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ORIGINAL PAPER

Left ventricular filling patterns in patients with previous myocardial infarction measured by conventional cine cardiac magnetic resonance

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Abstract To explore left ventricular filling patterns in patients with a history of previous myocardial infarction (MI) using time-volume curves obtained from conventional cine-cardiac magnetic resonance (CMR) examinations. Consecutive patients with a history of previous MI who were referred for CMR evaluation constituted the study population, and a consecutive cohort of sex and age-matched patients with a normal CMR constituted the control group. The following CMR diastolic parameters were evaluated: peak filling rate (PFR), time to PFR (tPFR), normalised PFR adjusted for diastolic volume at PFR (nPFR), and percent RR interval between end systole and PFR. Fifty patients were included, 25 with a history of previous MI and 25 control. The mean age was 59.6 ± 13.9 years and 27 (54%) were male. Within the control group, age was significantly related to PFR (r = −0.53, $p = 0.007$), whereas among patients with previous MI age was not related to PFR (r = −0.16, $p = 0.44$). PFR (252.4 ± 96.7 ml/s vs. 316.0 ± 126.4 ml/s, $p = 0.05$) and nPFR (1.6 ± 1.2 vs. 3.3 ± 1.5, $p < 0.001$) were significantly lower in patients with previous MI, whereas no significant differences were detected regarding tPFR (143.0 ± 67.5 ms vs. 176.2 ± 83.9 ms, $p = 0.13$) and % RR to PFR (18.1 ± 9.7% vs. 20.6 ± 12.2%, $p = 0.44$). MI size was related to LV ejection fraction (r = −0.76, $p < 0.001$), PFR (r = −0.40, $p = 0.004$), nPFR (r = −0.52, $p < 0.001$) and left atrium area (r = 0.40, $p = 0.004$). Patients at the lowest PFR quartile (<200 ml/s) showed a larger MI size (Q1 26.5 ± 25.5%, Q2 15.5 ± 20.9%, Q3 6.3 ± 12.4%, Q4 8.8 ± 14.1%, $p = 0.04$). At multivariate analysis, MI size was the only independent predictor of the lowest PFR ($p = 0.017$). Infarct size has an impact on LV filling profiles, as assessed by conventional cine CMR without additional specific pulse sequences.

Keywords Ischemic cardiomyopathy · Diastolic function · Velocity-encoding · Tagging · Heart failure · Coronary artery disease

Abbreviations

MRI	Magnetic resonance imaging
CMR	Cardiovascular magnetic resonance
MI	Myocardial infarction
LV	Left ventricle
RV	Right ventricle
LVEF	Left ventricular ejection fraction

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PFR Peak filling rate
nPFR Normalised peak filling rate
tPFR Time to peak filling rate

Introduction

The advances witnessed in cardiovascular magnetic resonance (CMR) imaging, particularly in left ventricular (LV) systolic function analysis and late gadolinium enhancement (LGE) techniques, have rapidly expanded the role of CMR in patients with heart failure [1, 2]. However, almost half of patients with heart failure have preserved left ventricular ejection fraction (LVEF), leading to a growing interest in the assessment of diastolic function during the last decade [3]. The identification of diastolic dysfunction has important implications for risk stratification and selection of treatment strategies. There are several approaches to assess diastolic function using CMR, including velocity encoding imaging and tissue tagging [4, 5]. In parallel to echocardiography, velocity encoded imaging can evaluate transmitral early diastolic and atrial systolic flow and peak velocities, as well as pulmonary vein flow patterns. Nevertheless, both techniques require additional specific breath-hold pulse sequences that extend an already time-consuming diagnostic procedure, being this particularly relevant in patients with limited breath-hold capabilities. Conversely, time-volume curves obtained directly from conventional cine CMR provide parameters of LV filling properties and have recently shown promise to discriminate patients with diastolic dysfunction [6].

Coronary artery disease is associated with increased myocardial stiffness, leading to impaired left ventricular relaxation. We therefore sought to explore the ability of conventional cine CMR to assess left ventricular filling patterns in patients with a history of previous myocardial infarction (MI) using time-volume curves obtained from conventional cine-CMR examinations.

