%)
- Mild iron load	-
- Moderate iron load	-
- Severe iron load	3 (6.7%)

* Values are presented as mean ± 2SD.

Comparison of Diastolic Functional Variables Between the Normal and Thalassemia Groups

Diastolic function was graded on a scale of 0 to 3, representing normal (no diastolic dysfunction), Grade I dysfunction, Grade II dysfunction, and Grade III dysfunction, respectively. On assessment by echocardiography, 16% of the patients with thalassemia (18 patients) had a normal diastolic function, while 6.7% (2 patients) had Grade I, 3.3% (1 patient) had Grade II, and 26.7% (8 patients) had Grade III diastolic dysfunction.

Similarly, in CMR, 18 patients (16%) had a normal diastolic function, while 2 patients (6.7%) had Grade I, 1 patient (3.3%) had Grade II or pseudonormal, and 8 patients (26.7%) had Grade III diastolic dysfunction.
All the control subjects were noted to have a normal diastolic function in both CMR and echocardiography.
Of the 29 patients with thalassemia, the mean E value in echocardiography was 97.4±16.2 cm/s. The mean E value of the normal group was significantly lower (81.2±14.9; *P*<0.01). The mean A value in echocardiography for the thalassemia group was 60.2±19.9, while the mean for the normal group was 50.3±9.0. No significant difference was detected in the mean of the A value between these 2 groups in echocardiography (*P*=0.068). The mean E/A ratio in the thalassemia group measured in echocardiography was 1.76±0.59, while the mean value in the normal group was 1.59±0.18. No significant difference was noted in the mean value between these 2 groups (*P*=0.349). As for the deceleration time, the mean value in echocardiography for patients with thalassemia was 182.8±42.2, while the mean for the normal group was 164.4±30.9, with no significant difference (*P*=0.134).
When measured by CMR, the mean early diastolic peak velocity in the normal group was 86.6±12.9, while the mean value for the thalassemia group was 78.5±20.1. No significant difference was detected in the E value in CMR between these 2 groups (*P*=0.154). The mean late diastolic peak velocity in the normal group was 54.7±9.9, while the mean value in the thalassemia group was 46.6±13.1. No significant difference was observed in the A value between the thalassemia and normal groups (*P*=0.038).
As regards the E/A ratio measured in CMR, the mean value was 1.62±0.15 in the normal group and 1.76±0.53 in the thalassemia group. No significant difference was noted between these 2 groups (*P*=0.261). The mean deceleration time also showed no significant difference between the normal and thalassemia groups (155.7±48.1 and 160.3±36.5, respectively; *P*=0.719).

Table 2: Mitral inflow diastolic parameters in the normal and thalassemia groups

		E value (cm/s)	A value (cm/s)	E/A Ratio	Deceleration Time (ms)
Echocardiography Findings	Normal	81.2 ± 14.9	50.3 ± 9.0	1.59 ± 0.18	164.4 ± 30.9
	Thalassemia	97.4 ± 16.2	60.2 ± 19.9	1.76 ± 0.59	182.8 ± 42.2
CMR Findings	Normal	86.6 ± 12.9	54.7 ± 9.9	1.62 ± 0.15	155.7 ± 48.1
	Thalassemia	78.5 ± 20.1	46.6 ± 13.1	1.76 ± 0.53	160.3 ± 36.5

* All values are presented as mean ± 2SD
CMR, Cardiac magnetic resonance imaging

Table 3: Correlations of the E and A values between echocardiography and CMR

Correlations Between the Modalities	Pearson Correlation	Significance	
E value	0.301*	*P*=0.04	Significant
A value	0.343*	*P*=0.04	Significant

CMR, Cardiac magnetic resonance imaging

Table 4: Correlations of the E and A values between echocardiography and CMR

Correlations Between the Modalities	Pearson Correlation	Significance	
E/A Ratio	0.745**	*P*<0.001	Strongly Significant
Deceleration Time	0.219	*P*=0.152	Not Significant

CMR, Cardiac magnetic resonance imaging

Table 5: Correlations between diastolic parameter values in echocardiography and the diastolic index in CMR

Diastolic index Relationships With	Correlation	Significance	
Echo E value	0.081	*P*=0.597	Not Significant
Echo A value	-0.251	*P*=0.097	Not Significant
Echo E/A Ratio	0.325*	*P*<0.05	Significant
Echo Deceleration Time	-0.072	*P*=0.638	Not Significant

CMR, Cardiac magnetic resonance imaging

The mean A value was 56.7±17.5 cm/s in echocardiography and 49.5±12.6 cm/s in CMR. There was no significant difference in the mean A value between echocardiography and CMR (*P*=0.636).
The mean E/A ratio was 1.72±0.43 in echocardiography and 1.70±0.48 in CMR. There was no statistically significant difference in the E/A ratio between echocardiography and CMR (*P*=0.061).
The mean deceleration time was 176.3±39.2 milliseconds in echocardiography and 158.7±40.5 milliseconds in CMR. There was a statistically significant difference in the deceleration time between echocardiography and CMR (*P*=0.036).