Methods

Study population

The present was an investigator-driven observational study that aimed to explore LV filling patterns of patients with a previous history of MI using conventional cine CMR. To that end, consecutive patients with a history of previous MI (>3 months) who were referred to our institution for assessment of the extension of necrosis by CMR were retrospectively selected from our database and constituted the study population, and a consecutive cohort of sex and age-matched patients with a normal CMR constituted the control group. Patients with moderate to severe valvular heart disease were excluded, as well as patients with pericardial disease, atrial fibrillation and non-ischemic cardiomyopathy. A normal CMR was defined as the presence of a normal size of cardiac chambers, normal T1 and T2 myocardial signal, normal pericardium thickness and signal, normal great vessel anatomy, absence of moderate to severe valvular heart disease, absence of congenital heart disease or intracavitary masses, absence of late gadolinium enhancement, and normal global and regional ventricular function. The clinical definitions used were as follows: diabetes mellitus was defined if the patient had a fasting glucose level >1.26 g/l, if this risk factor was documented in the medical record, or if the patient was receiving dietary, oral drug, or insulin treatment. Hypercholesterolemia was defined if the patient had a total cholesterol level of more than 200 mg/dl, if this risk factor was documented in the medical record, or if the patient was receiving any lipid-lowering treatment. Arterial hypertension was defined if systolic blood pressure was >140 mmHg or diastolic blood pressure was >90 mmHg, if this risk factor was documented in the medical record, or if the patient was receiving antihypertensive treatment.

CMR acquisition

All CMR exams were performed using an MRI system (Achieva 3.0 Tesla, Philips Healthcare, Cleveland, OH) equipped with a Quasar Dual gradient system (maximum gradient amplitude 80 mT/m; maximum slew rate 200 mT/m/sec). A six-element cardiac phased-array coil was used for signal reception and cardiac synchronization was performed using a vector electrocardiogram. Cine-CMR images were acquired in 8–10 contiguous short-axis slices from the level of the mitral valve annulus through the LV apex using a commercially available steady-state free precession pulse sequence. Technical parameters

were as follows: TR/TE (ms) 3.4/1.7; flip angle 45°; section thickness 8 mm; matrix 144 × 157; field of view 320 mm; voxel size 2.0 × 2.0 mm; number of phases 30; temporal resolution 49.3 ms. For detection of the presence, extent and location of infarcted myocardium, a breath-hold, T1-weighted, contrast-enhanced inversion-recovery segmented gradient echo sequence (TR/TE (ms) 4.8/2.3; flip angle 25°; section thickness 10 mm; matrix 184 × 154; field of view 320 mm; voxel size 1.75 × 1.95 mm; minimum inversion time delay 79.3 ms) was used. These LGE images were acquired 10 min after manual intravenous administration of 0.2 mmol/kg of a commercially available gadolinium chelate of diethylenetriamine pentaacetic acid bismethoxyethylamide (gadoversetamide, Mallinckrodt, St. Louis, USA) through an antecubital vein, using identical long- and short-axis planes to the cine images, except for the most apical short-axis slice, which was excluded because it can be affected by partial-volume effects.

Image analysis

All MR imaging studies were analyzed offline in a dedicated workstation (Viewforum; Philips Healthcare) by an observer blinded to the clinical history. LV end-diastolic volume (EDV) and LV end-systolic volume (ESV) were calculated using the Simpson method and LVEF was calculated as [EDV − ESV]/EDV × 100. Basal image position was defined as the basal-most image encompassing at least 50% circumferential myocardium. Myocardial mass was obtained on the basis of end-diastolic endocardial and epicardial contours, and calculated as the product of myocardial volume and specific density of myocardial tissue (1.05 g/ml).

At LGE MR imaging, MI was considered present if signal intensity of the infarcted myocardium exceeded two standard deviations of that of the remote myocardium, and MI size was defined using a 17-segment LV model [7].

For assessment of left ventricular filling patterns, manual contour detection of the endocardial border was performed excluding papillary and trabecular structures across all end diastolic temporal phases using short axis images from base to apex, and subsequently copied to all temporal phases by automatic border detection. If necessary, manual correction was performed during diastole. The following CMR diastolic parameters were evaluated: (1) peak filling rate (PFR): maximal LV filling rate defined by maximal change in LV volume between sequential temporal phases (Δ volume/Δ phase); (2) time to PFR (tPFR): time interval between end systole and PFR; (3) normalised PFR (nPFR): PFR adjusted for diastolic volume at PFR; and (4) percent RR interval between end systole and PFR: (tPFR/RR interval) × 100.

The study was approved by our institution′s ethics committee, and all the patients enrolled gave their written informed consent.

Statistical analysis

Discrete variables are presented as counts and percentages. Continuous variables are presented as mean ± SD or median (25th, 75th percentile) whenever appropriate. Comparisons among groups were performed using independent Student *t* tests, χ^2 tests, Fisher′s exact tests, one way analysis of variance and Jonckheere-Terpstra tests, as indicated. Pearson′s correlation coefficients were used to detect any association between variables. Logistic regression analysis was performed using the forward-Wald method to identify potential predictors of the lowest PFR quartile. A two-sided *p* value of less than 0.05 indicated statistical significance. Statistical analyses were performed with the SPSS software, version 13.0 (Chicago, Illinois, USA).

Results

Fifty patients were included, 25 consecutive patients with a history of previous MI and 25 consecutive age and sex-matched control cases. The mean age was 59.6 ± 13.9 years and 27 (54%) patients were male. Diabetes, hypertension and hypercholesterolemia were more prevalent in patients with a previous history of MI (Table 1). CMR was indicated in patients with a history of previous MI to assess the extent of necrosis and presence of viable myocardium in patients with typical chest pain (n = 10) and dyspnoea (n = 15). Premature ventricular contractions, atypical chest pain, family history of sudden death, and syncope were indications of CMR in control patients, with all CMR exams being eventually unremarkable.

Table 1 Demographics and CMR parameters

	Previous MI (n = 25)	Control (n = 25)	*p* value
Demographical characteristics			
Age ± SD	61.8 ± 12.4	57.4 ± 15.2	0.26
Male (%)	15 (56%)	10 (44%)	0.57
Diabetes mellitus (%)	6 (24%)	0 (0%)	0.02
Hypertension (%)	17 (68%)	5 (20%)	0.001
Dyslipidemia (%)	16 (64%)	6 (24%)	0.01
Current smoking (%)	4 (16%)	3 (12%)	0.99
Previous smoking (%)	8 (32%)	1 (4%)	0.02
Heart rate ± SD	74.5 ± 23.3	66.6 ± 11.4	0.17
LV systolic function and morphology			
LV diastolic diameter (mm)	54.9 ± 9.4	45.0 ± 5.2	<0.001
LV systolic diameter (mm)	41.7 ± 11.8	28.6 ± 4.1	<0.001
LV diastolic volume (ml)	147.2 ± 64.2	91.3 ± 19.8	<0.001
LV systolic volume (ml)	98.0 ± 61.6	34.1 ± 11.2	<0.001
LV ejection fraction (%)	37.8 ± 14.9	63.1 ± 7.2	<0.001
Myocardial mass (grams)	95.3 ± 24.9	72.4 ± 16.4	<0.001
RV diastolic volume (ml)	90.2 ± 32.8	90.4 ± 29.7	0.98
RV systolic volume (ml)	43.4 ± 27.1	36.3 ± 14.5	0.26
RV ejection fraction (%)	55.6 ± 12.0	60.5 ± 5.7	0.07
Left atrium area (cm^2)	25.4 ± 9.8	19.8 ± 5.3	0.01
Right atrium area (cm^2)	19.7 ± 6.1	18.1 ± 5.0	0.33
LV diastolic function			
PFR (ml/s)	252.4 ± 96.7	316.0 ± 126.4	0.05
tPFR (ms)	143.0 ± 67.5	176.2 ± 83.9	0.13
nPFR	1.6 ± 1.2	3.3 ± 1.5	<0.001
% RR to PFR (%)	18.1 ± 9.7	20.6 ± 12.2	0.44

LV left ventricular, *RV* right ventricular, *PFR* peak filling rate, *tPFR* time to PFR, *nPFR* normalized PFR, *%RR to PFR* percent of the RR interval between end systole and PFR

LV systolic function and morphology

LV end diastolic volume (147.2 ± 64.2 ml vs. 91.3 ± 19.8 ml, $p < 0.001$), LV end systolic volume (98.0 ± 61.6 ml vs. 34.1 ± 11.2 ml, $p < 0.001$) and left atrium area (25.4 ± 9.8 cm^2 vs. 19.8 ± 5.3 cm^2, $p = 0.01$) were significantly larger in patients with a history of previous MI, and LV ejection fraction was significantly lower (37.8 ± 14.9% vs. 63.1 ± 7.2%, $p < 0.001$). No differences were detected between groups concerning right ventricular (RV) volumes, although a trend towards a lower RV ejection fraction was detected in patients with a history of previous MI (55.6 ± 12.0% vs. 60.5 ± 5.7%, $p = 0.07$).

Twenty-one (84%) patients with a history of previous MI had evidence of LGE, with MI size of 29.2 ± 19.8%. No evidence of LGE was found in control patients.

LV diastolic function

PFR (252.4 ± 96.7 ml/s vs. 316.0 ± 126.4 ml/s, $p = 0.05$) and nPFR (1.6 ± 1.2 vs. 3.3 ± 1.5, $p < 0.001$) were significantly lower in patients with previous MI, whereas no significant differences were detected regarding tPFR (143.0 ± 67.5 ms vs. 176.2 ± 83.9 ms, $p = 0.13$) and % RR to PFR (18.1 ± 9.7% vs. 20.6 ± 12.2%, $p = 0.44$) Table 2.