Correlations of Diastolic Parameters Between Echocardiography and CMR

- *Correlations of the E and A waves between echocardiography and CMR*
  Table 3 summarizes the correlations of the E and A values between echocardiography and CMR. The E value showed a positive correlation between echocardiography and CMR (*r*=0.301, *P*=0.04). The A value had a moderate correlation between echocardiography and CMR (*r*=0.343, *P*=0.02).
- *Correlations of the E/A Ratio and the deceleration time between echocardiography and CMR*
  Table 4 summarizes the relationship between the E/A ratio and the deceleration time between echocardiography and CMR. There was a statistically strong correlation in the E/A ratio between echocardiography and CMR (*r*=0.745, *P*<0.001). Nevertheless, the deceleration time correlated poorly between the measurements in echocardiography and CMR (*r*=0.236, *P*=0.118).
- *Sensitivity, specificity, and predictive value for transmitral flow in CMR in predicting diastolic function*
  In the routine clinical setting, transmitral flow is taken as a parameter in determining the diastolic function of the heart by echocardiography. These parameters measured in CMR demonstrate a high positive predictive value (81.8%) and a high negative predictive value (94.1%), in keeping with high sensitivity and specificity (Table 8).

Correlations in the Grading of Diastolic Function Between CMR and Echocardiography

Diastolic function was graded based on normal, Grade I (impaired relaxation), Grade II (pseudonormal), and Grade III (restrictive). Diastolic function was graded both in CMR and echocardiography, based on the values of the E/A ratio and the deceleration time. There was a strong significant correlation in the grading of diastolic function between these 2 modalities (*r*=0.731**, *P*<0.001).

LV Diastolic Index

- *Correlations between the diastolic index in CMR and diastolic parameters in echocardiography*
  Table 5 shows the correlations between the values of the diastolic parameters measured in echocardiography and the diastolic indices measured by using fractional area change of the LV in the

short-axis view of CMR. Of all the parameters, only the E/A ratio demonstrated a statistically significant, but weak, correlation with the diastolic index (r=0.325*, P<0.05). The rest of the diastolic parameters in echocardiography (the E value, the A value, and the deceleration time) had poor correlations with the diastolic index (P=0.597, P=0.097, and P=0.638, respectively).

DISCUSSION

The present study recruited a small sample of patients with thalassemia (n=29) and a small normal group (n=16); therefore, the study population consisted of 45 subjects. There are only a few comparable studies investigating the correlation in diastolic parameters between echocardiography and CMR in patients with thalassemia. A study by Rubinshtein et al[7] investigated the correlations of diastolic parameters between echocardiography and CMR in patients with cardiac amyloidosis, with the number of patients comparable to that of our study (n=38).

Using transmitral flow, Behairy et al[6] compared diastolic function parameters between CMR and echocardiography in patients with ischemic heart disease. In comparison with that study, our study population is young (62.2% in the age group of 10–29 years). This may be due to the fact that most patients with iron overload and thalassemia are in the age group of 10 to 40 years based on their life expectancy and blood transfusion duration. Furthermore, ischemic heart disease is usually seen in the older age group.

Cardiomyopathy in patients with thalassemia caused either by anemia or by the iron loading of the heart is the leading cause of mortality in transfusion-dependent patients. Early identification of heart failure is vital as there is a need for the optimization of iron chelation therapy. Since diastolic dysfunction usually presents earlier than systolic dysfunction, this may assist in the cardiac management of patients with thalassemia. Therefore, some LV function parameters have been assessed in previous studies to determine their ability to identify early myocardial iron overload, which may aid the optimization of chelation therapy to prevent the early development of heart failure.

Based on our findings in patients with thalassemia, diastolic parameters in CMR showed weak correlations with diastolic parameters in echocardiography for peak early filling (the E wave) and peak late filling (the A wave) but showed a strong significant correlation with the E/A ratio. There was also a good agreement on the Bland–Altman plot, as well as excellent inter-rater reliability (particularly the E/A ratio), suggestive of the ability of the phase-contrast CMR to predict the diastolic function of the heart, especially via the transmitral flow method. This is comparable to a study by Behairy et al,[6] who found an excellent agreement between the E/A ratio in CMR and echocardiography, albeit in a different cohort of patients. Rubinshtein et al[7] also noted moderate correlations in the E wave, the A wave, the E/A ratio, and the deceleration time between these 2 modalities, with a good agreement. The possible reasons why the absolute values of the E and A waves in these 2 modalities only show weak correlations (r=0.301 and r= 0.343, respectively) could be technical differences between phase-contrast CMR and Doppler echocardiography. Previous studies have noted that it is already expected that phase-contrast CMR will yield slightly lower peak velocities than Doppler echocardiography because of its lower temporal resolution.[8] Still, these differences should not affect the E/A ratio, which is regarded as an important index of LV diastolic filling.

We also found no significant correlations in the deceleration time between phase-contrast CMR and Doppler echocardiography. This is also possibly due to the low temporal resolution of phase-contrast CMR, leading to its poor ability to measure the deceleration time and the isovolumetric relaxation time, both of which are regarded as important parameters of diastolic function in echocardiography.[8]

CMR has been considered the gold standard for systolic function evaluation, mainly due to its high reproducibility of measurements.[7] Apropos of diastolic function, echocardiography is an established technique because it is fast and inexpensive. However, in patients with thalassemia, CMR has an incremental value over echocardiography, particularly because it can determine patients' myocardial iron loading. Thus, in these patients, CMR with comprehensive assessments, including the assessment of diastolic function, will be extremely useful with only an additional 5 to 10 minutes to the overall scan time.

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