Overall, the median PFR was 275 ml/s (interquartile range 200; 353). Patients with the lowest PFR quartile (<200 ml/s) showed larger MI size (Q1 26.5 ± 25.5%, Q2 15.5 ± 20.9%, Q3 6.3 ± 12.4%, Q4 8.8 ± 14.1, $p = 0.04$) and a trend towards a

Table 2 CMR parameters according to the peak filling rate quartile

Peak filling rate	Lowest quartile	2nd quartile	3rd quartile	Highest quartile	*p* value
Myocardial infarction size (%)	26.5 ± 25.5	15.5 ± 20.9	6.3 ± 12.4	8.8 ± 14.1	0.04
LVED diameter (mm)	53.0 ± 10.9	47.5 ± 8.7	47.6 ± 8.0	51.2 ± 7.7	0.34
LVES diameter (mm)	39.3 ± 14.2	33.6 ± 10.1	33.4 ± 9.8	33.8 ± 8.7	0.45
LVED volume (ml)	134.9 ± 80.7	112.0 ± 43.8	106.6 ± 39.1	121.3 ± 41.8	0.58
LVES volume (ml)	90.2 ± 76.3	58.7 ± 44.5	51.2 ± 39.8	60.6 ± 41.3	0.26
LV ejection fraction (%)	41.4 ± 18.8	52.6 ± 16.4	54.9 ± 16.2	54.2 ± 15.1	0.14
Stroke volume (ml)	41.4 ± 7.7	49.0 ± 14.4	51.2 ± 11.6	52.7 ± 15.7	0.10
Left atrium area (cm^2)	22.1 ± 10.8	22.9 ± 8.1	21.4 ± 6.6	24.3 ± 7.4	0.85
RV ejection fraction (%)	56.4 ± 6.1	59.4 ± 11.3	60.1 ± 9.1	56.6 ± 12.1	0.14

LVED to left ventricular end diastolic, *LVES* to left ventricular end systolic, *RV* right ventricular

lower stroke volume (Q1 41.4 ± 7.7 ml, Q2 49.0 ± 14.4 ml, Q3 51.2 ± 11.6 ml, Q4 52.7 ± 15.7 ml, $p = 0.10$).

At multivariate analysis, after correcting for age, hypertension, heart rate, LV end diastolic volume, LV end systolic volume, LVEF and left atrium area, MI size was the only independent predictor of the lowest PFR ($p = 0.017$).

Relationships between diastolic parameters and age, and MI size

Within the control group, age was significantly related to the PFR ($r = -0.53, p = 0.007$), nPFR ($r = -0.46$, $p = 0.02$), and tPFR ($r = 0.46$, $p = 0.02$). On the other hand, among patients with a history of previous MI age was not related to PFR ($r = -0.16, p = 0.44$), nPFR ($r = -0.26$, $p = 0.21$), or tPFR ($r = 0.12$, $p = 0.56$).

MI size was related to LVEF ($r = -0.76$, $p < 0.001$), LV end diastolic diameter ($r = 0.61$, $p < 0.001$), LV end diastolic volume ($r = 0.54$, $p < 0.0001$), LV end systolic volume ($r = 0.64$, $p < 0.0001$), PFR (Fig. 1, $r = -0.40$, $p = 0.004$), nPFR ($r = -0.52$, $p < 0.001$) and left atrium area ($r = 0.40$, $p = 0.004$).

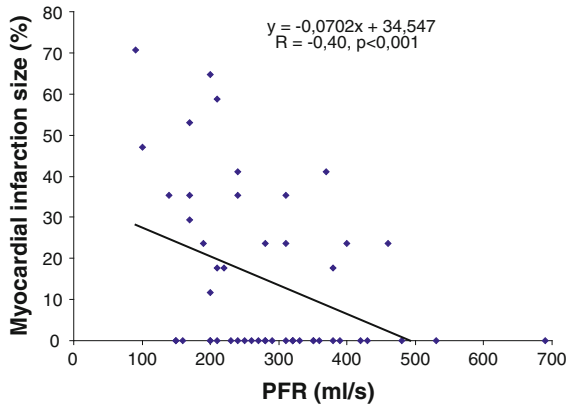

Fig. 1 Relationship between myocardial infarction size and peak filling rate

Discussion

Over the past few years, CMR has become the reference standard for assessment of LV volumes, myocardial mass and systolic function. One of the major limitations of CMR is its duration. In the clinical scenario, tight MRI schedules are mainly occupied by non-cardiovascular procedures. Accordingly, a restricted amount of time is usually available to perform a comprehensive CMR, which requires assessment of both systolic and diastolic LV function. In addition, patients with heart failure typically have limited breath-hold capabilities. Overall, these conditions demand straight forward CMR procedures, with focus in the systolic function and LGE enhancement techniques, and usually exclude diastolic function assessment with additional pulse sequences such as velocity encoding CMR and tissue tagging.

Recently, Kawaji et al. [6] demonstrated that conventional cine CMR has the ability to identify patients with diastolic dysfunction. Nevertheless, assessment of diastolic function by means of cine CMR has been scarcely investigated.

To our knowledge, our study is the first to explore LV filling patterns in patients with a history of previous MI using time-volume curves obtained directly from conventional cine CMR that were not customized for diastolic assessment. Our findings can be summarized as follows: (1) infarct size has an impact on LV filling profiles, as assessed by conventional cine CMR without additional specific pulse sequences; (2) age is related to diastolic CMR parameters within the control group, but not in patients with a history of previous MI.

Radionuclide angiography and CMR studies have previously identified an association between both decreased PFR and prolonged tPFR, and the presence of diastolic dysfunction [6, 8]. Indeed, in the seminal study of Mancini et al., patients with coronary artery disease had significantly lower PFR and longer tPFR both at rest and during exercise [8].

In the present study, and in line with those previous findings, patients with a history of previous MI showed distinctive LV filling patterns, particularly a significantly lower PFR and nPFR compared to control patients. Indeed, MI size was identified as the only independent predictor of the lowest PFR quartile. Although echocardiography was not performed as the reference standard, and supported by the aforementioned evidence validating PFR as a marker of LV diastolic dysfunction, it is likely that patients at the lowest PFR quartile had severe diastolic dysfunction, a significant predictor of death after MI [9]. It should be stressed that both the tPFR and the newly described parameter percent of the RR interval between end systole and the PFR did not differ between groups. Furthermore, although left atrium area was significantly larger in patients with previous MI, there was no evidence of its relation to any CMR diastolic parameter. Left atrium size has been largely associated to LV filling pressures and has important prognostic implications; therefore such paradoxical findings might be potentially attributed to the presence of a U-shaped curve effect that should be better explored in larger studies [10].

Aging is related to increased extracellular matrix fibrillar collagen deposits resulting in impairment of diastolic function [11]. In order to explore the influence of age in diastolic CMR parameters, the study population was divided into two groups. Within the control group, we found a significant inverse relationship between age and PFR/nPFR, and a significant positive correlation between age and tPFR. Conversely, age was not related to CMR diastolic parameters among patients with previous MI.

CMR is rapidly emerging as a robust diagnostic method to provide a comprehensive cardiac analysis, and has the potential to become a one-stop-shop imaging tool. Nevertheless, to date, CMR remains limited by its typically extended duration amid rigid non-cardiac MRI schedules. Thus, there is a need to exploit the available time for CMR, minimizing the number of sequences to the strictly necessary.

Our study extends previous findings about the valuable LV diastolic parameters that can be obtained during conventional cine CMR commonly used to assess systolic function and should encourage the routine assessment of diastolic function during CMR. This approach has been formerly disputed since it was believed to be time-consuming for post-processing [6]. However, advances in software versions based on differences in signal intensity between blood and myocardium have lead to reasonably accurate automatic border detection, though usually requiring subtle manual correction of temporal phases during diastole.

Limitations

A number of limitations should be recognized. A relatively small population was included, potentially leading to selection bias. The cross sectional nature of our investigation precludes making assumptions about potential prognostic implications of the findings. Prospective studies with larger populations might address the clinical impact of these findings. Previous studies have already demonstrated the ability of cardiac MR to assess diastolic function, therefore our study was not aimed to attempt the validation of the method. Conversely, we sought to explore whether patients with a history of previous MI had distinctive diastolic filling patterns as assessed by cine CMR. Notwithstanding, doppler echocardiography would have allowed us to precisely identify patients with normal and abnormal diastolic function, particularly in control patients. Finally, although control patients had normal CMR exams, healthy volunteers were not enrolled for this study.

Conclusions

Conventional cine CMR, without additional specific pulse sequences, allows the evaluation of the impact of infarct size on left ventricular filling profiles. Among all CMR diastolic parameters evaluated, PFR and nPFR were the most affected by the presence and size of MI.

Conflicts of interest We declare that Dr. Gaston A. Rodriguez-Granillo has received research support from Philips Healthcare. None of the other authors have conflicts of interest to disclose.

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